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## Department of Chemistry of the M V Lomonosov Moscow State University



This issue of the Journal is devoted to the 250th anniversary of the M V Lomonosov Moscow State University (MSU), an outstanding event in the history of culture, education and science in Russia. From the very moment of the foundation of Moscow University, studies into various chemical processes and training of students in fundamental chemistry formed a significant part of its educational and research activities. The interest in specific characteristics of substances and their possible interconversions initiated by M V Lomonosov is being realised in the wide-ranging research activities which encompass virtually all areas of modern chemistry. At the beginning, chemical investigations were carried out by the Department of Physics and Mathematics up to the establishment, in 1929, of the Department of Chemistry as an independent structural division of Moscow University.

The structure of the Department of Chemistry developed over decades reflects the evolution of scientific ideas, scientific schools and priorities characteristic of chemical education and science at different stages of its development.

Traditionally, the divisions and laboratories of the Department were grouped around physicochemical, organic and inorganic cycles. The advent and explosive development of a science of macromolecules and polymeric materials resulted in the establishment of a Division of Polymer Science, while the growing interest of chemists in processes occurring in living matter gave an impetus to the establishment and further development of the Divisions of Chemistry of Natural Compounds and Chemical Enzymology.

The indissoluble unity of educational and research processes is the main prerequisite for the fruitful development of the Department of Chemistry and its advancement. Today, the Department of Chemistry admits annually 215 students from various regions of Russia. During the first five semesters, the students receive

fundamental chemical knowledge. In the second semester of the third year, the students are allowed to choose a division, a laboratory and a research group that interests them most. The fourth and fifth years are devoted to specialised lecture courses, practical and research work. The educational cycle is terminated by the defence of a diploma work, which usually represents an expert study in one of the most advanced fields of chemistry. A large (~100 people) contingent of graduates take a postgraduate course at the Department of Chemistry and complete their education by presentation of a Ph.D. thesis. This is actually the end of the eight-year educational cycle, which is aimed at the training of high-level specialists.

The staff members of the Department, being interested in retention of the highest level of teaching chemistry in modern higher school and attraction of the most talented and capable secondary school graduates to the Department, develop high educational standards. In large measure, this task is fulfilled through the involvement of schoolchildren in annual federal and international multilevel chemical olympiads.

The most advanced level of education and research at the Department of Chemistry of MSU is maintained owing to long-standing traditions, rich experience of research work and significant contributions by the most outstanding representatives of Russian chemical science to its development. Academicians A N Nesmeyanov, A V Novoselova, N N Semenov, N M Emanuel, V A Kargin, P A Rehinder, A N Frumkin, V I Spitsin, I P Alimarin and the Corresponding Members I V Berezin, Ya I Gerasimov and many others have worked at the Department of Chemistry of MSU at different times. At present, the divisions of the Department are headed by Academicians V A Kabanov (Division of Polymer Science), N S Zefirov (Division of Organic

Chemistry), V V Lunin (Division of Physical Chemistry), Yu D Tretyakov (Division of Inorganic Chemistry), Yu A Zolotov (Division of Analytical Chemistry), A A Bogdanov (Division of Chemistry of Natural Compounds), A L Buchachenko (Division of Chemical Kinetics) as well as by Professors S D Varfolomeev (Division of Chemical Enzymology), O A Petrii (Division of Electrochemistry), B D Summ (Division of Colloidal Chemistry), S F Dunaev (Division of General Chemistry), E A Karakhanov (Division of Petrochemistry and Organic Catalysis), V M Fedoseev (Division of Radiochemistry), V V Avdeev (Division of Chemical Technology and Novel Materials), Yu A Kuzyakov (Division of Laser Chemistry). Each of the Department's divisions is an independent research-and-educational centre which specialises in a particular branch of modern chemical science.

Academicians N A Plate, I P Beletskaya, N F Bakeev and the Corresponding Members of RAS A B Zezin, A L Volynsky and I V Melikhov are working successfully at the Department of Chemistry of MSU. The Department is one of the leading multidisciplinary research-and-educational establishments in Russia. Over 1000 teachers and researchers are working in the Department. Every year, staff members of the Department of Chemistry publish 1100 scientific papers and participate in 15–20 congresses, conferences and symposia. About 150 Ph.D. and D.Sci. theses are defended at specialised councils of the Higher Attestation Commission.

As regards the quality of research and citation rates of published papers, the highly fruitful research-and-education activities in the Department of Chemistry account for its high prestige both inside the country and abroad.

This issue of the Journal 'Russian Chemical Reviews' comprises reviews reflecting the scientific interests of different research groups working at the Department of Chemistry of MSU.

The review by Academician V A Kabanov 'Polyelectrolyte complexes in solution and in bulk' considers various reactions between oppositely charged polymeric molecules in aqueous solutions which result in the formation of insoluble (stoichiometric) and soluble (non-stoichiometric) interpolyelectrolyte complexes. Thermodynamics, kinetics and mechanisms of reactions of charged polyelectrolytes and the formation of interpolymeric complexes, which represent a special family of polymeric materials, are considered. Some unusual phenomena are described. Thus soluble non-stoichiometric polymeric complexes manifest properties of linear polyelectrolytes, but often behave as amphiphilic block copolymers. The nature of the forces controlling the behaviour of the complexes and properties of multilayer materials obtained by alternation of polycations and polyanions are discussed.

The review by Dr. A A Galkin and Academician V V Lunin 'Subcritical and supercritical water: a universal medium for chemical reactions' is devoted to the discussion of the properties of water in the sub- and supercritical states. The unique properties of water in the aforementioned states as media for chemical reactions are demonstrated. A wide range of problems including some peculiarities of experimenting with water in its sub- and supercritical states, chemical characteristics of reactions of organic compounds in these media, synthesis of nanocrystalline oxides and application of sub- and supercritical water in various waste utilisation processes are discussed.

The review by Academician Yu A Zolotov *et al.* 'Sorption preconcentration of microcomponents for chemical analysis' is devoted to one of the most important trends in analytical chemistry developed by the Division over decades, *viz.*, sorption preconcentration. This procedure is based on the use of various synthetic and natural sorbents and enables a significant increase in the detection limits of analytes. The use of various methodological approaches and design of hybrid and combined variants of analysis allow one to determine, with a high level of efficiency, a broad range of compounds including organic and inorganic substances.

The review by Prof. S D Varfolomeev *et al.* 'Catalytic sites of hydrolases: structures and catalytic cycles' deals with the description of the structures and functions of active sites of enzymes. A detailed analysis of modern computer databases of protein structures is given. Methods for identification of active sites of enzymes based on the analysis of computer databases are considered. The structural paradox of enzymatic catalysis, which suggests that the practically infinite variability of protein structures within the framework of a concrete catalytic task is confined to a limited number of catalytic site structures responsible for the catalytic act, is discussed for the example of a special class of enzymes, *viz.*, hydrolases.

The review by Prof. T S Oretskaya *et al.* 'Covalent binding of modified nucleic acids to proteins as a method for investigation of specific protein–nucleic acid interactions' is devoted to the study of specific interactions between proteins and nucleic acids. Covalent binding of modified nucleic acids to proteins is considered as a method of investigation. Methods for the introduction of modifications in the structures of nucleic acids, synthesis of photoactive derivatives and structures of 'nucleic acid–protein' conjugates formed upon enzymatic reactions are discussed. The development of these methods allows identification of a specific site in a protein bound to a nucleic acid.

The main emphasis in the review by Prof. E A Karakhanov *et al.* 'Design of supramolecular metal complex catalytic systems for organic and petrochemical synthesis' is laid on supramolecular metal-complex systems. The formation of active sites, which involves macrocyclic receptor molecules, opens up prospects, new in principle, for the design of catalysts for hydrogenation, hydroformylation, carbonylation, hydroxylation, *etc.*

The issue includes only some of the reviews prepared by researchers of the Department of Chemistry and dedicated to the 250th anniversary of the Moscow State University. One of the next issues of the Journal will also be devoted to this jubilee event. We are sure that the reviews presented herein as well as those designed for publication in the subsequent issues of the Journal will be interesting for a broad circle of readers and will shed additional light on the main trends and level of research carried out by the Department.

Academician V V Lunin  
Professor S D Varfolomeev

# Polyelectrolyte complexes in solution and in bulk

V A Kabanov

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**Abstract.** The review surveys the thermodynamics, kinetics and reaction mechanisms of oppositely charged polyelectrolytes in aqueous solutions giving rise to insoluble stoichiometric or soluble non-stoichiometric interpolyelectrolyte complexes. The mechanisms of polyelectrolyte exchange reactions are discussed. Equilibrated non-stoichiometric interpolyelectrolyte complexes show a dual behaviour in aqueous solutions. On the one hand, they behave as usual linear polyelectrolytes and, on the other hand, they exhibit properties of amphiphilic block copolymers. The addition of low-molecular-weight salts to solutions of interpolyelectrolyte complexes usually leads to redistribution of electrostatically bound chains and phase separation. Analysis of these processes is of key importance in assigning these complexes to a special family of polymeric materials. Selected data on the conformations of polyions in solid interpolyelectrolyte complexes are given and their thermomechanical properties in the swollen state are considered. The bibliography includes 117 references.

## I. Introduction

Interpolyelectrolyte complexes (IPECs) belong to a special family of polymeric compounds<sup>1–6</sup> formed through cooperative electrostatic interactions between polycations with polyanions upon mixing of aqueous solutions of oppositely charged polyelectrolytes. Depending on the charge ratio and the degree of polymerisation of the starting polyelectrolytes, either non-stoichiometric water-soluble or stoichiometric insoluble IPECs exhibiting low swelling in water can be prepared.

An analysis of the state of the art in research on IPECs, which was based essentially on the results of investigations performed over many years at the Chair of High-Molecular-Weight Compounds of the Department of Chemistry of the Moscow State University, has been presented recently in the introductory chapter of Ref. 7. This chapter was used as the basis for the present review.

In the 1930s, researchers working in the field of colloidal chemistry found that, under particular conditions, mixing of aqueous solutions of oppositely charged natural polyelectrolytes

characterised by a relatively low charge density on the macromolecules (for example, gelatins and gum arabic) leads to phase separation and formation of liquid coacervates.<sup>8–10</sup> Further studies of such systems have been aimed primarily at characterising the conditions of phase separation by experimental and theoretical methods.<sup>11,12</sup>

Solid IPECs exhibiting low swelling in water have also been known for many years. Synthetic polyelectrolytes with a high linear charge density have become available at least from the early 1960s.<sup>1,13–15</sup> Later, the practical use of these compounds has attracted attention. For example, insoluble IPECs proved to be highly efficient as ecologically safe hydrophilic binders, which prevent soil erosion by wind and water. Composites based on such IPECs were used, for instance, for suppressing the formation of radioactive aerosols in the contaminated dusting areas of the Chernobyl disaster. Industrial tests showed that insoluble IPECs are much more efficient than individual polyelectrolytes, which are generally used for coagulation of colloidal dispersions, in particular, of metallurgical slags (see, for example, Ref. 16). Insoluble IPECs were also successfully tested as biocompatible coatings for blood-contacting medical materials (including chemisorbents) and other biological liquids (see, for example, Ref. 17).

There also some other promising fields of application of IPECs. One of them is being extensively developed and deals with the preparation of thin films consisting of alternating nano-size polycation and polyanion layers. These films are prepared by successive deposition of oppositely charged polyelectrolytes from aqueous solutions on various surfaces.<sup>7</sup>

The existence of water-soluble interpolyelectrolyte duplexes was supported by several examples<sup>18,19</sup> and the general conditions and criteria for their formation were revealed, which proved to be valid for most pairs of oppositely charged polyions.<sup>3,5,20,21</sup> These are considerable achievements, which marked the onset of a new stage of investigation of IPECs associated with the possibility of employing all modern physical and physicochemical methods generally used in studies of macromolecules in solution (light scattering, analytical ultracentrifugation, viscosimetry, gel-permeation chromatography, *etc.*). Fundamental data obtained by these methods gave a deeper insight into the structural organisation and behaviour of IPECs not only in solutions but also in the bulk. These investigations also opened new fields of application of IPECs, in particular, in biotechnology, medicine, and modelling of biological systems.<sup>22–26</sup> For example, it appeared that interpolyelectrolyte duplexes involving DNA plasmids or single-stranded antisense oligonucleotides as polyanions can penetrate rather easily through biological membranes analogously to viri-

V A Kabanov Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation.  
Fax (7-095) 939 01 74, tel. (7-095) 939 55 83,  
e-mail: Kabanov@genebee.msu.su

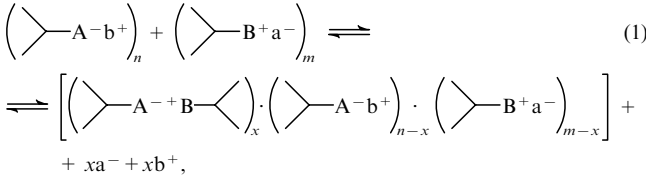
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ons. Nowadays, this phenomenon is used for delivering genetic material to cells to transfect or block specified genome regions.<sup>25</sup>

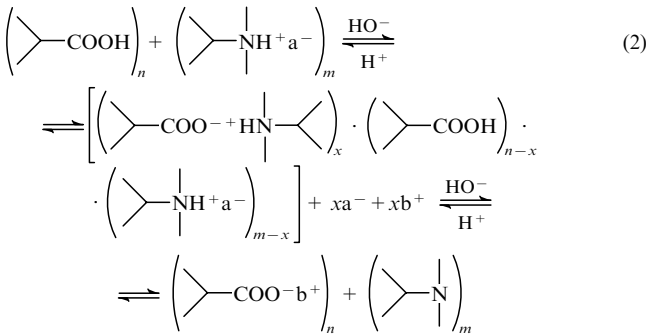
## II. Interpolyelectrolyte reactions and solution behaviour of interpolyelectrolyte complexes

The simplest procedure for the preparation of IPECs involves mixing of two aqueous solutions containing polyanions and polycations, respectively. The reaction of two strong polyelectrolytes can be represented as follows:



where  $\text{A}^-$  and  $\text{B}^+$  are acidic and basic side groups, respectively, and  $\text{a}^-$  and  $\text{b}^+$  are counterions.

An interaction between two weak polyelectrolytes can be described by the following scheme:



The degree of conversion  $\Theta$  in these reactions is determined as the ratio of the number of salt bonds (ion pairs) formed between polyions under particular conditions to their maximum possible number

$$\Theta = \frac{x}{m}, \text{ if } n \geq m,$$

and

$$\Theta = \frac{x}{n}, \text{ if } n < m.$$

The formation of duplexes from weak polyelectrolytes can be controlled by varying pH of the medium.<sup>3,6</sup> In these cases, IPECs can be prepared in equilibrium conditions by gradual acidification or alkalisation of the reaction mixture.

The degree of conversion  $\Theta$  can be calculated from the results of potentiometric titration.<sup>3,6</sup>

For a weak polyacid,

$$\Theta = \frac{m_b/V + [\text{H}^+] - \sqrt{K_a c_0}}{c_0}, \quad (3)$$

for a weak polybase,

$$\Theta = \frac{m_a/V + [\text{OH}^-] - \sqrt{K_b c_0}}{c_0}. \quad (4)$$

In these equations,  $m_a$  or  $m_b$  are the numbers of moles of the acid or base, respectively, added to the mixture,  $V$  is the volume of the reaction mixture,  $K_a$  and  $K_b$  are the characteristic ionisation constants of the polyacid and the polybase, respectively, and  $c_0$  is the concentration of one of the polyelectrolytes.

Typical plots of  $\Theta$  vs. pH, which were calculated from experimental titration curves of weak polyelectrolytes in the presence of oppositely charged polyions, are shown in Fig. 1. Solid lines enclose the pH region where IPECs are formed and

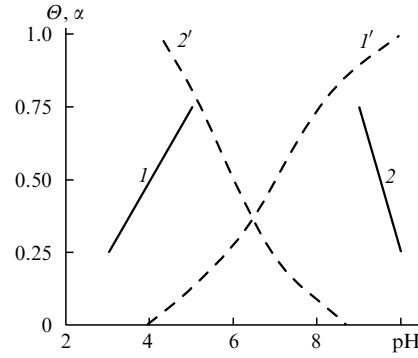


**Figure 1.** Typical plots of the degrees of conversion ( $\Theta$ ) in reactions of weak polyelectrolytes (1, 2) and their starting degrees of ionisation ( $\alpha$ ) (1', 2') vs. pH in aqueous solutions.

exist in the reaction system in the absence of low-molecular-weight salts. If one polyelectrolyte is weak, whereas another polyelectrolyte is strong, the range of existence is limited only by one curve either on the left or on the right, respectively. Figure 1 shows also the plots of the degree of ionisation  $\alpha$  of individual polyelectrolytes vs. pH. It can be seen that polyacids and polybases whose degree of ionisation depends on pH become much stronger in the presence of oppositely charged polyions.

The value of  $\Delta\text{pH}(\Theta, \alpha)$  is a measure of the free energy ( $\Delta G_{cs}$ ), which is a driving force for the complexation process. This parameter characterises a cooperative multicentre interaction between the oppositely charged units of polyion chains at  $\Theta = \alpha$

$$\Delta\text{pH}(\Theta, \alpha) = \frac{\Delta G(\alpha) - \Delta G(\Theta)}{2.3 RT} = \frac{\Delta G_{cs}(\Theta, \alpha)}{2.3 RT}. \quad (5)$$

Here  $\Delta G(\alpha)$  and  $\Delta G(\Theta)$  are the free energies of ionisation of a weak polyelectrolyte in the absence and in the presence of an oppositely charged polyion, respectively.

Equation (3) is written on the assumption that each ionised group of the polyelectrolyte that is titrated forms a salt bond (ion pair) with an oppositely charged polyion. This situation is close to reality if the ratio of the numbers of ionising groups of the components ( $Z = m/n$ ) is equal to unity. For  $Z \neq 1$ , Eqn (3) is valid if the total number of ionising groups in a weak polyelectrolyte is smaller than that in the fully ionised strong polyelectrolyte.

A decrease in the free energy corresponding to the shift of the equilibria (1) and (2) toward IPECs takes place primarily due to an increase in the entropy caused by release of low-molecular-weight counterions, which are initially localised in the vicinity of polyelectrolyte coils. However, depending on the composition and structure of the oppositely charged polyions, other factors, for example, hydrophobic interactions, hydrogen bonds, charge transfer, etc., can contribute substantially to their coupling.

In terms of the commonly accepted classification, the processes (1) and (2) correspond to the ion exchange and neutralisation reactions, respectively. However, in relation to interacting polyelectrolytes, these processes can be considered as coupling reactions of oppositely charged polyions.

Interpolyelectrolyte complexes can also be prepared by polymerisation of ionic monomers on oppositely charged polyions serving as matrices.<sup>27</sup> In this case, the total change in the free energy includes two terms

$$\Delta G_{tp} = \Delta G_p + \Delta G_{cs}, \quad (6)$$

where  $\Delta G_p$  is the free energy of polymerisation in the absence of a matrix. The negative value of  $\Delta G_{cs}$  is thermodynamically favourable for the formation of a polymer. This factor may be of decisive importance if polymerisation of a free monomer is thermodynamically impossible ( $\Delta G_p > 0$ ):  $\Delta G_{tp}$  remains negative if

$|\Delta G_{cs}| > |\Delta G_p|$ . In other words, a polyion matrix, being a potential component of IPEC, shifts the polymerisation–depolymerisation equilibrium toward the oppositely charged polyion.

A factor analogous to  $\Delta G_{cs}$  is responsible for clustering of protein globules with oppositely charged linear polyions upon complexation of polyelectrolytes with proteins<sup>28–30</sup> and for aggregation of ionic surfactants in solutions and hydrogels of oppositely charged polyelectrolytes at surfactant concentrations substantially lower than the critical micelle concentration (CMC).<sup>31–37</sup> In reality, both these processes consist in ‘polymerisation’ of protein globules or surfactant ions on the oppositely charged polymer matrices.

For a particular structure of polyelectrolytes, the ability of IPEC to dissolve or swell in water depends on  $Z$ ,  $\Theta$ , the ratio of the degrees of polymerisation of the oppositely charged polyions and the composition of an aqueous phase (the nature and concentration of low-molecular-weight salts, pH, the presence of organic additives, *etc.*). If  $Z = 1$  and  $\Theta$  is close to unity, the interpolyelectrolyte reaction affords stoichiometric IPECs, which are always insoluble but swell in water to some degree.

Under particular conditions, most pairs of oppositely charged polyelectrolytes give water-soluble IPECs.<sup>3, 5, 20, 21</sup> At  $Z = 1$ , the solubility of duplexes can be achieved only at  $\Theta < 1$ , *i.e.*, for products of the incomplete reaction (2).<sup>20</sup> In this case, free units of polyions (which are not involved in interchain salt bonds) act as hydrophilic fragments, which retain IPEC particles in solution.

Water-soluble duplexes can be prepared also at  $\Theta$  equal or close to unity, provided that  $Z \neq 1$  or that the degree of polymerisation of an excess polyion, *viz.*, a host polyelectrolyte (HPE), is higher than the degree of polymerisation of another polyion present in a deficient amount, *viz.*, a guest polyelectrolyte (GPE). Then the solubility condition can be written as follows:

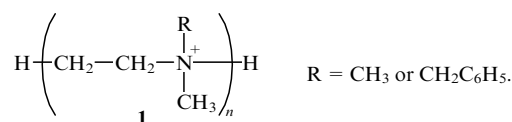
$$\varphi = \frac{[\text{GPE}]}{[\text{HPE}]} < \varphi_c < 1,$$

where  $\varphi$  is the ratio of the numbers of the charged GPE and HPE units in IPEC particles. In the case of a uniform distribution of GPE over HPE,

$$\varphi = Z.$$

The critical value  $\varphi_c$  is determined by the maximum population of HPE by GPE chains. At  $\varphi$  higher than  $\varphi_c$ , hydrophilicity of excess single-stranded regions of the chains is insufficient to retain all IPEC particles in solution. For most known systems,  $\varphi_c$ , which is determined primarily by the chemical structures of interacting polyelectrolytes, varies from 0.2 to 0.6.

In the pH region, enclosed by the potentiometric titration curves 1 and 2 (see Fig. 1), the cooperative character of multi-centre electrostatic coupling provides high resistance of IPECs to dissociation into the individual starting components. The effective dissociation constant at  $\Theta$  close to unity sharply decreases with increasing degree of polymerisation of GPE and approaches zero even for rather short oligomers. For example, in the case of polymer homologues of quaternised linear ethyleneimine (**1**) interacting with poly(methacrylate) (PMA) polyanions, the degree of dissociation of IPEC has become negligibly small already for octamers.<sup>4, 38</sup> Analogous results were obtained in studies of the reactions of oligophosphates with poly(*N*-dimethylaminoethyl methacrylate) (PDMAEMA)<sup>39</sup> and the reactions of oligo-2,5-ionenes with polyacrylate (PA) polyanions.<sup>40</sup>



Consequently, IPECs produced in the absence of low-molecular-weight salts do not virtually dissociate into individual components once a particular critical length of polyions is achieved.

If one of the polyions can exist in solution in a specific ordered conformation (for example, like ionic polypeptides or DNA), an oppositely charged polyelectrolyte can either stabilise or destabilise this conformation upon complexation.<sup>6, 24</sup> For example, the  $\alpha$ -helical conformation of free poly-L-lysine (PL) is stable only in strongly alkaline media where this compound is uncharged. Upon protonation of amino groups in a mixed aqueous–ethanolic solution, this conformation of PL is transformed into an uncoiled conformation already at pH 9–8.5. It should be noted that even completely protonated PL in the PL–PMA duplex retains the  $\alpha$ -helical conformation in a much broader pH range. The helix–coil transformation occurs only at pH 3.5–4.0, at which IPEC decomposes due to protonation of the  $\text{COO}^-$  groups of PMA.<sup>6</sup> In other words, complexation stabilises the  $\alpha$ -helix of PL. The opposite situation is observed for poly-L-glutamic acid (PGA). The  $\alpha$ -helical conformation of PGA is stable in acidic aqueous solutions and is transformed into a random-coil conformation as pH increases to 6.0–6.5. By contrast, the helix–coil transformation in the PGA–linear polyethyleneimine (PEI) system occurs already at pH 3.0–4.0, *i.e.*, in the pH region where the PGA–PEI polyelectrolyte complex is formed. Consequently, binding of the PEI polycation to the negatively charged  $\alpha$ -helix is thermodynamically less favourable compared to binding to the negatively charged PGA random coil.<sup>6</sup> Another example refers to DNA. It is known that, in an aqueous solution, the double helix of native DNA exists in the B form. Upon the formation of native DNA duplexes with polycations, the B form is transformed into the more compact C or A form.<sup>24</sup>

## 1. Kinetics and mechanisms of polyelectrolyte coupling, exchange and substitution reactions

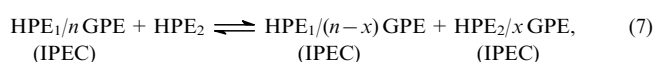
The course of a coupling reaction of two strong polyelectrolytes in salt-free media can be monitored by any method that allows one to measure the amounts of low-molecular-weight counterions released (elemental analysis, conductometry, ion-specific potentiometry, *etc.*). The limitations of the sensitivity of these methods arise when the interpolyelectrolyte reactions are performed in the presence of low-molecular-weight salts at concentrations substantially higher than the base-mole concentration of interacting polyelectrolytes.

If one polyelectrolyte is a weak polyacid or a weak polybase, the degree of conversion  $\Theta$  can be determined by measuring pH.<sup>6</sup> However, this method is applicable only in a pH range where  $\Theta$  is no higher than 0.4–0.5 (40%–50%).<sup>24</sup>

It is convenient to perform quantitative investigations of the formation and transformations of soluble IPECs by luminescence quenching. For this purpose, it is necessary to label one of the oppositely charged polyions with a chemically bonded luminescence group and to choose the second polyion such that it can interact with the former group and quench luminescence. The portion of labelled polyions interacting with quencher polyions can be calculated at any pH both in the presence and absence of low-molecular-weight salts by measuring the luminescence intensity and using the corresponding calibrations.

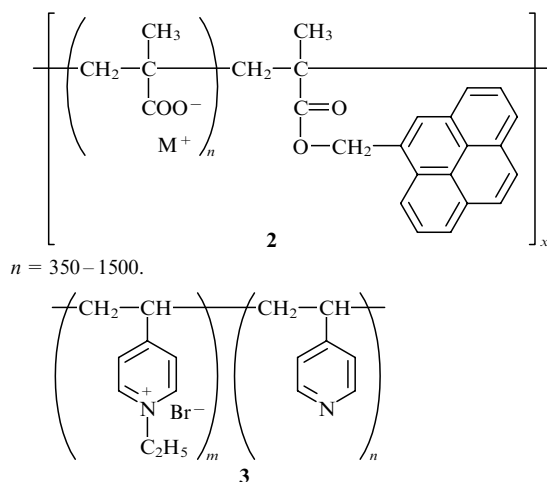
Luminescence quenching was used to study the kinetics of the coupling reactions of typical polyelectrolyte pairs. The conditions under which soluble IPECs dissociate into the starting components were determined. Direct experimental evidence for the ability of various soluble IPECs to be involved in competitive exchange and substitution reactions with other polyions was documented and the kinetics of these reactions was quantitatively studied.<sup>41–44</sup> It should be noted that the earlier study of the behaviour of DNA duplexes with poly(*N*-ethyl-4-vinylpyridinium) bromide in aqueous solutions<sup>18</sup> also provided indirect evidence for the possible polyion exchange.

Polyion exchange and substitution reactions can be represented in the general form as follows:



where  $n$  or  $x$  is the number of the GPE chains in IPEC particles. In terms of the above-mentioned approach, this process is a polyion exchange reaction if HPE<sub>1</sub> and HPE<sub>2</sub> are identical and a polyion substitution reaction if HPE<sub>1</sub> and HPE<sub>2</sub> differ in chemical structure. Different HPE segments can also exchange GPE polyions within one IPEC particle. This exchange is, in essence, equivalent to migration of GPE inside the HPE coil and serves as the mechanism of rearrangements within the complex giving rise to an equilibrium inner structure of IPEC particles and resulting in optimisation of their interactions with the environment.

In most kinetic studies,<sup>41–48</sup> fractions of polymethacrylic acid labelled with fluorescent anthryl or pyrenyl groups (PMA\*)<sup>49</sup> (one label per 350–1500 repeated units) (2) served as a polyanionic component. The (*N*-ethyl-4-vinylpyridinium)–vinylpyridine copolymer (PVP) (3) was used as the polycationic component.



This copolymer was prepared by quaternisation of poly-4-vinylpyridine fractions with bromoethane.<sup>50</sup> The number of quaternised units (*i.e.*, the linear positive-charge density) was specified by varying the degree of quaternisation (in %)

$$\beta = \frac{m}{m+n} 100.$$

Most experiments described below (unless otherwise indicated) were carried out with the use of PVP whose degree of quaternisation was close to 100%. Quaternary vinylpyridinium units located in proximity to the anthryl and pyrenyl groups can quench fluorescence.

The kinetics of a typical coupling reaction of polyions was studied using the reaction of NaPMA\* with PVP as an example.<sup>45,47</sup> The formation of the PMA\*–PVP complex leads to a decrease in the fluorescence intensity of PMA\* due to quenching of the pyrenyl labels with the quaternary vinylpyridinium units of PVP. The reaction mixture was prepared by the rapid addition of a calibrated aqueous PVP solution (0.02 ml) into a cell containing a calibrated aqueous NaPMA\* solution (1.5 ml) with continuous stirring in such a way that the reagents were mixed for no longer than 2–4 s. The concentrations of the starting solutions were chosen so as to prepare a complex of the desired final composition. As can be seen from Fig. 2, mixing of the reagents in the absence of a salt is accompanied by a sharp decrease in the fluorescence intensity to a particular constant value. This corresponds to the rapid formation of contacts between PMA\* and PVP (curve 1). However, the decrease in the fluorescence intensity is smaller than that expected in the case of formation of the equilibrated PMA\*–PVP interpolyelectrolyte complex of the desired composition (*cf.* curves 1 and 1'). Moreover, mixing of the same reagents in the presence of NaCl (0.03 mol litre<sup>−1</sup>) leads to a substantially larger initial decrease in the fluorescence intensity (*cf.* curves 2 and 2' in Fig. 2).

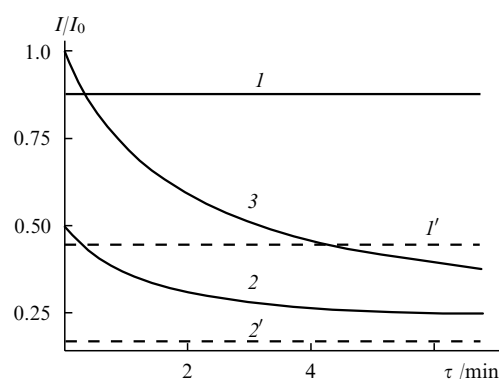
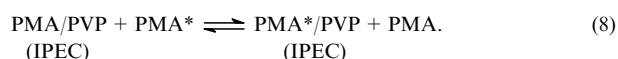


**Figure 2.** Typical kinetic curves of interpolyelectrolyte coupling and exchange reactions.<sup>47</sup>

$I$  and  $I_0$  are the current and starting fluorescence intensities, respectively, of PMA\*; (1) NaPMA\* ( $P_w = 4.4 \times 10^3$ , one label per 600 monomer units) + PVP ( $P_w = 2.0 \times 10^2$ ,  $\beta = 95\%$ ) in the absence of a salt,  $[NaPMA^*] = 8.6 \times 10^{-8}$  mol litre<sup>−1</sup> (with respect to the polyion),  $Z = [PVP]/[NaPMA^*] = 0.2$ ; (2) the same reaction in the presence of sodium chloride (0.03 mol litre<sup>−1</sup>); (3) IPEC (PMA–PVP) + NaPMA\*,  $[NaPMA^*] = [IPEC] = 8.6 \times 10^{-8}$  mol litre<sup>−1</sup>,  $P_w = 4.4 \times 10^3$ ,  $\varphi = 0.2$ ,  $T = 20^\circ\text{C}$ , pH 10,  $\Theta \rightarrow 1$ ; (1') the equilibrium limit for the curve 1; (2') the equilibrium limit for the curves 2 and 3; (3) the curve for pure polyion exchange.

Stop-flow measurements demonstrated that the fast step of polyion coupling reactions corresponding to an instantaneous drop observed in the kinetic curves is characterised by the rate constant of  $\sim 10^9$  litre mol<sup>−1</sup> s<sup>−1</sup>. This value is close to the expected bimolecular rate constant of diffusion collisions of polyelectrolyte coils in a dilute solution.<sup>45,47</sup> Diffusion collisions of oppositely charged polyions lead to their association due to formation of random interchain salt bonds, *i.e.*, the formation of IPEC. However, at very low concentrations of simple salts or in their absence, rearrangements of randomly coupled polyions in exchange reactions are hindered. Hence, the resulting IPEC associates are 'frozen' in a non-equilibrium state (see curve 1 in Fig. 2). In the presence of a sufficiently large amount of a salt, the rate of polyion exchange, on the contrary, sharply increases. As a result, the initially non-equilibrated IPEC associates are rearranged with time and reach an equilibrium state, which is characterised by the maximum possible number of salt bonds between the interacting polyions. In other words, primary associates are transformed into equilibrated particles of the PMA\*–PVP interpolyelectrolyte complexes (see curve 2 in Fig. 2). The pyrenyl labels attached to the PMA\* chains give rise to additional hydrophobic interactions, due to which PMA\*–PVP particles become more stabilised than PMA–PVP particles. As a consequence, the PMA\* polyanions replace the PMA polyanions in the complex particles. Therefore, the kinetic curve 2 in Fig. 2 can be qualitatively considered as a superposition of the curves 1 and 3. In other words, the presence of one pyrenyl group per several hundreds of monomer units in the PMA\* chain appears to be sufficiently large for this chain to replace the chain of usual unmodified PMA initially bound to the PVP polycation.

For soluble IPECs, the polyion exchange reaction involving the transfer of one GPE (PVP) chain from HPE<sub>1</sub> (PMA) to HPE<sub>2</sub> (PMA\*) in a dilute solution was demonstrated<sup>46,47</sup> to be characterised by second-order kinetics with respect to the concentrations of the polymers involved in the reaction (IPEC and PMA\*).



The experimental kinetic curves fit well to straight lines in the coordinates of the equation

$$\frac{q}{1-q} = k_2[PMA^*]_0 t, \quad (9)$$

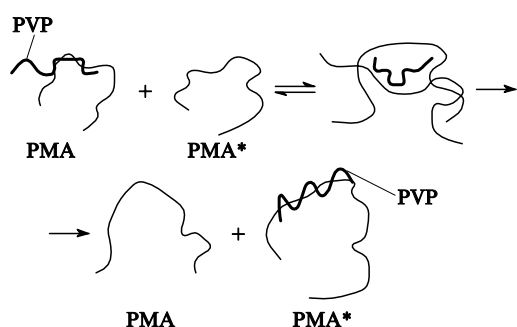
**Table 1.** Rate constants of the exchange reactions between the PMA–PVP interpolyelectrolyte complexes and NaPMA\* at pH 10,  $\theta \rightarrow 1$ ,  $T = 20^\circ\text{C}$ .

| No | [NaPMA*] $\times 10^9$<br>/mol litre $^{-1}$ | $P_w \times 10^3$ |     | $\beta$ (%) | [NaCl]<br>/mol litre $^{-1}$ (see <sup>a</sup> ) | $k_2 \times 10^5$<br>(see <sup>a</sup> ) |
|----|----------------------------------------------|-------------------|-----|-------------|--------------------------------------------------|------------------------------------------|
|    |                                              | PVP               | PMA |             |                                                  |                                          |
| 1  | 3                                            | 0.6               | 3.9 | 95          | 0.08                                             | 5.1                                      |
| 2  | 7                                            | 0.6               | 3.9 | 95          | 0.08                                             | 5.0                                      |
| 3  | 15                                           | 0.6               | 3.9 | 95          | 0.08                                             | 4.7                                      |
| 4  | 40                                           | 0.6               | 3.9 | 95          | 0.06                                             | 1.2                                      |
| 5  | 40                                           | 0.6               | 3.9 | 95          | 0.07                                             | 2.6                                      |
| 6  | 40                                           | 0.6               | 3.9 | 95          | 0.08                                             | 5.1                                      |
| 7  | 40                                           | 0.6               | 3.9 | 95          | 0.09                                             | 8.7                                      |
| 8  | 33                                           | 0.1               | 4.4 | 95          | 0.04                                             | 2.0                                      |
| 9  | 33                                           | 0.1               | 1.0 | 95          | 0.04                                             | 2.0                                      |
| 10 | 28                                           | 0.6               | 4.4 | 95          | 0.07                                             | 1.5                                      |
| 11 | 28                                           | 0.32              | 4.4 | 95          | 0.07                                             | 6.0                                      |
| 12 | 28                                           | 0.2               | 4.4 | 95          | 0.07                                             | 11.0                                     |
| 13 | 28                                           | 0.1               | 4.4 | 95          | 0.07                                             | 23.0                                     |
| 14 | 23                                           | 0.2               | 2.8 | 89          | 0.035                                            | 0.2                                      |
| 15 | 23                                           | 0.2               | 2.8 | 80          | 0.035                                            | 0.7                                      |
| 16 | 23                                           | 0.2               | 2.8 | 69          | 0.035                                            | 2.6                                      |
| 17 | 23                                           | 0.2               | 2.8 | 62          | 0.035                                            | 16.2                                     |
| 18 | 23                                           | 0.2               | 2.8 | 55          | 0.035                                            | 36.1                                     |

**Note.**  $P_w(\text{PMA}) = P_w(\text{PMA}^*)$ , PMA\* contains one pyrenyl label per 350 units.

<sup>a</sup> In litre mol $^{-1}$  s $^{-1}$ .

where  $q$  is the degree of conversion in the reaction (8), and  $[\text{PMA}^*]_0 = [\text{PMA}]_0 = [\text{IPEC}]_0$  are the starting molar concentrations of the reagents. The absolute rate constant ( $k_2$ ) of the transfer of the GPE chain from one HPE chain to another under various conditions can be determined according to Eqn (9). As can be seen from Table 1, the constant  $k_2$  is independent of the concentrations of the compounds involved in the reaction (runs 1–3 and 6), which is consistent with Eqn (9). It should be emphasised that the constant  $k_2$  is also independent of the degree of polymerisation of HPE (PMA) (runs 8 and 9), but this constant decreases substantially with increasing degree of polymerisation of GPE (PVP) (runs 10–13). Under the experimental conditions,  $k_2$  varied in a range of  $10^4$ – $10^6$  litre mol $^{-1}$  s $^{-1}$ , *i.e.*, it is 3–5 orders of magnitude smaller than the estimated rate constant of diffusion collisions between the interacting particles. The results of investigations suggest that the transfer occurs in the intermediate ternary complex (PMA...PVP–PMA\*) generated as a result of the mutual penetration of the chains of the starting IPEC and NaPMA\* upon their random collisions in solution. This complex presented in Scheme 1 serves as a ‘transition state’ in the bi-macromolecular polyion exchange reaction. Under the above-mentioned experimental conditions, only some collisions are productive. There are, on the average,  $10^3$ – $10^5$  ineffective collisions per event of transfer of PVP from PMA to PMA\*. The strong dependence of  $k_2$  on both the salt concentration (runs 4–7)



Scheme 1

and the linear charge density of the PVP chains (runs 14–18) is in complete agreement with the proposed reaction mechanism.

The polyion exchange processes with the involvement of IPEC particles containing more than one GPE chain are described by polychronic kinetics. However, factors governing these more complex reactions are qualitatively similar to the considered above simplest second-order reaction.<sup>43</sup> In particular, their rates also depend substantially on the concentrations of the additives of simple salts. This is confirmed by the following data:

| [NaCl] $\times 10^3$ /mol litre $^{-1}$ | 0                       | 35  | 70 | 100   |
|-----------------------------------------|-------------------------|-----|----|-------|
| Half-life /s                            | reaction does not occur | 240 | 6  | < 1.5 |

$\{P_w(\text{NaPMA}^*) = P_w(\text{NaPMA}) = 3 \times 10^3, P_w(\text{PVP}) = 2 \times 10^2; [\text{NaPMA}^*] = [\text{NaPMA}] = [\text{IPEC}] = 4 \times 10^{-3}$  base-mol litre $^{-1}$ ,  $\varphi = 0.33$ ; pH 10,  $T = 20^\circ\text{C}$ ).

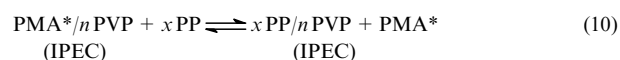
The presence of salts substantially affects the polyion substitution reactions as well.<sup>39, 40, 44, 48, 51–53</sup> The replacement of the PMA\* polyanions in the PMA\*–PVP polyelectrolyte complex with the polyvinyl sulfate (PVS) polyanions is completely hindered in a salt-free solution but it is strongly accelerated in the presence of NaCl, as evidenced by the following results:

| [NaCl] $\times 10^3$ /mol litre $^{-1}$ | 0                       | 2   | 4  | 6  | 8 | 10    |
|-----------------------------------------|-------------------------|-----|----|----|---|-------|
| Half-life /s                            | reaction does not occur | 600 | 60 | 13 | 5 | < 1.5 |

$\{P_w(\text{NaPMA}^*) = 3 \times 10^3, P_w(\text{PVS}) = 1.3 \times 10^3, P_w(\text{PVP}) = 2 \times 10^2; [\text{IPEC}(\text{PMA}^* - \text{PVP})] = 4 \times 10^{-3}$  base-mol litre $^{-1}$ ,  $\varphi = 0.2$ ; [PVS] = [PVP]; pH 10,  $T = 20^\circ\text{C}$ ).

In substitution reactions, not only the kinetics but also the position of equilibrium depend substantially on the chemical nature of polyions. In particular, polyanions containing the sulfonate or sulfate group in the repeated monomer unit (PVS, polyethylene sulfonate, heparin, *etc.*) generally replace polycarboxylates (for example, PA or PMA) in polyelectrolyte complexes containing ammonium as the polycation.<sup>40</sup> The driving force for the substitution is a specific (in addition to Coulombic) affinity of the sulfonate or sulfate group for protonated or quaternary amino groups.

The dramatic influence of the degree of polymerisation of competitive polyelectrolytes and the chemical nature of a low-molecular-weight salt on the equilibrium degree of conversion was observed in the polyion substitution reaction of the PMA\* (HPE)–PVP (GPE) interpolyelectrolyte complexes with polyphosphates (PP) with different degrees of polymerisation<sup>48</sup>



A change in the equilibrium degree of conversion  $q_e$  in the forward reaction (10) with increasing concentration of the additives of simple salts is illustrated by Fig. 3. It can be seen that, all other factors being the same, the curve shape depends substantially on the degree of polymerisation of PP (Fig. 3a) and the nature of the cation of the salt present as an additive (Fig. 3b). At high salt concentrations, these differences are associated with the sign change. For PPs possessing the longest chain (230 monomer units), the equilibrium (10) in a 0.3 M aqueous NaCl solution at fixed base-mole concentrations of all polymers completely shifts to the right, whereas this equilibrium for short-chain PPs (20 monomer units) completely shifts to the left. For PPs with intermediate degrees of polymerisation,  $q_e$  has intermediate values. For PPs with a fixed chain length (70 monomer units), the equilibrium (10) in a 0.3 M LiCl solution completely shifts to the right, whereas this equilibrium in a 0.3 M KCl solution completely shifts to the left. Analogous phenomena were not observed in non-polymer systems. Moreover, this phenomenon can, apparently, be considered as a model of biologically important rearrangements, which occur in cells with the involvement of oppositely charged natural polyelectrolytes. Under the reaction conditions, inter-





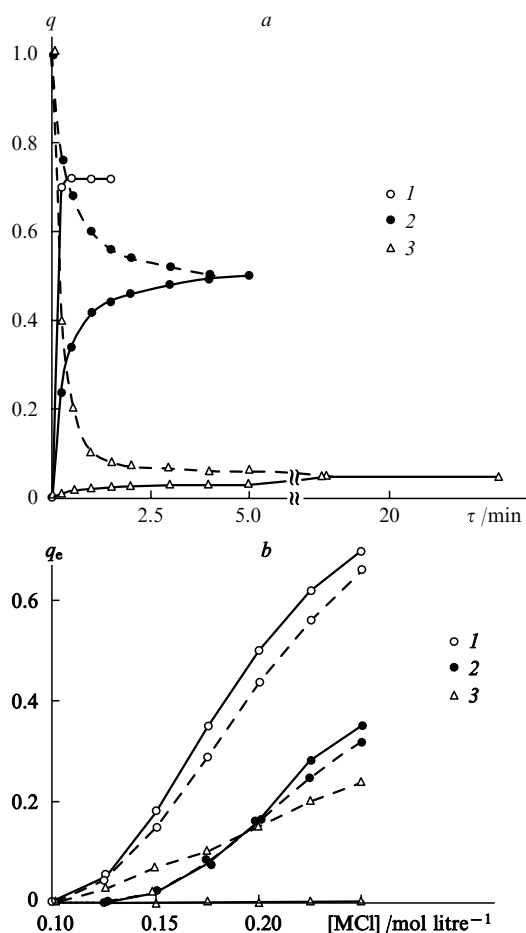


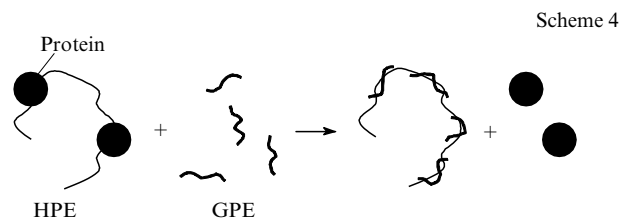
**Figure 4.** Kinetics of the interpolyelectrolyte substitution reaction (12) at different concentrations of NaCl (a) and the influence of the salt on the position of equilibrium of this reaction with native and denaturated DNA (b);<sup>31</sup>

(a)  $[NaCl] = 0.25$  (1),  $0.20$  (2) and  $0.125$  mol litre<sup>-1</sup> (3); (b) sodium salt (1), potassium salt (2), lithium salt (3); solid lines refer to native DNA and dashed lines correspond to denaturated DNA.

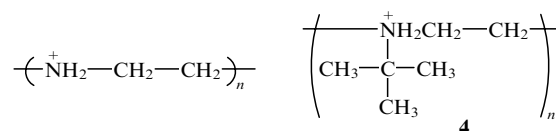
DNA is involved in the reaction (12). Actually, in the case of native DNA, unlike denaturated DNA, the equilibrium completely shifts to the PVP–PMA\* interpolyelectrolyte complex throughout the LiCl concentration range under study. Apparently, this difference is attributable to the fact that  $Li^+$  cations have a higher affinity for native DNA than for denaturated DNA. This fact is yet another example of the influence of specific interactions superimposed on usual Coulombic attractions.

Not only linear but also dendritic polyelectrolytes (dendrimers),<sup>22–24</sup> globular proteins<sup>28,29</sup> and other charged compact particles, for example, sols of polysilicic acid,<sup>54–60</sup> can serve as GPEs in the formation of IPECs. These IPECs remain in solution provided that the diameter of globules is much smaller than the contour length of linear HPE, and the population of HPE (the charge ratio) is no higher than a particular critical value. The mechanism of their formation is analogous to the above-considered mechanism of linear polyion coupling, and the equilibrium can be reached through rearrangements analogous to the above-described polyion exchange reactions. It should be noted that linear polyions with a rather high charge density on the chain generally replace globular particles, for example, proteins, in the starting IPEC (Scheme 4).<sup>29</sup>

Polyion exchange reactions, which play a decisive role in the establishment of equilibrium in IPEC-containing systems, can be hindered or completely frozen even in the presence of low-molecular-weight salts, if Coulombic interactions between poly-



ions are enhanced due to other types of interactions, such as hydrophobic interactions, donor–acceptor bonds, *etc.* A typical example is the different solution behaviour of two similar non-stoichiometric IPECs containing identical polyanionic components, *viz.*, NaPA or NaPMA, as HPE but different GPEs, *viz.*, either linear PEI polycations or poly(*tert*-butyl aziridine) (PTBA) polycations. The latter has a linear charge density identical to that of protonated PEI (see structure 4). Both interpolyelectrolyte complexes can exchange GPE at room temperature. However, at high temperatures ( $40–60$  °C), at which hydrophobic interactions play a larger role, the PTBA chains, unlike the PEI chains, are fixed within the complex and do not migrate from one particle to another.<sup>61</sup>



Other examples of the critical phenomena typical of polyion exchange reactions are considered below.

## 2. Properties of equilibrated non-stoichiometric interpolyelectrolyte complexes in solution

Nonstoichiometric IPECs can be considered as block copolymers containing free hydrophilic segments of HPE chains and relatively hydrophobic GPE–HPE domains.<sup>3,5</sup> In dilute solution, the behaviour of such equilibrated water-soluble IPECs (see above) is to some extent similar to the behaviour of usual polyelectrolytes. Methods for the preparation of soluble equilibrated non-stoichiometric IPECs composed of various GPE–HPE pairs were documented.<sup>62–64</sup> These methods have been also reviewed in detail in the publication.<sup>3</sup>

Studies by analytical ultracentrifugation,<sup>54,62,63</sup> gel-permeation chromatography<sup>65</sup> and light scattering<sup>3,5,29,64,66</sup> demonstrated that equilibrated water-soluble non-stoichiometric IPECs, which were prepared in dilute solutions from rather narrow molecular-weight fractions of HPEs and GPEs, occur as individual polymer particles. They are characterised by high compositional homogeneity and a narrow molecular-mass distribution. The characteristics of the PDMAEMA–PP polyelectrolyte complexes, which were prepared according to different procedures, are given in Table 2. Figure 5a shows the Zimm plot for a solution of the thermodynamically equilibrated PDMAEMA–PP complex studied by quasi-elastic light scattering. This plot is similar to typical plots constructed by processing the light scattering data for solutions of usual polymers. Analysis of the characteristics given in Table 2 demonstrated that the procedure for the preparation of complexes has virtually no effect on the measured molecular mass ( $M_w$ ), the radius of gyration ( $R_g$ ), the second virial coefficient ( $A_2$ ) and the sedimentation coefficient ( $S_c$ ). However, the above-mentioned characteristics (except for  $M_w$  compensated due to release of counterions) are sensitive to the composition of IPEC. The characteristics of equilibrated non-stoichiometric IPECs in dilute aqueous salt solutions are given in Table 3. It can be seen that  $R_g$  and  $A_2$  decrease, whereas  $S_c$  increases as the GPE/HPE ratio increases, *i.e.*, as the effective charge of HPE decreases in the range of  $0 < \varphi < \varphi_c$ . At  $\varphi < \varphi_c$ , IPECs listed in Table 3 exist in dilute solutions as individual particles: each particle includes one HPE polyion containing a particular number of GPE molecules.

**Table 2.** Characteristics of interpolyelectrolyte complexes prepared by titration methods {HPE = PDMAEMA ( $M_w = 6.3 \times 10^5$ ), GPE = PP ( $M_w = 6.6 \times 10^4$ ),  $\varphi = 0.33$ ,  $[\text{NaCl}] = 0.1 \text{ mol litre}^{-1}$ , pH 4.0}.

| Method of preparation of IPEC                         | $M_w \times 10^{-5}$ | $(R_g^2)^{1/2} / \text{nm}$ | $A_2 \times 10^4$ |
|-------------------------------------------------------|----------------------|-----------------------------|-------------------|
| Titration of HPE with a GPE solution                  | 7.7                  | 38                          | 3.3               |
| Titration of GPE with an HPE solution                 | 7.7                  | 39                          | 2.9               |
| Titration of a HPE–GPE mixture with hydrochloric acid | 7.2                  | 37                          | 2.8               |

However, the situation changes substantially as  $\varphi_c$  is approached. This is manifested primarily in a substantial change in the Zimm plot, which becomes similar to the plots characteristic of polymers in poor solvents. The molecular mass of soluble particles increases. This is indicative of the formation of IPEC aggregates, which do not dissociate upon dilution. Simultaneously, the absolute value of the second virial coefficient  $A_2$  sharply decreases and its sign changes from positive to negative (Fig. 5b, Table 3, run 8).

In dilute solutions, the tendency of non-stoichiometric IPEC particles to aggregation depends on the chemical nature of HPE and GPE. In particular, this tendency increases with increasing hydrophobicity of the starting polyelectrolytes. As an example let us consider the behaviour of IPEC formed by NaPA (HPE) and

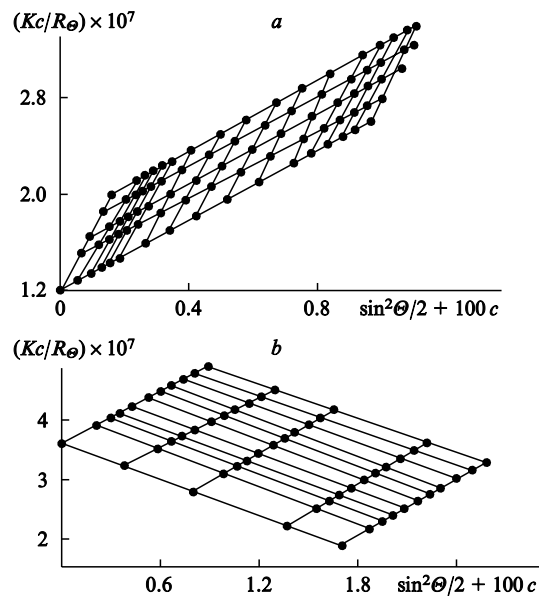
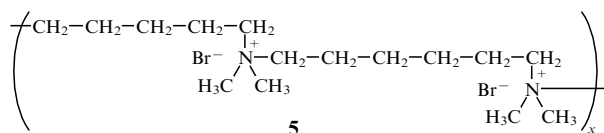


**Figure 5.** Zimm plots for a solution of the PDMAEMA–PP interpolyelectrolyte complex at  $\varphi = 0.33$  (a) and  $0.56$  (b) (see runs 6 and 8, respectively, in Table 3).  $K$  is the optical constant,  $c$  is the concentration,  $R_\theta$  is the scattering intensity at the  $\theta$  angle.

5,6-ionene bromide (IB) serving as GPE.<sup>67</sup> Each repeated unit of the IB polycation (5) contains 5.5 methylene groups and two methyl groups per charge.

**Table 3.** Characteristics of equilibrated non-stoichiometric interpolyelectrolyte complexes in dilute aqueous salt solutions (20 °C).<sup>3,5,58</sup>

| No                                                                                                           | $\varphi$ | Molecular mass of IPEC       |                              | $n_{\text{GPE}}$ (see <sup>a</sup> ) | $(R_{\text{g}}^2)^{1/2}$ /nm | $A_2 \times 10^4$ | $S_{\text{c}}/S_{\text{v}}$ | Other conditions                                  |
|--------------------------------------------------------------------------------------------------------------|-----------|------------------------------|------------------------------|--------------------------------------|------------------------------|-------------------|-----------------------------|---------------------------------------------------|
|                                                                                                              |           | $M_{\text{w}} \cdot 10^{-5}$ | $M_{\text{c}} \cdot 10^{-5}$ |                                      |                              |                   |                             |                                                   |
| Host polyelectrolyte — PDMAEMA; guest polyelectrolyte — NaPP ( $M_{\text{w}} = 1.7 \times 10^5$ )            |           |                              |                              |                                      |                              |                   |                             |                                                   |
| 1                                                                                                            | 0         | 6.3                          | —                            | —                                    | 51                           | 8.2               | 2.5                         | pH 4.0,<br>[NaCl] = 0.1 mol litre <sup>−1</sup>   |
| 2                                                                                                            | 0.07      | 7.15                         | 6.4                          | 1.4                                  | 48                           | 6.5               | 2.7                         |                                                   |
| 3                                                                                                            | 0.10      | 6.9                          | 6.4                          | 2.0                                  | 44                           | 5.9               | 2.8                         |                                                   |
| 4                                                                                                            | 0.13      | 7.35                         | 6.5                          | 2.3                                  | 43                           | 5.2               | —                           |                                                   |
| 5                                                                                                            | 0.20      | 6.75                         | 6.6                          | 3.9                                  | 40                           | 4.9               | 3.7                         |                                                   |
| 6                                                                                                            | 0.33      | 6.7                          | 6.8                          | 6.5                                  | 35                           | 2.9               | 6.0                         |                                                   |
| 7                                                                                                            | 0.50      | 7.0                          | 7.0                          | 10.0                                 | 27                           | 1.1               | 5.9                         |                                                   |
| 8                                                                                                            | 0.56      | 28.0                         | —                            | —                                    | 27                           | −0.45             | —                           |                                                   |
| Host polyelectrolyte — PDMAEMA, guest polyelectrolyte — NaPA ( $M_{\text{w}} = 1.4 \times 10^4$ )            |           |                              |                              |                                      |                              |                   |                             |                                                   |
| 9                                                                                                            | 0         | 5.3                          | —                            | —                                    | 48.5                         | 9.4               | 2.0                         | pH 4.5,<br>[NaCl] = 0.1 mol litre <sup>−1</sup>   |
| 10                                                                                                           | 0.125     | 5.5                          | 5.4                          | 2.1                                  | 47.5                         | 9.5               | 2.1                         |                                                   |
| 11                                                                                                           | 0.20      | 6.0                          | 5.5                          | 3.4                                  | 46.0                         | 9.0               | 2.3                         |                                                   |
| 12                                                                                                           | 0.33      | 5.6                          | 5.6                          | 5.6                                  | 43.5                         | 8.6               | 2.6                         |                                                   |
| 13                                                                                                           | 0.50      | 5.6                          | 5.8                          | 8.5                                  | 40.0                         | 7.6               | 3.3                         |                                                   |
| Host polyelectrolyte — NaPP, guest polyelectrolyte — 5,6-ionene bromide ( $M_{\text{w}} = 1.4 \times 10^4$ ) |           |                              |                              |                                      |                              |                   |                             |                                                   |
| 14                                                                                                           | 0         | 0.66                         | —                            | —                                    | —                            | 14.3              | 2.2                         | pH 7.0,<br>[NaCl] = 0.025 mol litre <sup>−1</sup> |
| 15                                                                                                           | 0.125     | 0.61                         | 0.73                         | 1.2                                  | —                            | 4.8               | 2.5                         |                                                   |
| 16                                                                                                           | 0.20      | 0.62                         | 0.78                         | 1.9                                  | —                            | 2.2               | 2.7                         |                                                   |
| 17                                                                                                           | 0.33      | 0.66                         | 0.85                         | 3.1                                  | —                            | 1.7               | 3.4                         |                                                   |

**Note.** The scattering intensities and refractive index increments were measured by varying the IPEC concentration at a constant concentration of a simple salt using dialysis of solutions of the samples against a solution of a common salt.<sup>64</sup> The molecular mass of IPEC of a given composition was calculated as follows:  $M_c = P_{\text{HPE}}[m_{\text{HPE}} + \varphi(m_{\text{GPE}} - m)]$ , where  $P_{\text{HPE}}$  is the degree of polymerisation of HPE,  $m_{\text{HPE}}$  and  $m_{\text{GPE}}$  are the molecular masses of the repeated units of HPE and GPE, respectively,  $m$  is the molecular mass of the salt eliminated upon coupling of polyelectrolytes;  $S_c$  was determined at a constant IPEC concentration of 0.35 mass %. <sup>a</sup> For all complexes,  $n_{\text{HPE}} = 1$ .

**Table 4.** Characteristics of IPEC formed from NaPA (HPE) and 5,6-ionene bromide (GPE) ( $M_{wHPE} = 1.2 \times 10^5$ ,  $M_{wGPE} = 1.4 \times 10^4$ , pH 7.2,  $[NaBr] = 0.025 \text{ mol litre}^{-1}$ ,  $20^\circ\text{C}$ ).

| No | $\varphi$ | $M_w \times 10^{-5}$ | $n$ |      | $A_2 \times 10^3$ |
|----|-----------|----------------------|-----|------|-------------------|
|    |           |                      | HPE | GPE  |                   |
| 1  | 0.07      | 1.8                  | 1   | 1.4  | 11.8              |
| 2  | 0.10      | 1.8                  | 1   | 1.8  | 10.3              |
| 3  | 0.13      | 1.8                  | 1   | 2.4  | 7.4               |
| 4  | 0.20      | 2.6                  | 2   | 7.3  | 3.8               |
| 5  | 0.33      | 3.8                  | 3   | 18.0 | 1.9               |

These groups are not sufficiently hydrophobic to suppress the solubility of the starting IB in water. However, in the presence of these groups, the affinity of IB–PA binary domains of IPEC for each other, apparently, increases. As can be seen from Table 4, the IB–PA particles undergo aggregation at  $\varphi \geq 0.2$  (these values are, however, substantially smaller than  $\varphi_c$ ) in contrast to IPECs listed in Table 3. Apparently, binary domains in aggregated IPECs form a water-insoluble core, while excess PA segments are exposed to water and form a crown, which imparts solubility to a particle as a whole.

Turning back to the experimental values of  $A_2$ , which decrease with increasing  $\varphi$ , recall that, according to the Donnan–Guggenheim theory,<sup>68</sup> the contribution of Coulombic repulsions between the charges of the polyion to the overall value of  $A_2$  can be expressed as follows:

$$A_{2el} = \frac{1000z_c^2\gamma^2}{4M^2I}, \quad (13)$$

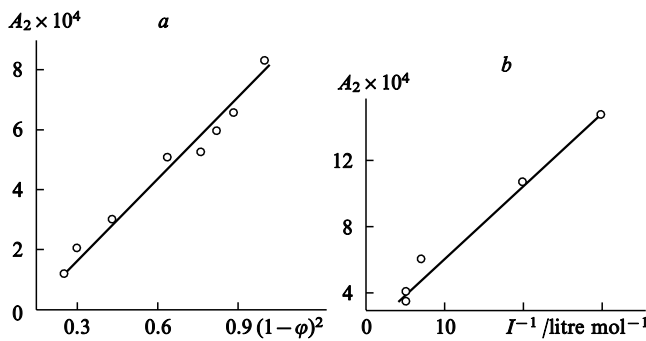
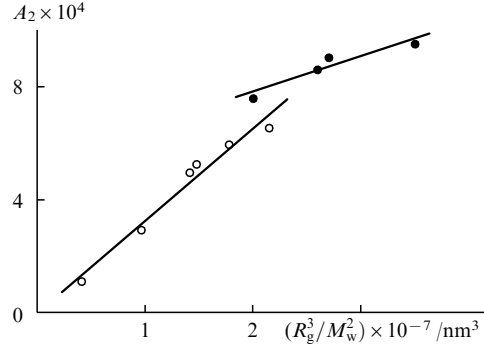
where  $z_c$  is the total charge of the polyion,  $\gamma$  is the degree of binding of the counterions to free HPE segments,  $M$  is the molecular mass of the polyion and  $I$  is the ionic strength equal to the concentration of a simple salt in solution. The effective charge of non-stoichiometric IPEC particles in the pH range corresponding to complete ionisation of HPE depends on  $\varphi$

$$\frac{z_c}{M} = \frac{1-\varphi}{M_0}, \quad (14)$$

where  $M_0$  is the molecular mass of the repeated HPE unit. From Eqs (13) and (14) it follows that

$$A_{2el} \sim \frac{(1-\varphi)^2}{I}. \quad (15)$$

Figure 6a shows the dependence of the experimental values of  $A_2$  on  $(1-\varphi)^2$  at a constant ionic strength, which is in good

**Figure 6.** Dependences of the second virial coefficient ( $A_2$ ) of solutions of IPECs prepared from PDMAEMA ( $M_w = 6.3 \times 10^5$ ) and NaPP ( $M_w = 1.7 \times 10^4$ ) on their compositions at a constant ionic strength  $I = [NaCl] = 0.1 \text{ mol litre}^{-1}$  (a) and on the ionic strength at a constant composition (b); (b):  $\varphi = 0.33$ ; pH 4.0,  $T = 20^\circ\text{C}$ .**Figure 7.** Second virial coefficients ( $A_2$ ) in the coordinates of the equation (16) for different systems (see Table 3).

agreement with relation (15). The latter is also applicable for the case where the ionic strength varies, whereas  $\varphi$  remains constant (Fig. 6b). Assuming that the radius of gyration of a polyelectrolyte coil is directly proportional to the radius of the equivalent sphere and that the charge in the vicinity of the polyelectrolyte chain is primarily compensated by counterions and in accordance with the excluded volume theory, we can write

$$A_2 \sim \frac{R_g^3}{M_w^2}. \quad (16)$$

The experimental data given in Table 3 agree well with relation (16) (Fig. 7).

The agreement between the experimental data and the above theoretical relations supports the conclusion that the behaviour of soluble equilibrated IPECs, whose compositions are in a range  $0 < \varphi < \varphi_c$ , in dilute solutions is analogous to that of usual polyelectrolytes with different charge densities.

The solution behaviour of non-stoichiometric IPECs formed upon complexation of linear HPE polyions with relatively small charged globular particles serving as GPE is similar to the behaviour of non-stoichiometric IPECs consisting of linear polyelectrolytes. In particular, this is true for cationic dendrimers,<sup>22–24</sup> which interact with linear polyelectrolytes with rather high degrees of polymerisation.

However, it should be emphasised that the above-described behaviour is untypical of IPECs formed by polyelectrolyte pairs, which are not prone to exchange reactions even if the starting components are taken in a non-stoichiometric ratio and an excess of polyions with a high degree of polymerisation is used. In such systems, the equilibrium is not established for kinetic reasons. Interpolyelectrolyte complexes formed by mixing polyamines or polyammonium salts with polysulfates or polysulfonates are examples of non-equilibrated systems. In such IPECs, interchain ion pairs are additionally stabilised by specific donor–acceptor interactions. In this case, complexation gives rise to relatively large IPEC aggregates containing a large amount of oppositely charged polyions. These aggregates are formed, in particular, in the reactions of sodium poly(styrene sulfonate) (NaPSS) with poly-*N,N*-dimethyl-*N,N*-diallylammonium chloride.<sup>69–72</sup>

### 3. Conversions of interpolyelectrolyte complexes in salt solutions

Typical plots of the reduced turbidity ( $\tau/\tau_{\max}$ ) vs. the ionic strength for HPE–GPE mixtures in water for  $Z < \varphi_c$ ,  $\Theta$  close to unity ( $Z = \varphi$ ) and at a HPE concentration lower than the crossover concentration are presented in Fig. 8a. The homogeneity region *I* corresponds to dilute solutions of equilibrated non-stoichiometric IPECs. These solutions are transparent, and IPEC particles in such solutions behave analogously to individual polyelectrolytes. It should be noted that the smaller  $\varphi$ , i.e., the lower the population of HPE by GPE particles, the wider the region *I*. In region *II*, the system is also homogeneous. However, at these concentrations of

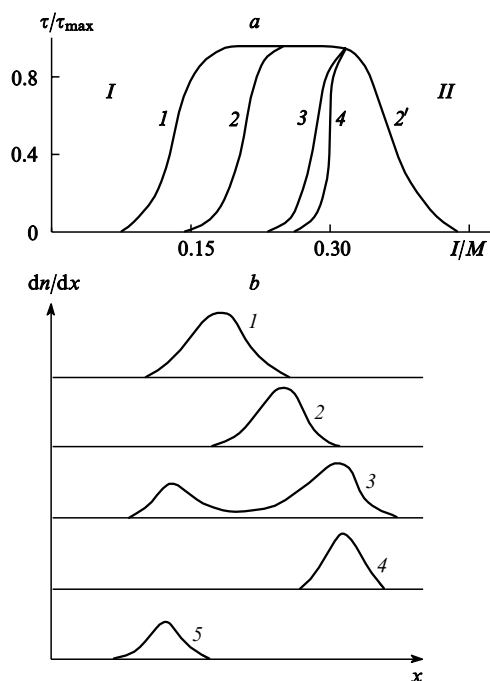


**Figure 8.** Phase behaviour of NaPMA ( $M_w = 2.6 \times 10^5$ )–PVP ( $M_w = 6.0 \times 10^4$ ) mixtures depending on the ionic strength, which was varied by the addition of NaBr (pH 7.5,  $T = 20^\circ\text{C}$ );<sup>71</sup> (a) plots of relative transmittance ( $\tau/\tau_{\max}$ ) vs. the ionic strength ( $I = [\text{NaBr}]$ ) at  $Z = 0.40$  (1), 0.33 (2, 2'), 0.25 (3), 0.40 (4); (b) sedimentograms of the mixtures at  $Z = 0.14$ ; (c) = 0.3 mass %,  $\omega = 56$  100 rpm,  $I = [\text{NaBr}] = 0.2$  (1), 0.35 (2), 0.48 mol litre<sup>-1</sup> (3); NaPMA (4) and PVP (5) at  $[\text{NaBr}] = 0.48$  mol litre<sup>-1</sup>.

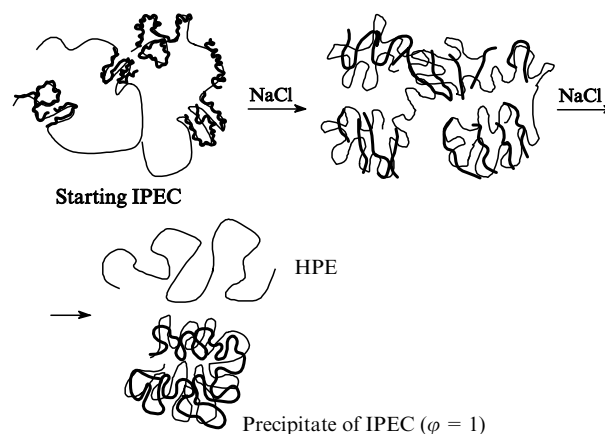
low-molecular-weight salts, IPECs do not exist. In solution, they dissociate into the starting components because the oppositely charged polyions are shielded from each other by low-molecular-weight counterions. In the regions characterised by high turbidity, which are observed for different  $Z$  at intermediate salt concentrations, phase separation occurs and the systems become heterogeneous. The sedimentograms of the HPE–GPE system at different salt concentrations (profiles 1–3) are compared in Fig. 8b with the sedimentograms of individual HPE and GPE (profiles 4 and 5). The profiles 1 and 2 are characterised by one sedimentation peak and belong to the homogeneity region I. The profile 3 has two peaks and corresponds to the heterogeneity region.<sup>3, 73</sup>

The phase behaviour of charge-non-stoichiometric mixtures of oppositely charged polyelectrolytes in salt solutions were studied in detail by light scattering methods, analytical and preparative ultracentrifugation, fluorimetry (in systems containing fluorescent-labelled HPE- and GPE-quenchers), phase composition analysis, *etc.*,<sup>73–80</sup> which provided deeper insight into the phenomenon as a whole.

An increase in the salt concentration within the homogeneity region I (see Fig. 8a) deteriorates the thermodynamic quality of the solvent, which, in turn, leads to a decrease in the particle size of dissolved IPECs. The limiting concentration of HPE populated by GPE chains (at higher concentrations, phase separation occurs), which is determined by  $\varphi_c(I)$ , also decreases. Hence, the higher the starting value of  $\varphi$ ,  $\varphi_0 = Z$ , the lower the critical ionic strength ( $I_c$ ), at which  $\varphi_c(I)$  decreases to  $\varphi_0$ , and the broader the region I (see Fig. 8a, curves 1–4). To minimise the free energy of the system as a whole at  $I > I_c$ , the IPEC particles should lose a part of GPE chains. This occurs by redistribution of GPE chains between HPE chains according to the above-described mechanism of interpolyelectrolyte exchange. As a result, the reaction system undergoes disproportionation to give stoichiometric IPEC as an

individual phase, while particles of non-stoichiometric IPEC of composition  $\varphi' = \varphi_c(I) < Z$  (i.e., depleted in GPE compared to the starting particles) remain in solution. A further increase in the salt concentrations within the heterogeneity region leads to an increase in the amount of the stoichiometric complex, which forms an individual phase and remains in equilibrium with soluble IPEC particles of composition  $\varphi'$ . Evidently, under conditions where  $\Theta$  is close to unity,  $\varphi'$  cannot be smaller than the ratio of the degrees of polymerisation of GPE and HPE. Then if  $\varphi_c(I) < P_{\text{GPE}}/P_{\text{HPE}}$ , free HPE chains remain in the supernatant after precipitation of stoichiometric IPEC (Scheme 5).<sup>81</sup> The maximum HPE concentration in the supernatant can be as high as  $[\text{HPE}]_\infty = [\text{HPE}]_0(1 - \varphi)$ , where  $[\text{HPE}]_0$  is its initial concentration.

Scheme 5



It should be noted that this phase behaviour of IPECs in salt solutions is not unambiguously determined by the ionic strength. The critical ionic strength  $I_c$  for each IPEC depends substantially on the nature of the HPE counterions.<sup>73</sup> The turbidimetric titration curves of the NaPA (HPE)–IB (GPE) polyelectrolyte complexes ( $\varphi = 0.33$ ) with various simple salts are presented in Fig. 9. A comparison of the curves 1–4 shows that the critical ionic strength  $I_c$  decreases in the series  $(\text{CH}_3)_4\text{N}^+$ ,  $\text{K}^+$ ,  $\text{Na}^+$ ,  $\text{Li}^+$  as the affinity of the cation for the  $\text{COO}^-$  group increases.<sup>81</sup> At the same time,  $I_c$  is independent of the nature of the coanions of HPE, in particular, of  $\text{F}^-$ ,  $\text{Cl}^-$  and  $\text{Br}^-$  (see Fig. 9, curves 2'–2'''). The above data are consistent with the dependences of the sedimentation coefficients on the ionic strength of a solution for the PMA (HPE)–PVP (GPE) interpolyelectrolyte complexes ( $\varphi = 0.37$ ) and free NaPMA at low concentrations of simple salts (i.e., under conditions where IPECs are still quite stable).<sup>77</sup> It appeared that the addition of NaCl in the ionic

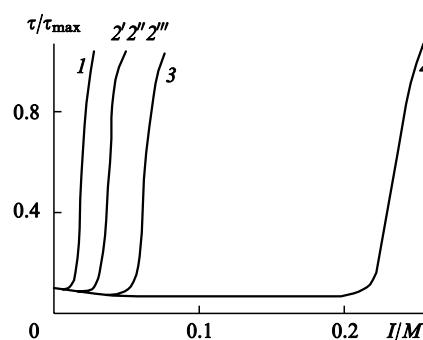


**Figure 9.** Plots of the relative transmittance ( $\tau/\tau_{\max}$ ) vs. the ionic strength for titration of IPEC formed in the NaPMA ( $M_w = 1.8 \times 10^5$ )–IB ( $M_w = 1.4 \times 10^4$ ) mixture ( $Z = \varphi = 0.33$ ) with solutions of LiCl (1); NaX, where X = F (2'), Cl (2''), Br (2'''); KCl (3);  $(\text{CH}_3)_4\text{NCl}$  (4); the concentration of IPEC in the solution was 0.01 mass %, pH 8.5,  $T = 20^\circ\text{C}$ .<sup>73</sup>

strength range  $0 < I < 0.1 \text{ mol litre}^{-1}$  leads to a substantial increase in  $S_c$  for both IPEC (from 1.7 to 4.35 Sv) and free NaPMA (from 1.3 to 2.5 Sv). This indicates that dissolved polymer particles become compact due to binding of the  $\text{Na}^+$  counterions to negatively charged PMA units. The  $(\text{CH}_3)_4\text{N}^+$  cations have a much lower affinity for carboxylate groups compared to the  $\text{Na}^+$  cations. Hence, an equal increase in the ionic strength upon the addition of tetramethylammonium chloride to the system leads to only a slight change in the sedimentation coefficients  $S_c$ . Similar effects were observed also for soluble non-stoichiometric IPECs formed by cationic HPEs and anionic GPEs but in relation to the chemical nature of low-molecular-weight anions. For example, IPEC consisting of poly-*N*-ethyl-4-vinylpyridinium fluoride (HPE) and PMA (GPE) ( $\varphi = 0.33$ ) decomposes at  $[\text{NaF}]_c = 0.2$ ,  $[\text{NaCl}]_c = 0.03$  and  $[\text{NaBr}]_c = 0.01 \text{ mol litre}^{-1}$ . This order corresponds to an increase in the affinity of halides for the pyridinium units of HPE. In this case,  $I_c$  is completely independent of the nature of simple cations.<sup>82</sup>

The salt concentration at which IPEC dissociates into the starting polyelectrolytes, which pass into solution, and the phase-separated systems are again homogenised (*i.e.*, pass into region II, see Fig. 8a) depends on the nature of both shielding counterions.<sup>78, 79</sup>

Figure 10 shows the plots of the relative fluorescence intensities of PMA\* (HPE), which is initially involved into the soluble non-stoichiometric PMA\*–PVP interpolyelectrolyte complex, vs. the concentrations of simple salts. The fluorescence intensity of the starting IPEC is low because of its quenching by the pyridinium rings of GPE. An increase in the fluorescence intensity in the course of titration of an IPEC solution with salts solutions is indicative of a decrease in the number of fluorescent labels in

HPE, which interact with the GPE units. This may be a consequence of dissociation of interpolyelectrolyte duplexes. A sedimentation study of the NaPMA\*–PVP electrolyte complexes in the corresponding salt solutions using a high-speed analytical ultracentrifuge equipped with a UV detector demonstrated that curves presented in Fig. 10 qualitatively describe the degree of cleavage of IPEC into the starting polyelectrolyte components.<sup>80</sup>

A comparison of the fluorimetric titration curves of a PMA\* (HPE)–PVP (GPE) solution with chlorides of various alkali metals and tetramethylammonium (Fig. 10a) demonstrated that the ability of low-molecular-weight cations to shield interacting oppositely charged polyions (thus inducing dissociation of IPEC) decreases in the series  $\text{Li}^+ > \text{Na}^+ > \text{K}^+ \gg (\text{CH}_3)_4\text{N}^+$ . The affinity of the cations for polyanions of polycarboxylic acids decreases in the same order.<sup>81</sup> Figure 10b displays the fluorimetric titration curves of the same IPEC with solutions of various tetramethylammonium halides. It can be seen that decomposition of IPEC can occur at a very low concentration of tetramethylammonium bromide (which determines the ionic strength of the solution), whereas the complex retains stability even at very high concentrations of tetramethylammonium fluoride. Tetramethylammonium chloride occupies an intermediate place. It should be noted that the affinity of halides for the PVP cations decreases in an analogous order.<sup>82</sup>

Analysis of the data presented in Fig. 10a shows that the fluorescence intensity noticeably decreases at concentrations of alkali metal halides substantially lower than those necessary for decomposition of IPECs. Apparently, the formation of compact IPEC particles through specific binding of alkali metal ions to excess PMA units facilitates fluorescence quenching within IPEC particles. Such a decrease is not observed in the presence of tetramethylammonium salts due to a substantially lower affinity of the  $(\text{CH}_3)_4\text{N}^+$  cations for  $\text{COO}^-$  groups.<sup>79</sup>

The threshold concentration of a low-molecular-weight salt necessary for decomposition of insoluble stoichiometric IPECs can be determined from a decrease in turbidity of the reaction mixture. This characteristic is independent of the degree of polymerisation of HPE, but it sharply increases (up to a certain limit) with increasing degree of polymerisation of GPE oligomers (Fig. 11).<sup>80</sup> However, it should be noted that a decrease in turbidity of the reaction mixture is not necessary indicative of the exhaustive cleavage of salt bonds and complete separation of the GPE and HPE chains, particularly, if GPE has a high molecular mass. Analysis of the results of sedimentation measurements demonstrated that a particular number of dynamic contacts between oppositely charged polyions can be retained even in a dilute solution, which appears in going through the clarification point. These contacts are completely broken only at higher salt concentrations.<sup>78</sup>

It should be emphasised that if the exchange of GPE between complex particles are, for one reason or other, forbidden, the

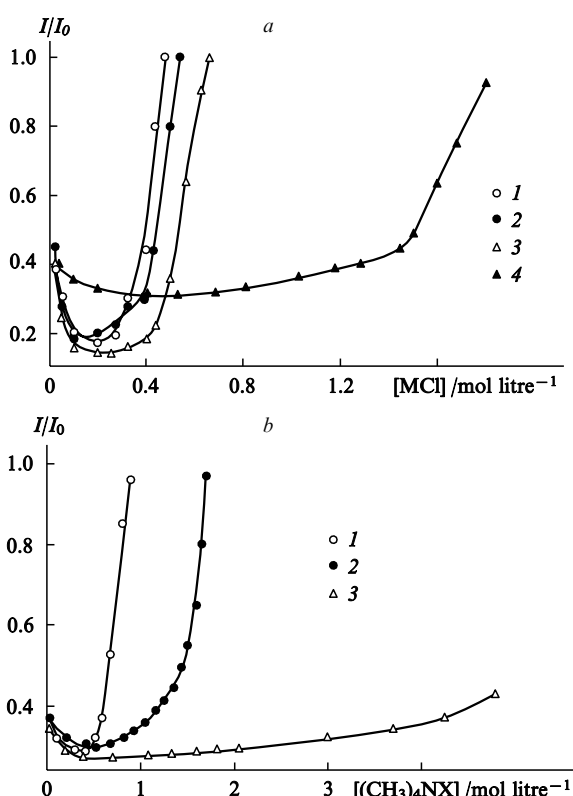


**Figure 10.** Plots of the relative fluorescence intensities ( $I/I_0$ ) of a solution of IPEC formed from NaPMA\* ( $P_w = 2150$ ) and PVP ( $P_w = 390$ ) vs. the concentrations of salts with various cations (a) and anions (b);  $Z = \varphi = 0.3$ ,  $[\text{PMA}^*] = 2 \times 10^3 \text{ base-mol litre}^{-1}$ , pH 9.5,  $T = 20^\circ\text{C}$  ( $I_0$  is the fluorescence intensity of free HPE in an analogous solution of the salt).<sup>77</sup> (a) M = Li (1), Na (2), K (3),  $(\text{CH}_3)_4\text{N}$  (4); (b) X = Br (1), Cl (2), F (3).

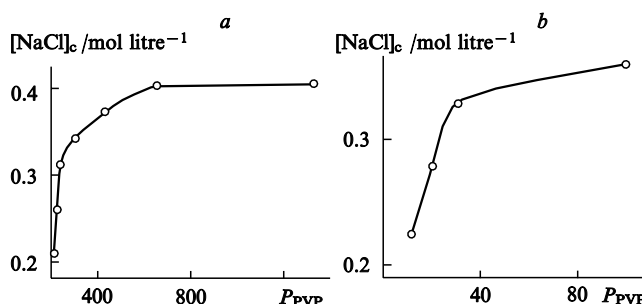


**Figure 11.** Change in the threshold concentration of sodium chloride necessary for dissociation of the PVP–PMA\* interpolyelectrolyte complexes at high (a) and low (b) degrees of polymerisation of PVP.  $P_w(\text{PMA}^*) = 3.9 \times 10^3$ ,  $\varphi = 0.30$ ,  $T = 20^\circ\text{C}$ .

addition of salts to solutions of non-stoichiometric IPECs does not lead to phase separation. In particular, the addition of NaCl to the above-mentioned solutions of the PA(or PMA)–PTBA polyelectrolyte complexes leads to phase separation at room temperature, but these solutions remain homogeneous at 40–60 °C because at these temperatures the polycation exchange is suppressed by hydrophobic interactions.<sup>59</sup> In PA (HPE)–PE (GPE) solutions, phase separation does not occur even at high salt concentrations if the HPE and GPE chains are linked not only through Coulombic interactions but also through a particular number of covalent bonds.<sup>74–77</sup> At a salt concentration sufficiently high for interpolyelectrolyte ion pairs to be broken, covalent bonds are retained. Hence, the IPEC particles behave here as graft copolymers present in a solution common to the main chain and grafted branches.

A new family of water-soluble IPECs referred to as block ionomer complexes (BIC) was documented.<sup>83–86</sup> These complexes include a block copolymer composed of an ionic and non-ionic water-soluble blocks. They can retain solubility even at  $Z = \varphi = 1$ , where  $Z$  is the charge ratio of the constituent polyelectrolytes. As an example we refer to the block ionomer complex formed by the diblock copolymer NaPMA ( $P = 188$ )–block-poly(ethylene oxide) ( $P = 176$ ) and PVP ( $P = 100$ ).<sup>83</sup> At  $Z = \varphi = 1$ , the BIC unimer contains a hydrophobic domain of the stoichiometric PMA–PVP interpolyelectrolyte complex covalently bonded to the hydrophilic poly(ethylene oxide) block, *i.e.*, it is virtually a complex amphiphilic macromolecule. The BIC unimers act as surfactants characterised by a particular critical micelle concentration. Actually, at concentrations higher than CMC, the unimers undergo aggregation to form polymer micelles, which contain an insoluble core assembled from IPEC domains and a crown consisting of poly(ethylene oxide) blocks. Due to the presence of the crown, micelles are soluble in water and are resistant to further aggregation. At the same time, BIC micelles can be involved in polyelectrolyte exchange reactions with homopolyelectrolytes (in particular, with NaPSS or NaPMA). Unlike all other polymer micelles, they undergo deaggregation upon the addition of low-molecular-weight salts. Deaggregation occurs due to destruction of the IPEC core caused by electrostatic shielding analogously to that described above for usual IPECs.<sup>83</sup>

Adsorption of polyelectrolytes on large oppositely charged surfaces can also be considered in terms of the IPEC formation. From this standpoint, adsorption of PVP on polystyrene latex particles coated with chemically bonded carboxyl groups was examined.<sup>87–92</sup> The diameter of latex particles ( $5 \times 10^2$  nm) was much larger than the contour line of the polyelectrolyte. The surface density of the carboxyl groups was  $\sim 5$  nm<sup>-2</sup>, and their  $pK_a = 6.8$ . At pH 9, at which all carboxyl groups are ionised, the starting electrophoretic mobility (EPM) of latex particles is negative. The dependence of EPM on  $Z$  is shown in Fig. 12. It can be seen that the surface charge decreases with increasing  $Z$  and becomes equal to zero at  $Z = 1$ . However in this case, in contrast to equilibrated stoichiometric IPECs formed in the reactions of completely ionised oppositely charged linear polyelectrolytes, a noticeable number of surface negative groups and positive units of the adsorbed polycations do not ‘find each other’ at the isoelectric point and, hence, cannot form contact ion pairs because of steric hindrance. The ‘unpaired’ units of the adsorbed polycations remain in loops and ‘free tails’. These units, as well as ‘unpaired’ surface charges, are neutralised by low-molecular-weight counterions. Hence, the surface layer formed at the isoelectric point retains centres, which can adsorb both excess polycations (charge inversion) and polyanions, if they are added to the reaction system.

Actually, charge inversion of latex particles occurs at  $Z > 1$ , which indicates that excess polycations are adsorbed on these particles. At the same time, the dependence of EPM on  $Z$  is insensitive to changes in the latex concentration, which suggests that PVP is strongly bound to the adsorbent surface. Actually, titration of latex with a PVP solution affords the free polyelec-

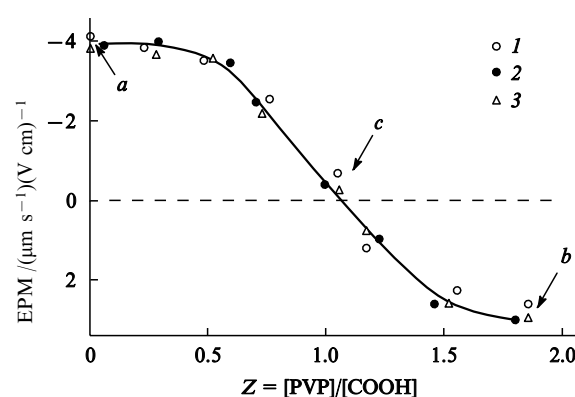
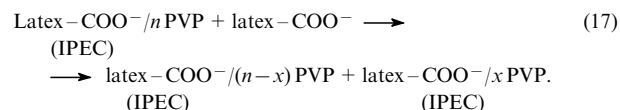


**Figure 12.** Dependence of the electrophoretic mobility of latex particles – PVP on the composition of their surface layer. The concentration of the latex particles /litre<sup>-1</sup>: (1)  $1.8 \times 10^{12}$ , (2)  $1.8 \times 10^{11}$ , (3)  $9.0 \times 10^9$ ; pH 9.0,  $T = 20$  °C.

trolyte, which is accumulated in solution only once it completely saturates the latex surface. In spite of this fact, the adsorbed polycations are easily exchanged between the latex particles through random collisions. This fact was established experimentally. The starting negatively charged latex (Fig. 12, arrow *a*) was mixed with an analogous latex, which was recharged with adsorbed PVP polycations (Fig. 12, arrow *b*). In the course of mixing, the latex particles bearing opposite charges undergo aggregation followed by spontaneous redispersion of these aggregates to individual particles whose size is identical to the particle size of the starting latex. However, EPM measured after redispersion has an intermediate value (Fig. 12, arrow *c*), which unambiguously indicates that mixing leads to redistribution of the adsorbed PVP polycations between the latex particles in the system.



Negatively charged small monolamellar liposomes (SML) display analogous behaviour in interactions with PVP.<sup>92,93</sup> Upon the addition of a PVP solution to a suspension of SML composed of the zwitterionic lipid, *viz.*, phosphatidyl choline (or dipalmitoyl phosphatidyl choline), and the anionic lipid, *viz.*, cardiolipin, the polycations are strongly adsorbed on the liposome surface. However, the subsequent addition of a NaPA solution leads to rapid removal of PVP from the surface due to formation of the even stronger PA–PVP interpolyelectrolyte complex. The SML–PVP complex, like usual IPECs, dissociates in the presence of low-molecular-weight salts (for example, NaCl). Both transformations are accompanied by complete regeneration of the starting SMLs.

The above examples reflect ‘ideal relations’ between polyelectrolytes and oppositely charged surfaces. This behaviour is typical only of systems, in which the electrostatic component plays the major role in adsorption. A different situation arises when other interactions (hydrogen bonds, hydrophobic or donor–acceptor interactions, *etc.*) are present in the system along with Coulombic attractions. In these systems, the polyion exchange or substitution does not occur, and the addition of low-molecular-weight salts does not cause desorption of polyions bound to the surface. For example, unlike PVP ( $\beta > 90\%$ ), PVP copolymers containing hydrophobic regions are not desorbed from the surface of the above-mentioned SMLs upon the addition of NaCl.<sup>93</sup>

Presumably, nonideal electrostatic or strong non-electrostatic adsorption of a soluble polyelectrolyte on the solid sorbent surface plays the key role in the technology of the preparation of thin monolayer IPEC films.<sup>7</sup> In this case, adsorption gives rise to the

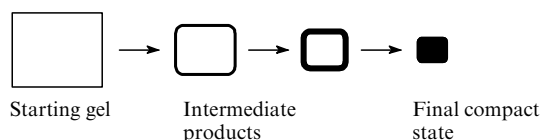
starting interface, which can strongly bind another oppositely charged polyelectrolyte as it comes in contact with its solution. This affords the first starting IPEC nanolayer. The latter serves as a basis for the formation and multiple reproduction of identical layers. These layers are deposited by successive immersion of the sorbent into solutions of oppositely charged polyelectrolytes. The factors suppressing polyelectrolyte exchange reactions are favourable for the retention of the continuity of each newly formed layer and regeneration of a 'sticky' interface necessary for each successive deposition.

### III. Complexation of polyelectrolytes with oppositely charged hydrogels

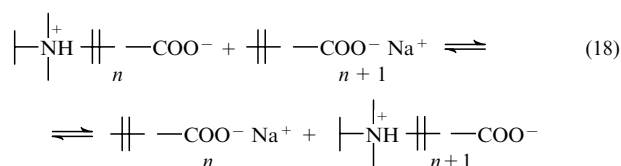
In the late 1980s, it was found that macroscopic samples of weakly cross-linked polyelectrolyte hydrogels (#PE) can adsorb oppositely charged linear polyelectrolytes from aqueous solutions to form cross-linked interpolyelectrolyte complexes (#IPEC).<sup>94,95</sup> Hydrogels containing 1–2 chemical cross-linkages per 200 repeated monomer units were investigated. In the initial state, their equilibrium degree of swelling was  $\sim 10^3$ . It appeared that complexation giving rise to #IPECs is controlled by the same factors as the reactions between oppositely charged linear polyelectrolytes. In the reactions involving weak polyelectrolytes as components, the pH range where #IPEC are formed and retain stability is bounded by the curves shown in Fig. 1.

Sorption of linear PEs was demonstrated to cause a sharp decrease in the volume of the hydrogel involved in the reaction (by 2–3 orders of magnitude). In the course of the interpolyelectrolyte reaction, a weakly swollen shell of the resulting #IPEC coexists with the strongly swollen core of the starting #PE. The coexisting regions are separated by a pronounced interface presented in Scheme 6.

Scheme 6

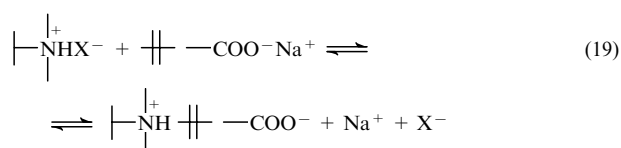


The sorption mechanism of soluble #PE involves two independent interpolyelectrolyte reactions. The adsorption-rate-determining step involves a 'relay-race' transfer of polyion segments from one fragment of the #PE network to another (initially vacant) through the interpolyelectrolyte exchange reaction



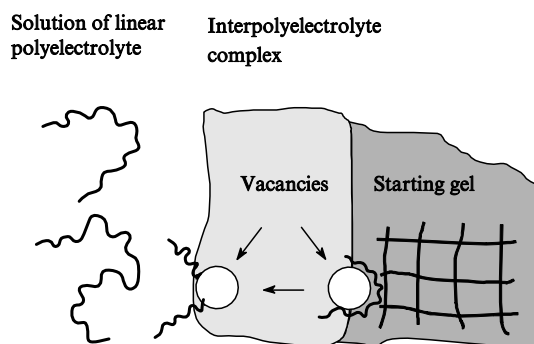
Each transfer event occurring at the shell/core interface and directed into the hydrogel phase affords a vacancy in the #IPEC shell, which becomes accessible for another segment of the polyion, thus allowing transfer in the same direction (Scheme 7).

As a result, the interface between the shell and the core moves to the centre of the sample involved in the reaction and the shell gradually extends over the whole starting #PE hydrogel. At the same time, charged vacancies together with their neutralising counterions move in the opposite direction and finally reach the interface between the #IPEC shell and the external solution, where they are bound to the oppositely charged polyions coming from the solution.



It is this coupling reaction that is the driving force for migration of polyions to the oppositely charged hydrogel. In other words, the free energy of the reaction (19) is consumed for the transport of polyions in the hydrogel phase, thus pushing the reaction (18).<sup>94</sup>

Scheme 7



Hence, the formation of #IPEC is thermodynamically controlled by the reaction (19), which occurs only under conditions (pH or the degree of ionisation of polyelectrolytes,  $\alpha$ , the ionic strength) where the equilibrium shifts to the left. Correspondingly, #IPEC dissociates if the equilibrium (19) shifts to the right. In this case, linear polyions go back into the solution and the starting #PE hydrogel is completely regenerated. The composition of the final #IPEC is also determined by  $\alpha$ .

The formation of #IPEC can be terminated in any intermediate step by ceasing the supply of polyions from the solution. If the conditions of stability of #IPEC are still met, the sharp interface between the shell and the core in the partially reacted sample (see Scheme 6) is not blurred and remains stationary for as long as desired. Hence, one can easily control the thickness of the #IPEC shell.

At the same time, the formation of #IPEC is kinetically controlled by the reaction (18).<sup>95</sup> The process is accelerated with increasing ionic strength (in the range of stability of IPEC) and with decreasing degree of polymerisation of the linear polyion. If the interpolyelectrolyte exchange reaction is forbidden for one reason or other, linear polyions do not penetrate into the #PE hydrogel. In this case, only a thin #IPEC film (its thickness is close to the diameter of the polyion) is formed on the hydrogel surface.<sup>96</sup> The data given in Table 5 describe the character of complexation of various #PE hydrogels with various linear polyelectrolytes. It can be seen that the factors suppressing the exchange reactions of soluble IPEC with linear polyelectrolytes (the presence of hydrophobic, sulfate or sulfonate groups in polymer chains) hinder the unlimited penetration of linear polyions into cross-linked hydrogels.

Cross-linked polyelectrolyte hydrogels can adsorb not only linear polyions but also oppositely charged globular proteins to form the corresponding #IPECs. This was exemplified for the first time by the reaction of strongly cross-linked sodium polyacrylate (#NaPA) hydrogel with lysozyme.<sup>97</sup> Later on, this phenomenon was studied in detail for sorption of cytochrome *c* and protamine by weakly cross-linked #NaPA hydrogels.<sup>98,99</sup> In particular, it was demonstrated that the number of salt bonds between the  $\text{COO}^-$  groups of #NaPA and the amino groups of the protein globule in salt-free systems is determined by pH, and the equilibrium composition of the final #IPEC formed in the presence of an excess protein in the reaction mixture is identical to the composition of IPEC precipitated by titration of a solution of linear NaPA with a solution of the corresponding protein. In the

**Table 5.** Character of complexation of cross-linked polyelectrolyte hydrogels with oppositely charged linear polyelectrolytes (20 °C).

| Linear polyelectrolyte | $M_w$             | Character of complexation |
|------------------------|-------------------|---------------------------|
| Hydrogel — #NaPA       |                   |                           |
| PVP                    | $3 \times 10^5$   | penetration inside        |
|                        | $1.5 \times 10^5$ | the same                  |
|                        | $0.5 \times 10^5$ | "                         |
| PDMAEMA                | $6 \times 10^4$   | "                         |
| PEI                    | $6 \times 10^4$   | "                         |
| Chitosan               | $2 \times 10^5$   | "                         |
| PVPD <sup>a</sup>      | $1.7 \times 10^3$ | surface adsorption        |
| Hydrogel — #PDMAEMA    |                   |                           |
| NaPA                   | $3.5 \times 10^5$ | penetration inside        |
| NaPMA                  | $2.7 \times 10^4$ | the same                  |
|                        | $1.6 \times 10^4$ | "                         |
| NaPSS                  | $3.0 \times 10^5$ | surface adsorption        |
| NaPVS <sup>b</sup>     | $4.4 \times 10^3$ | the same                  |
| Heparin                | $1.0 \times 10^5$ | "                         |

<sup>a</sup> The 70/30 *N*-ethyl-4-vinylpyridinium/*N*-dodecyl-4-vinylpyridinium copolymer. <sup>b</sup> Sodium poly(vinylsulfate).

intermediate steps of sorption of proteins by hydrogels from salt-free solutions, analogously to sorption of linear polyelectrolytes, the strongly swollen hydrogel core coexists with a well-defined compact shell of the resulting #IPEC, which is gradually thickened and finally takes up the whole starting hydrogel. However, the addition of low-molecular-weight salts to these systems, in contrast to the above-considered #PE/linear polyelectrolyte systems, not only affects the sorption kinetics but also radically changes the protein distribution within the partially reacted hydrogel, and the protein distribution changes from completely heterogeneous to virtually homogeneous.<sup>99</sup>

#### IV. Structures and mechanical properties of interpolyelectrolyte complexes in the bulk

Although IPECs have been studied for many years, their structures and properties in the bulk remain poorly known. Unfortunately, scarce data were published primarily in sources that are difficult to access and, hence, are unknown to a wide range of researchers.

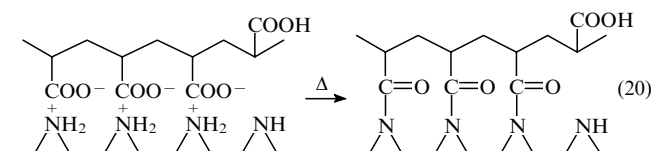
In early studies devoted to analysis of equilibria in coupling reactions of oppositely charged polyelectrolytes, IPECs were interpreted (on the basis of indirect evidence) as polymer compounds, in which polycations and polyanions are separated by more or less extended sequences composed of contact ion pairs coexisting with individual loops and tails. The latter can be considered as structural defects.<sup>100</sup> The higher the degree of conversion  $\Theta$ , the larger the percentage of paired units in such IPECs (see Fig. 1). The percentage of free hydrophilic units in the loops and tails determines the maximum degree of swelling of IPEC in water. Swelling is limited by sequences of ion pairs, which, under the conditions of existence of IPEC, are stabilised by cooperative Coulombic interactions.

Unlike the equilibrated soluble non-stoichiometric IPECs considered above, insoluble stoichiometric IPECs, even those prepared in dilute aqueous solutions, undergo aggregation and form compact globular particles whose sizes are generally no smaller than tens of micrometers.<sup>101–103</sup>

The presence of structural defects in stoichiometric IPECs may be associated with ‘freezing’ of random interchain ion contacts, which appear in early steps of fast coupling reactions of polyions, resulting in the formation of IPEC particles as an individual phase. Then subsequent rearrangements of chains necessary for correction of defects proceed very slowly, partic-

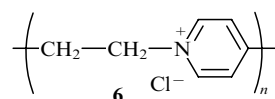
ularly in the absence of low-molecular-weight salts. Slow relaxation of non-equilibrated IPECs prepared by neutralisation of strong polyacids with strong polybases was documented.<sup>14, 103</sup> However, if factors responsible for the formation of non-equilibrium structures are excluded, for example, in the preparation of stoichiometric IPECs by polymerisation of an ionic polymer on an oppositely charged polyelectrolyte matrix, the resulting products can be rather well ordered.<sup>104–107</sup>

Generally, steric incompatibility between the interacting constituent polyelectrolytes is the main reason for the presence of structural defects in IPECs. The majority of known IPECs are coupling products of sterically irregular polyions. Such IPECs are X-ray amorphous. Studies by the ion-exchange equilibrium method demonstrated that at least 20%–30% of pairs of oppositely charged units in these IPECs are spatially separated.<sup>108</sup> In particular, even the product of the completed reaction of linear PEI with atactic PAA, whose chains are characterised by rather good steric compatibility, is X-ray amorphous. The IR spectroscopic study<sup>109</sup> demonstrated that at  $Z = 1$ , about 20% of the carboxy and imino groups in this IPEC are not involved in ion pairs but are located in structural defects. At the same time, domains of the PEI–PA interpolyelectrolyte complexes formed by contact ion pairs have, apparently, good short-range order. This is evidenced by the fact that heating of a dry PEI–PA film leads to the quantitative ‘transformation’ of the interpolyelectrolyte ion pairs into covalent amide bonds to form a ladder structure.



The carboxy and amino groups occupying defect sites are not involved in this reaction.<sup>109–111</sup>

However, the aforesaid does not mean that crystalline IPECs cannot be prepared by direct mixing of oppositely charged polyelectrolytes. In particular, IPECs, which were prepared by mixing solutions of ionene (6) and isotactic NaPA<sup>107</sup> or NaPP,<sup>112, 113</sup>



are characterised by a very high degree of crystallinity. In any case, stereoregularity and particular steric compatibility between oppositely charged polyelectrolytes are, apparently, the necessary conditions for IPEC crystallisation.

Important data on the conformations of individual chains in solid IPEC consisting of high-molecular-weight PMAK and chitosan ( $M_w = 1.9 \times 10^5$ ,  $Z = 1$ ), were obtained by small-angle neutron scattering.<sup>114</sup> A mixture of usual PMAK [PMAK(H),  $M_w = 3 \times 10^5$ ] and 2% deuterated PMAK [PMAK(D),  $M_w = 1.1 \times 10^5$ ,  $M_w/M_n = 1.25$ ] was used as the polyanion. Samples of IPEC as 0.1-mm-thick homogeneous films were prepared from solutions of polyelectrolytes in a common solvent, viz., an aqueous formic acid solution. Films formed after evaporation of the solvent were thoroughly washed with water and dried *in vacuo*, as was described in the study.<sup>115</sup> Samples of PMAK, which were used for measuring unperturbed sizes of the PMAK(D) chains, were prepared as thin films from an aqueous solution containing 2 mol.% PMAK(D) and 98 mol.% PMAK(H). In these experiments, PMAK(H) films were used as reference samples. Small-angle neutron scattering measurements were carried out in the scattering vector ( $Q$ ) range  $4 \times 10^{-5} \leq Q \leq 8 \times 10^{-4} \text{ nm}^{-1}$ , where  $Q = 4\pi(\sin\theta)/\lambda$ ,  $2\theta$  is the scan angle and  $\lambda = 3.03 \times 10^{-2} \text{ nm}$  is the average wavelength of the incident neutron beam. The spectral half-width was  $\Delta\lambda/\lambda = 0.35$ .



In the case of PMAK(D) strongly 'diluted' with PMAK(H), intramolecular interference from PMAK(D) may be ignored. Then, the Debye equation for coil-like chains

$$I(Q)^{-1} = I(0)^{-1} \left( 1 + \frac{Q^2 R_g^2}{3} \right) \quad (21)$$

is fulfilled at  $QR_g < 1$ , where  $I(Q)$  and  $I(0)$  are the scattering intensities at  $Q \neq 0$  and  $\theta = 0$ , respectively.

Since chitosan and PMAK(H) are characterised by virtually equal scattering densities, the radius of gyration of the PMAK(D) chain in IPEC was determined from Eqn (16). Figure 13 displays the plots of  $I(Q)^{-1}$  vs.  $Q^2$  for IPEC and PMAK samples at small scattering vectors  $Q$ . The observed equality of the extrapolated values of  $I(Q)^{-1}$  suggests that the contrast PMAK(D) chains in both samples are uniformly distributed and are not aggregated. For PMAK(D) in the PMAK(H) matrix,  $R_g = 10.2 \pm 0.3$  nm exactly corresponds to the expected unperturbed size. By contrast,  $R_g = 17.5 \pm 0.5$  nm for PMAK(D) in the IPEC matrix, which is indicative of a noticeable elongation of the PMAK coils interacting with chitosan. However, the shape of these elongated coils deviates only slightly from the Gaussian. Processing of the neutron scattering data for PMAK(D) in the PMAK(H) matrix (Fig. 14, curves 1 and 2) at  $QR > 5$  gives  $I(Q) \sim Q^{-2}$ , which is complete agreement with the Gaussian distribution. For PMAK(D) in the IPEC matrix,  $I(Q) \sim Q^{-2.2}$ .

Unfortunately, the above-described experiments are, to my knowledge, the only example of studies of the IPEC structure in the solid state by small-angle neutron scattering. Undoubtedly, further systematic investigations in this field will be highly informative and useful.

Air-dry amorphous IPECs in the bulk are transparent fragile materials. For most of them, water serves as a common plasticiser: IPEC films weakly swollen in water (tens of percentage at  $Z = 1$ ) are flexible and elastic. Homogeneous IPEC films can be formed from solutions of the corresponding polyelectrolytes, if their

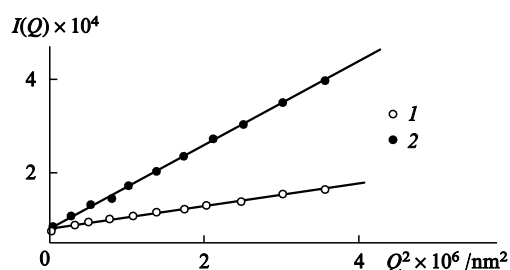


**Figure 13.** Initial regions of the small-angle neutron scattering curves for PMAK(D) in the PMAK(H) matrix (1) and for PMAK(D) in the matrix of the PMAK – chitosan interpolyelectrolyte complex (2).

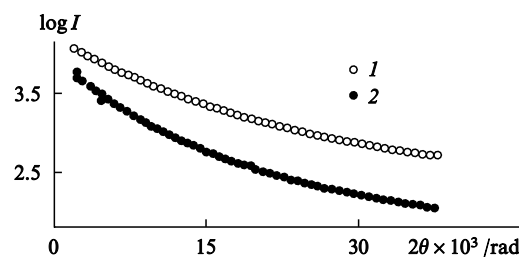
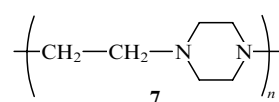


**Figure 14.** Full experimental small-angle neutron scattering curves for PMAK(D) in the PMAK(H) matrix (1) and for PMAK(D) in the matrix of the PMAK – chitosan interpolyelectrolyte complex (2).

premature electrostatic binding to each other in solution is prevented in one way or another. For a pair of strong polyelectrolytes, mixed aqueous-organic solvent containing a shielding low-molecular-weight salt (for example, NaCl or NaBr) and a volatile organic component (for example, acetone or dioxane) are used, which hinders salting-out of the polyelectrolytes from the solution. After evaporation of the mixed solvent, the films are repeatedly washed with water to remove inorganic salts.<sup>1, 15, 116</sup> In the case of weak polyelectrolytes, their premature binding in solution can be prevented by shifting pH for a time from the stability range of IPEC to an acidic or basic region (see Fig. 1). This is achieved by adding a volatile acid (for example, formic or acetic acid) or a volatile base (for example, ammonia or trimethylamine).<sup>115</sup>

The mechanical properties of IPECs formed by pairs of strong polyelectrolytes have not been studied systematically. However, it was noted that the most strong water-swelling IPEC films, which were tested as potential ion-exchange and separating membranes for salting-out of water, are formed at  $Z = 1$ , *i.e.*, when the maximum number of interpolyelectrolyte salt bonds per unit volume are present.<sup>1</sup>

A more complex situation occurs with IPEC membranes involving weak polyelectrolytes,<sup>115</sup> in particular, poly(ethylenepiperazine) (7) (PEP,  $M_n = 3 \times 10^5$ ) and PAA ( $M_n = 3 \times 10^5$ ).



Their mechanical properties were studied in detail.<sup>117</sup> Films of different compositions  $Z = [\text{PAA}]/[\text{PEP}]$  were prepared from 50% aqueous formic acid. Load – deformation curves describing the viscoelastic properties of equilibrium swollen films of PAA – PEP interpolyelectrolyte complexes of composition  $Z \geq 1$  immersed in aqueous solutions are presented in Fig. 15a. The majority of water-swollen PECs are characterised by analogous

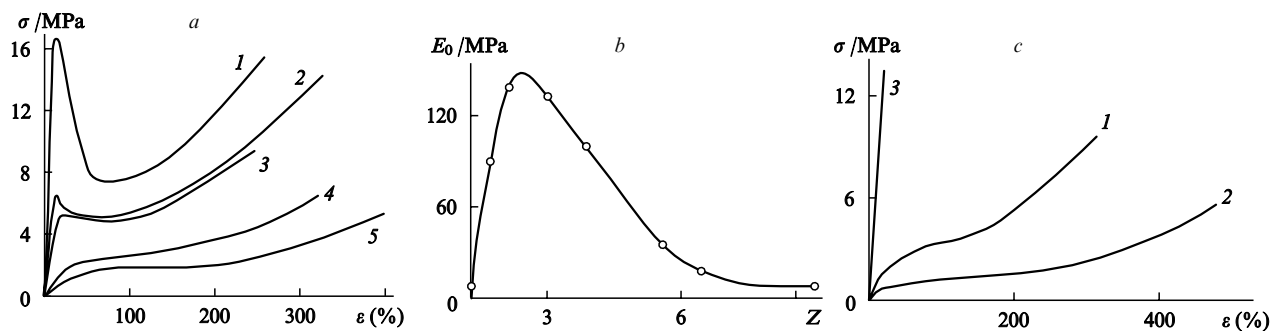


**Figure 15.** Viscoelastic properties of the PAA – PEP interpolyelectrolyte complexes;

(a) load – deformation curves for IPECs of various compositions in an aqueous solution, pH 6.0,  $T = 20^\circ\text{C}$ ;  $Z = [\text{PAA}]/[\text{PEP}] = 2$  (1), 1.5 (2), 5 (3), 7 (4), 1 (5); (b) the plot of the initial Young's modulus of IPEC vs. the composition; (c) load – deformation curves for IPEC ( $Z = 1$ ) in water (1), an aqueous NaCl solution (5 mass %) (2) and dioxane (3).

load–deformation curves. However, in contrast to IPECs consisting of a pair of strong polyelectrolytes, the maximum rupture stress (Fig. 15a) and Young's modulus (Fig. 15b) are observed at  $Z = 2$  rather than at  $Z = 1$ . In other words, PAA-rich films are most strong. The minimal equilibrium degree of swelling corresponds to the same composition ( $\sim 35\%$ ). At  $Z < 1$ , the strength of the films is even smaller than that at  $Z = 1$ . Undoubtedly, the role of intermolecular salt bonds, which reinforce a film structure, in these materials is as important as in IPECs formed by strong polyelectrolytes. In particular, this is evident from a consideration of the load–deformation curves presented in Fig. 15c. It can be seen that a sample, which was initially immersed in a solution of a low-molecular-weight salt responsible for shielding of salt bonds between the oppositely charged polyions and then tested in the same medium, is characterised by much smaller initial Young's modulus and yield stress. At the same time, the replacement of water with a water–dioxane mixture or pure dioxane leads to substantial strengthening of IPEC films due to an increase in stability of the ion pairs as a result of a decrease in the polarity of the medium. Nevertheless, analysis of the mechanical behaviour of PAA–PEP films containing excess PAA demonstrates that additional hydrogen bonds also contribute substantially to stabilisation of the IPEC structure. For example, the initial Young's moduli of films of PAA–PEP interpolyelectrolyte complexes decrease with increasing temperature (Fig. 16). For PAA-rich IPECs, the Young's moduli decrease more substantially and are characterised by more pronounced cooperativity.

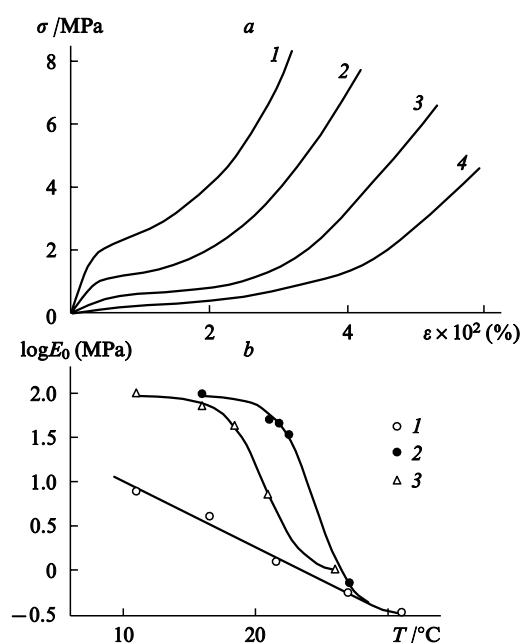


**Figure 16.** Temperature dependence of the viscoelastic properties of the PAA–PEP interpolyelectrolyte complexes in an aqueous solution, pH 6.0; (a) load–deformation curves measured at 10 (1), 20 (2), 30 (3), 40 °C (4); (b) the temperature dependence of the initial Young's modulus,  $Z = 1$  (1), 3 (2), 5 (3).

## V. Conclusion

Vital functions of any complex biological construction were determined not only by precisely programmed molecular structures of the starting constituent biopolymers but also by the controlled mechanisms of their self-assembly and reorganisation. The structures of supramolecular biological particles are formed as a result of establishment of balance between superimposed

multipoint interactions, some of them being oppositely directed (hydrogen, hydrophobic and donor–acceptor bonds, electrostatic attraction and repulsion). Hence, along with retention of extraordinary stability under particular conditions, biological structures can undergo rearrangements and substantial reorganisation even upon insignificant changes in the environmental medium. These characteristic features are, to some extent, typical also of IPECs constructed from synthetic polyelectrolytes. The phenomena, characteristic features and their interpretation presented in this review may be useful in controlling the synthesis, structure and properties of IPECs prepared for various technical and biomedical applications.

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<sup>a</sup> — *Polym. Sci. (Engl. Transl.)*

<sup>b</sup> — *Pharm.-Chem. J. (Engl. Transl.)*

<sup>c</sup> — *Dokl. Chem. (Engl. Transl.)*

<sup>d</sup> — *Mol. Biol. (Engl. Transl.)*

<sup>e</sup> — *Colloid. J. (Engl. Transl.)*

# Subcritical and supercritical water: a universal medium for chemical reactions

A A Galkin, V V Lunin

## Contents

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**Abstract.** The results of studies on the properties of subcritical and supercritical water are generalised. The possibility of using such water as a solvent, a reagent or a catalyst in chemical reactions is considered. Primary attention is paid to specific features of experimental research under hydrothermal conditions. Prospects for use of subcritical and supercritical water in heterogeneous catalysis for the preparation of nanocrystalline materials with predictable properties and for solving environmental problems are discussed. The bibliography includes 208 references.

## I. Introduction

Over billions of years subcritical and supercritical water has been involved in the formation of ores and minerals in Earth's depths.<sup>1</sup> The beginning of research on supercritical fluids dates back to 1822. At that time, experiments with different solvents at high temperatures and pressures were first carried out by Cagniard de la Tour who discovered the critical points of substances.<sup>2</sup> The supercritical state of a substance is a state characterised by the disappearance of distinctions between the liquid and gaseous phases. In the nineteenth century, the development of chemistry of supercritical fluids was not so rapid. It was not until 1896 that Villard reported the first detailed review concerning the properties of a group of substances in the supercritical state.<sup>2</sup> In the twentieth century, environmental safety problems and improvement of the efficiency of chemical plants became topical. Because of this, interest increased in studying the properties of substances in the supercritical state. At present, the unique physicochemical properties of supercritical fluids are widely used in extraction and chromatographic separation of substances, in production of various materials and detoxification of liquid waste.<sup>2–4</sup> In addition, intensive research has been carried out on the possibility of using supercritical fluids in organic and inorganic synthesis and in homogeneous and heterogeneous catalysis.<sup>5–9</sup> Table 1 lists the critical parameters, *viz.*, the critical temperature ( $T$ ), pressure ( $P$ )

and density ( $\rho$ ) of the most widely used solvents. The scatter of the numerical values of these parameters for different substances is rather large, from nearly 282 K and 5 MPa for ethylene to almost 647 K and 22 MPa for water.

**Table 1.** Critical point parameters of solvents.<sup>5, 10</sup>

| Solvent                          | $T$ /K | $P$ /MPa | $\rho$ /kg m <sup>-3</sup> |
|----------------------------------|--------|----------|----------------------------|
| C <sub>2</sub> H <sub>4</sub>    | 282.1  | 5.041    | 214                        |
| Xe                               | 289.5  | 5.840    | 1110                       |
| CO <sub>2</sub>                  | 303.9  | 7.375    | 468                        |
| C <sub>2</sub> H <sub>6</sub>    | 305.2  | 4.884    | 203                        |
| N <sub>2</sub> O                 | 309.4  | 7.255    | 452                        |
| NH <sub>3</sub>                  | 405.3  | 11.350   | 235                        |
| C <sub>2</sub> H <sub>5</sub> OH | 513.7  | 6.137    | 276                        |
| H <sub>2</sub> O                 | 646.9  | 22.060   | 322                        |

Chemistry of subcritical and supercritical fluids belongs to the most rapidly progressing fields of chemical science. To date, a great body of experimental data on the properties of tens of substances at near-critical temperatures and pressures has been accumulated. Research on the properties of subcritical and supercritical water and on processes involving this substance occupies a particular place. It should be noted that supercritical water is still of limited use due to the high critical point parameters (see Table 1). However, one should keep in mind that water is the most abundant, cheap, safe and environmentally pure solvent. Because of this, water seems to be of crucial importance for further development of the chemistry of supercritical fluids.

This review summarises the available results obtained in basic and applied studies on the properties of subcritical and supercritical water and corresponding chemical processes. We present a consistent treatment of the physicochemical properties of water at elevated temperatures and pressures, experimental features and problems posed when using subcritical and supercritical water and the possibilities of using subcritical and supercritical water as a solvent, reagent and catalyst of inorganic and organic chemical reactions. The emphasis is placed on the prospects for application of subcritical and supercritical water in heterogeneous catalysis, in the fabrication of nanocrystalline materials with predictable properties and in solving the environmental pollution problem, which belongs to the most important problems of modern times.

**A A Galkin, V V Lunin** Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax (7-095) 939 45 75, tel. (7-095) 939 33 22, e-mail: galkin@kge.msu.ru (A A Galkin), tel. (7-095) 939 45 75, e-mail: vvlunin@kge.msu.ru (V V Lunin)

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## II. Physicochemical properties of subcritical and supercritical water

At a temperature of 295 K and a pressure of 0.1 MPa, water is a polar solvent with a density of  $1000 \text{ kg m}^{-3}$ , a dielectric constant,  $\epsilon$ , of 79.73 and an ionic product,  $K_w$ , of  $10^{-14}$  (see Ref. 11). Raising the temperature and pressure causes significant changes in the properties of water and aqueous solutions. Changes in the thermodynamic parameters are reflected in the phase diagrams of water and corresponding multicomponent systems. The properties of water, as a solvent, vary owing to variation of its dielectric constant, conductivity, ionic product and the structure of the H bond network. Changes in the viscosity, heat capacity, diffusion coefficients and density influence the transport characteristics of aqueous solutions.

It should be noted that the physicochemical properties of water at the critical point are changed continuously rather than in stepwise manner. The characteristics of supercritical water are intermediate between those of the liquid and gas (Table 2).

**Table 2.** Characteristics of water under different conditions.

| Characteristic                                                   | Water under normal conditions | Supercritical water   | Super-heated steam    |
|------------------------------------------------------------------|-------------------------------|-----------------------|-----------------------|
| $T/\text{K}$                                                     | 298                           | 723                   | 723                   |
| $P/\text{MPa}$                                                   | 0.1                           | 27.2                  | 1.4                   |
| $\rho/\text{kg m}^{-3}$                                          | 998                           | 128                   | 4.19                  |
| $D/\text{m}^2 \text{ s}^{-1}$ (see <sup>a</sup> )                | $7.74 \times 10^{-8}$         | $7.67 \times 10^{-6}$ | $1.79 \times 10^{-5}$ |
| Thiele modulus                                                   | 2.82                          | 0.0284                | 0.0122                |
| $\epsilon$                                                       | 78                            | 1.8                   | 1.0                   |
| $-\log K_w$                                                      | 14                            | 21                    | 41                    |
| Solubility of $\text{O}_2/\text{C}_x\text{H}_y/\text{kg m}^{-3}$ | $8 \times 10^{-3}/?$          | $\infty/\infty$       | $\infty/?$            |

<sup>a</sup> Diffusion coefficient.

### 1. The density

At subcritical temperatures and pressures, water can exist in the liquid and gaseous states (Fig. 1). Under isothermal conditions,

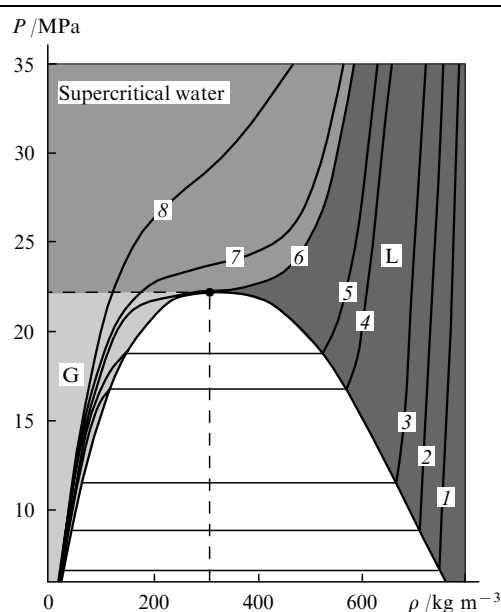


**Figure 1.** Phase diagram of water at elevated temperatures and pressures.  $T/\text{K}$ : 553 (1), 573 (2), 593 (3), 623 (4), 633 (5), 647 (6), 653 (7) and 673 (8); G is gas and L is liquid.

the density of water changes continuously in both phases; a density jump occurs only at the gas–liquid interface. At the critical point, this interface disappears and the density of water becomes equal to nearly  $300 \text{ kg m}^{-3}$ . However, in the near-critical region water is characterised by an infinite compressibility, which allows the density of water to be changed over a very wide range by (only slightly) varying the temperature and pressure. For instance, the density of water is halved as the temperature increases by only 6 K at a pressure of 22 MPa.<sup>12</sup> A supercritical water density of  $1000 \text{ kg m}^{-3}$  can also be achieved; however, this requires a pressure of 750 MPa to be applied at 673 K.<sup>13</sup>

Carrying out chemical reactions in aqueous solutions usually requires control of the reagent concentrations, temperature and pressure. On going to subcritical and supercritical water one should also control the density of the medium because minor variations of this parameter can significantly influence the rate constants for reactions and the distribution of reaction products.<sup>10, 14</sup> The reason is that some characteristics of water, *e.g.*, the dielectric constant, ionic product, viscosity and thermal conductivity change in parallel with the density. Using controllable variation of the density of subcritical and supercritical water, one can vary the properties of water, as a solvent, and control the physicochemical processes proceeding in the medium.

### 2. The dielectric constant and ionic product

The temperature dependence of the ionic product of water measured at a constant pressure exhibits an extremum (Fig. 2). In the subcritical region the ionisation constant of  $\text{H}_2\text{O}$  reaches a maximum value, which is three orders of magnitude higher than the value typical of normal conditions. Therefore, subcritical water is a rich source of  $\text{H}^+$  and  $\text{OH}^-$  ions (see Ref. 15); in other words, it can serve not only as a polar solvent but also as a self-neutralising acid–base catalyst. This offers great prospects for carrying out various catalytic reactions and hydrolysis in the subcritical region. As the critical point is approached, the parameter  $\log K_w$  abruptly decreases and then monotonically decreases in the supercritical region (see Fig. 2).

The dielectric constant of water measured at a constant pressure continuously decreases as the temperature increases. At  $T = 573 \text{ K}$  and a density of  $700 \text{ kg m}^{-3}$ , the dielectric constant of water is four times lower than that of acetone.<sup>10</sup> Supercritical water can be treated as a non-polar ‘organic’ solvent because its dielectric constant approaches a value of six.<sup>16</sup>

It should be noted that the subcritical and supercritical states of water are usually attained in various units of steam and nuclear power plants. Corresponding technological processes are thoroughly controlled. Therefore, a great body of experimental data on the properties of water at elevated temperatures and pressures was accumulated. Treatment of these data allowed the equations

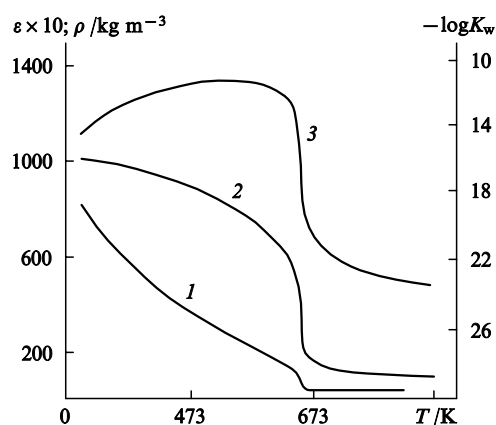


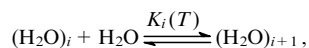
**Figure 2.** Temperature dependences of the dielectric constant (1), density (2) and ionic product of water (3) at a pressure of 24 MPa.



for calculation of the ionic product and dielectric constant of water over wide ranges of temperature and pressure to be derived.<sup>17,18</sup>

### 3. Hydrogen bonds

Under normal conditions all water molecules are interconnected by a network of hydrogen bonds. This provides an explanation for many physicochemical properties of water. Association of water molecules leading to formation of hydrogen bonds can be described by the following reaction:



where  $i = 1, 2, \dots, \infty$  and  $K_i$  is the equilibrium constant for association.

At room temperature and atmospheric pressure, the  $(\text{H}_2\text{O})_{i+1}$  aggregates can comprise up to 100 molecules.<sup>19</sup> The formation of hydrogen bonds is an exothermic process; therefore, the equilibrium constant  $K_i$  decreases as the temperature increases.<sup>10</sup> Near the critical point the structure of water changes significantly, namely, an infinite network of hydrogen bonds is destroyed and water exists as separate clusters with a chain structure.<sup>20</sup> In the supercritical region, molecules within these clusters remain hydrogen bonded. At 673 K and a water density of  $850 \text{ kg m}^{-3}$ , up to 50% of the total amount of hydrogen bonds are broken.<sup>21</sup> A computer simulation showed that the number of water molecules in the clusters strongly depends on the density of the supercritical fluid. For instance, in the low density region ( $T = 673 \text{ K}$ ,  $\rho = 167 \text{ kg m}^{-3}$ ) water clusters comprise up to ten molecules, but as the density increases ( $T = 772 \text{ K}$ ,  $\rho = 528 \text{ kg m}^{-3}$ ), the number of molecules in certain clusters can exceed twenty. At a high density of supercritical water ( $T = 680\text{--}771 \text{ K}$ ,  $\rho = 972\text{--}1284 \text{ kg m}^{-3}$ ), all molecules are again interconnected by hydrogen bonds, but there are also a few clusters comprised of less than fifteen molecules that temporarily are not involved in the common infinite network of H bonds.<sup>20</sup>

It is this breakdown of hydrogen bonds on going to the critical point that is responsible for the decrease in the dielectric constant, changes in the dynamic viscosity and an increase in the self-diffusion coefficient of water.<sup>22</sup> Indeed, for a molecule in a liquid to be mobile, free space and weakened interactions with neighbouring molecules are needed. Water molecules not involved in the system of hydrogen bonds are more mobile; this is responsible for the increase in the self-diffusion coefficient of water.

### 4. Solubility of substances in subcritical and supercritical water

The solubility of inorganic and organic compounds in subcritical and supercritical water is governed by the dielectric constant of the medium. A decrease in the dielectric constant on going to the critical point causes an increase in the solubility of organic compounds and a decrease in the solubility of inorganic ionic compounds. Supercritical water can be mixed with oxygen, hydrogen and hydrocarbons in any proportion. Generally, the solubility of substances in water increases with temperature (provided a constant density of water) and with pressure (under isothermal conditions). Since slight variations of the state parameters near the critical point lead to significant changes in all physicochemical characteristics of water, even minor changes in the pressure and temperature can result in complete dissolution or, contrarily, precipitation of oxides and salts from solutions.<sup>1,2</sup>

In the supercritical state, water molecules are clustered round the solute molecules; this causes local density fluctuations. On adding a substance, the density of the system near the critical point can increase to such an extent that the molar volume of the solute decreases by one or two orders of magnitude.<sup>23</sup>

A decrease in the dielectric constant of water at elevated temperature and pressure is responsible for significant changes in the structure of electrolyte solutions. Namely, under subcritical and supercritical conditions water molecules cannot efficiently

screen ions; therefore, rearrangement of hydration shells and ion pairing occur.<sup>24–26</sup> For instance, nearly 50% of water molecules are lost in the first hydration shell of the  $\text{Ni}^{2+}$  ion in a nickel bromide solution at 698 K and 69 MPa.<sup>24</sup> If under normal (not critical) conditions nickel ions in aqueous solutions are octahedrally coordinated by water molecules (coordination number equals six), in supercritical water the  $\text{H}_2\text{O}$  molecules in the hydration shell are replaced by bromide anions and there are only 2.5 water molecules per  $\text{Ni}^{2+}$  cation. A similar ‘ion dehydration’ effect in supercritical water was also observed in sodium chloride<sup>25,27</sup> and strontium nitrate and zinc nitrate solutions.<sup>26,28</sup> A Raman spectroscopy study showed that replacement of water molecules in the hydration shells of ions under near-critical conditions leads to appreciable strengthening of cation–anion interactions and the number of ion pairs (here, cations are tightly bound to anions) increases.

A decrease in the number of water molecules surrounding an ion usually facilitates ion diffusion.<sup>29</sup> However, considering the conductivity of electrolyte solutions in the supercritical region, one should take into account two competing factors, *viz.*, the number of water molecules in the hydration shell of the ion and the strength of the interaction between the ion and water molecules. The former factor dominates in the high-density region while the latter dominates at low density of supercritical water. Because of this, the electric conductivity plots for electrolyte solutions can exhibit extrema.<sup>29</sup>

### 5. Multicomponent systems

Efficient use of subcritical and supercritical water in various chemical and technological processes is impossible without investigating the phase diagrams of corresponding multicomponent systems. First of all, this is necessary in order to determine the temperatures, pressures and component concentrations corresponding to a monophasic system. Indeed, operation with a homogeneous medium allows one to avoid the diffusion-related difficulties associated with mass transfer through the interface. For instance, the rate constant for cellulose hydrolysis increases abruptly on going from subcritical to supercritical water, thus providing an explanation for the transition from a heterogeneous to homogeneous reaction.<sup>30</sup>

Adding substances to water significantly complicates the water phase diagram. Phase equilibria studies in multicomponent systems near the critical point of water face some experimental problems; for this reason, computer simulation is often used.

To date, tens of phase diagrams of binary and ternary systems such as  $\text{H}_2\text{O} - \text{C}_x\text{H}_y$ ,<sup>13,23,31–33</sup>  $\text{H}_2\text{O} - \text{CO}_2$ ,<sup>13</sup>  $\text{H}_2\text{O} - \text{O}_2$ ,<sup>34</sup>  $\text{H}_2\text{O} - \text{NaCl}(\text{NaOH}, \text{KCl})$ ,<sup>35</sup>  $\text{H}_2\text{O} - \text{CH}_4 - x\text{F}_x$ ,<sup>36</sup>  $\text{H}_2\text{O} - \text{Na}_2\text{SO}_4$ ,<sup>37</sup>  $\text{CF}_4(\text{CHF}_3) - \text{H}_2\text{O} - \text{NaCl}$ <sup>36</sup> and  $\text{NaCl} - \text{Na}_2\text{SO}_4 - \text{H}_2\text{O}$ <sup>38</sup> are available. All phase equilibria at high temperatures and pressures can be described by five schematic phase diagrams which were considered in detail in Ref. 2.

In practice, it is convenient to use projections of the  $P - T - x$  diagrams on the  $P - T$  plane. Figure 3 presents the critical curves (lines connecting the critical points of individual components) plotted in the  $P - T$  coordinates for a number of binary systems.<sup>13</sup> If water and the second component have similar properties (as is the case of, *e.g.*, the system  $\text{H}_2\text{O} - \text{NH}_3$ ), the critical curve connecting the critical points of the two pure components in the  $P - T$  diagram is continuous. If the polarity of the solute differs appreciably from that of water, the critical curve will consist of two portions. The upper portion issues from the critical point of the pure component with the higher boiling temperature and then the curve goes either to the region of high pressures and temperatures (as for the systems  $\text{H}_2\text{O} - \text{Ar}$  and  $\text{H}_2\text{O} - \text{H}_2$ ) or initially to the low-temperature region and then, after passing through a minimum, to the region of high temperatures and pressures (as for the systems  $\text{H}_2\text{O} - \text{C}_6\text{H}_6$  and  $\text{H}_2\text{O} - \text{CO}_2$ ). Adding an electrolyte to water appreciably shifts the critical point of water.

The critical curves bound the homogeneity region of binary systems, namely, above the critical curve we deal with a mono-

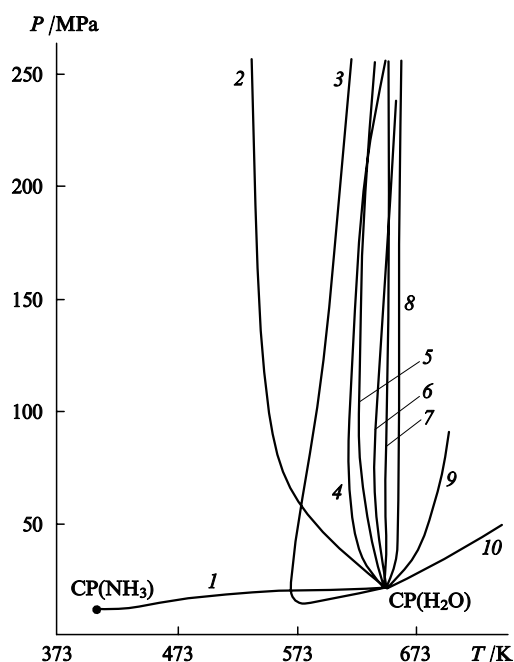


**Figure 3.** Critical curves for binary systems  $\text{NH}_3\text{--H}_2\text{O}$  (1),  $\text{CO}_2\text{--H}_2\text{O}$  (2),  $\text{C}_6\text{H}_6\text{--H}_2\text{O}$  (3),  $\text{Xe--H}_2\text{O}$  (4),  $\text{CH}_4\text{--H}_2\text{O}$  (5),  $\text{N}_2\text{--H}_2\text{O}$  (6),  $\text{H}_2\text{--H}_2\text{O}$  (7),  $\text{Ar--H}_2\text{O}$  (8),  $\text{HCl--H}_2\text{O}$  (9) and  $\text{NaCl--H}_2\text{O}$  (10).<sup>13</sup> CP( $\text{H}_2\text{O}$ ) and CP( $\text{NH}_3$ ) are the critical points of water and ammonia, respectively.

phase system. At  $T > 673$  K, all hydrocarbons, hydrogen and oxygen can be mixed with supercritical water in any proportion. In particular, adding oxygen to a water–methane (70% : 30%) mixture can lead to combustion ( $T = 723$  K,  $P = 100$  MPa); under these conditions, electrolysis of supercritical water can proceed without formation of the gas phase on electrodes.<sup>13</sup>

## 6. Homogeneous and heterogeneous catalysis

Among the most promising application avenues of subcritical and supercritical water are homogeneous and heterogeneous catalyses. Recently, a few reviews concerning the use of supercritical fluids in catalysis were published.<sup>5,9,39</sup> Unfortunately, subcritical and supercritical water is of limited use in the field so far. We would like to point out some advantages of the use of water in the near-critical region in various catalytic processes. Subcritical and supercritical water can serve as:

- a non-toxic solvent whose physicochemical properties can be ‘tuned’ in an optimised fashion to perform particular catalytic reactions;
- an efficient acid–base catalyst in homogeneous catalysis;
- a reagent and/or medium for preparing nanocrystalline heterogeneous catalysts with specified properties.

All these functions will be discussed below taking particular reactions and processes as examples.

It is convenient to consider the advantages of using supercritical water in catalysis taking a hypothetical heterogeneous reaction of gas A with liquid B on the surface of catalyst C as an example.<sup>5</sup> Figure 4 presents the concentration profiles of gas A for the same reaction carried out in water under normal conditions and in supercritical water. In the former case we deal with a ternary system ‘gas + liquid + solid catalyst’ (Fig. 4a).

The concentration profile of gas A for the same reaction in supercritical water is quite different (Fig. 4b). In this case, the gas and the liquid can be mixed in any proportion and we deal with a binary system ‘supercritical fluid + solid catalyst’. Now, diffusion-related problems associated with mass transfer at the gas–liquid interface (processes 1 and 2) are absent. In addition, diffusion of reagents towards the supercritical fluid/catalyst inter-

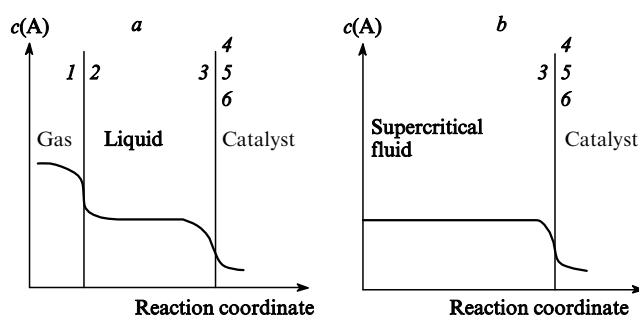


**Figure 4.** Concentration profiles of gas A in the course of a heterogeneous catalytic reaction carried out in water under normal conditions (a) and in supercritical water (b).<sup>5</sup>

Process: gas diffusion towards the gas/liquid interface (1), gas adsorption at the interface and gas diffusion in the bulk of the liquid (2), gas diffusion and liquid diffusion towards the liquid/catalyst interface (3), gas diffusion and liquid diffusion in the porous structure of catalyst (4), gas adsorption and liquid adsorption at the surface of the catalyst (5) and reaction between the gas and liquid molecules at the surface of the catalyst, desorption of reaction products and their diffusion in the bulk of the liquid phase (6).

face and in pores of the catalyst (processes 3 and 4) proceeds much faster owing to the low viscosity of supercritical water. Thus, the catalytic reaction in the supercritical water proceeds in the kinetic region and its rate and, hence, selectivity can be controlled by varying the temperature and pressure. Probably, the poisoning and coking rates of the catalyst in supercritical water will be much lower due to the low viscosity of the medium, shorter time of contact between reagents and the surface of catalyst and high diffusion coefficients of reagents and reaction products.<sup>40</sup>

The activity and selectivity of heterogeneous catalysts are complex functions of their chemical compositions and the morphology and macrostructure parameters. Structure imperfection, state of the surface, nature of active centres and the concentration and distribution of impurity phases are governed by the synthesis conditions and heat treatment regime of the catalyst. The use of subcritical and supercritical water for preparing catalysts is quite promising for the design of new efficient nanocrystalline catalytic systems and for modification of the properties of traditional catalysts and supports.<sup>41–44</sup>

## III. Specific features of experimental research using subcritical and supercritical water

Experiments with water at elevated temperatures and pressures require taking particular care and use of tailor-made equipment suitable for operation under extreme conditions. The end products of hydrothermal synthesis as well as the rates and selectivities of processes in subcritical and supercritical water are to a great extent determined by not only the properties of water but also the experimental technique, reactor material, being also dependent on the accuracy of maintenance of the specified temperature (pressure) and other parameters.

### 1. Batch and flow reactors

Reactions in subcritical and supercritical water can be carried out in batch and flow reactors. The simplest batch reactor is an autoclave placed inside a powerful heater and connected to temperature and pressure transducers (Fig. 5). In most cases the pressure in the batch reactor depends on the water filling degree; however, it can also be maintained using an external compressor or a pump. Reactions in these reactors can proceed both isothermally and under temperature gradient conditions.<sup>45</sup>

The vast majority of the studies on subcritical and supercritical media were carried out in batch reactors. However, from our point of view, this reactor design is for some reasons



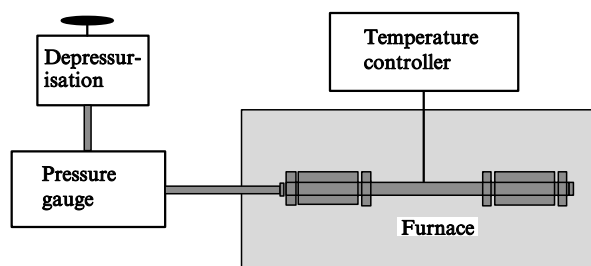


Figure 5. Scheme of a batch reactor.

inappropriate for experimental research. For instance, if a reaction is followed by a release of gaseous products, it is difficult to maintain the density of the medium at a constant level in the batch reactor. Target organic synthesis in these systems is nearly impossible because variations of the reagent and product concentrations in the course of experiments can change the mechanisms of the processes occurring in the system, thus making the interpretation of the results obtained more difficult.

Batch reactors are appropriate only for carrying out recrystallisation processes and obtaining single crystals and minerals.<sup>46</sup> All other experiments in subcritical and supercritical water can be more conveniently performed in highly efficient flow systems that are also easy to control. In addition, laboratory flow systems can be scaled with ease to commercial plant level.

A scheme of a typical experimental flow system for operation with subcritical and supercritical water is shown in Fig. 6. Using a high pressure pump, water is continuously supplied to the system of powerful heaters at a specified rate and is heated to the desired temperature. A solution of reagents is continuously supplied to the system using the second pump. Mixing of the two flows at the inlet of the reactor is followed by physicochemical transformations of the reagents in subcritical and supercritical water. After passage through the reactor the reaction mixture is cooled to room temperature and then collected at the system's outlet. The pressure in the reactor is maintained by a back pressure regulator. If needed, one can use additional pumps for separate supply of several reagents to the reactor. For instance, oxidation reactions of organic compounds in supercritical water can be designed in such a way that one pump will supply the organic compound and the other pump will supply the oxidiser, *e.g.*, hydrogen peroxide.

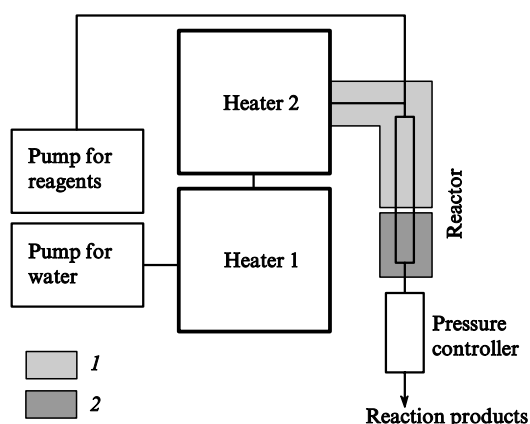


Figure 6. Scheme of an experimental flow reactor for operation with subcritical and supercritical water. Heating zone (1) and cooling zone (2).

The duration of a reaction in a flow reactor ( $\tau$ ) depends on the specific volume of water under the experimental conditions ( $v/\text{m}^3 \text{ kg}^{-1}$ ), on the reaction mixture consumption ( $M_f/\text{kg s}^{-1}$ ) and on the volume of the reaction zone ( $V/\text{m}^3$ )

$$\tau = \frac{V}{M_f v}.$$

Typically, the duration,  $\tau$ , is of the order of a few seconds for a flow reactor,<sup>43</sup> being much shorter than for the batch reactors.

Near the critical point the heat capacity of water tends to infinity; therefore, powerful heaters are needed to attain the supercritical state. These can be conventional electric furnaces as well as other heat sources, *e.g.*, microwave radiators.<sup>47</sup>

To establish the mechanisms of the reactions proceeding in subcritical and supercritical water, it is of great interest to study processes *in situ* using various spectral methods. To this end, the reactor can be equipped with a tailor-made optical cell suitable for operation under hydrothermal conditions.<sup>7, 48</sup>

When carrying out reactions in flow systems, the possibility of reactor blockage due to precipitation of various substances (*e.g.*, inorganic salts and oxides) should be taken into account.<sup>49</sup> In order to avoid reactor blockage, it is appropriate to periodically pass a solvent through the reactor to remove organic and inorganic sediments.<sup>50</sup>

Extraction processes used in household and industrial waste management and in modification of the properties of various systems involve treatment of solid materials with subcritical and supercritical water, which can hardly be done in flow reactors. Specific pumps for operation with aqueous suspensions function only if solid particles have a particular size. To solve this problem, a system was designed with simultaneous supply of the solid phase and subcritical or supercritical water to the batch reactor.<sup>51</sup> After a specified time the reaction products are removed from the reactor and a new portion of reagents is supplied to the system. This design combines the advantages of the flow and batch reactors.

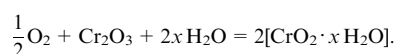
## 2. Corrosion problem

Perhaps, the most complicated problem in operating with subcritical and supercritical water is corrosion of experimental setups. Even deionised supercritical water is a highly corrosive medium, which causes destruction of the alloys the reactors are made of.<sup>52</sup> When performing chemical reactions involving organic and inorganic substances under hydrothermal conditions, researchers deal with oxidant, salt, acid and base solutions that are corrosive media even under normal conditions. In this connection, the search for materials that are corrosion stable at high temperatures and pressures is a topical problem in chemistry of subcritical and supercritical water.<sup>53, 54</sup>

Corrosion studies<sup>52, 54–62</sup> of various materials in subcritical and supercritical water showed that stainless steel, nickel alloys, titanium, tantalum, noble metals and ceramics undergo severe destruction in the presence of salts, acids or gases.<sup>61</sup>

The mechanism of water corrosion at high temperatures and pressures is somewhat different from the conventional water corrosion mechanism. Electrochemical corrosion usually involves two or more conjugated redox reactions on different sides of the corroding metal. The low conductivity of supercritical water hampers ion transfer between the centres of the conjugated redox reactions; therefore, in this case corrosion is a result of the one-step reaction of, *e.g.*, oxygen or HCl with the metal.<sup>58</sup>

The corrosion stability of many metals and alloys is due to the formation of passivating oxide films on their surfaces. However, metal oxides become reactive in supercritical water. For instance,  $\text{Cr}_2\text{O}_3$  is dissolved to give chromic acid<sup>57</sup>



Because of this, chromium and some Cr-based alloys corrode in supercritical water. Only the G-30 alloy (29.4% Cr, 40.1% Ni, 14.5% Fe, 5.1% Mo, 2.9% W + Co + Cu) exhibits a high corrosion stability against aqueous solutions containing oxygen and chloride ion at 693 K and a pressure of 40 MPa.<sup>60</sup>

Sometimes, in order to avoid corrosion, the inside of metallic reactors is covered with ceramics. However, often this does not make the situation better, because out of more than thirty investigated ceramic materials only pure alumina and  $\text{Al}_2\text{O}_3\text{--ZrO}_2$  ceramics did not severely corrode in supercritical water containing hydrogen peroxide and hydrochloric acid.<sup>59</sup>

#### IV. Hydrothermal synthesis of nanocrystalline oxide materials

Recently, interest in nanocrystalline materials has been growing increasingly because of the unique physicochemical properties of these objects. It was established that the majority of the properties of solids become size-dependent as the particle size decreases down to a few interatomic distances in one, two or three dimensions. Nanocrystalline metallic and oxide powders with specified morphologies, phase compositions and properties of the bulk phase and the surface are needed to produce a variety of new generation materials such as sensors, semiconductors, fuel cells, high-density ceramics, efficient heterogeneous catalysts and sorbents.

At present, nanocrystalline materials are obtained using the sol–gel technique, codeposition, hydrolysis of alkoxides, organometallic synthesis, pyrolysis, gas-phase methods and detonation synthesis. Most of the methods mentioned above involve a number of stages and are labour-consuming, which complicates the wide use of nanocrystalline materials (even well-studied materials!) in technological processes. In this connection development of new, high-performance methods of fabrication of nanomaterials becomes topical.

Among the most promising methods of fabrication of oxide nanocrystalline materials is hydrothermal synthesis (a heterogeneous reaction in water at  $T > 373$  K and  $P > 0.1$  MPa).<sup>45</sup> When synthesising various oxides, the reaction conditions can be varied over a wide range, *i.e.*, it is possible to carry out hydrothermal synthesis both under mild conditions at moderate temperatures and pressures<sup>47, 63</sup> and in supercritical water.<sup>8, 43</sup> The hydrothermal method is used to obtain nanocrystalline oxide powders with specified particle sizes and phase compositions and well-developed specific surface area, which often cannot be attained using conventional techniques. The method also permits preparation of nanocrystalline metastable phases that cannot be synthesised under normal conditions.<sup>64, 65</sup>

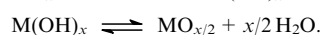
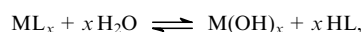
For a long time, single crystals and minerals were mainly obtained by hydrothermal synthesis in batch reactors. The authors of most recent studies on the synthesis of nanocrystalline simple and complex oxide systems in subcritical and supercritical water [*e.g.*, solid solutions with fluorite structures  $\text{Ce}_{1-x}\text{M}_x\text{O}_{2-\delta}$  ( $\text{M} = \text{Eu}, \text{Sm}, \text{La}, \text{Pr}, \text{Ca}, \text{Sr}, \text{Gd}, \text{Y}$ ),<sup>66–70</sup>  $\text{ZrO}_2\text{--CaO}$  (see<sup>71</sup>) and  $\text{ZrO}_2\text{--Y}_2\text{O}_3$ ,<sup>72</sup> perovskites  $\text{BaTiO}_3$ ,  $\text{SrTiO}_3$  and  $(\text{Ba}_{1-x}\text{Sr}_x)\text{TiO}_3$ ,<sup>73–75</sup> simple oxides  $\text{HfO}_2$ ,<sup>76</sup>  $\text{Y}_2\text{O}_3$ ,<sup>77</sup>  $\text{ZnO}$ ,<sup>78</sup>  $\text{Cu}_2\text{O}$  and  $\text{CuO}$ ,<sup>43, 79</sup>  $\text{Fe}_3\text{O}_4$ ,<sup>80</sup>  $\text{CeO}_2$ ] also used batch reactors.<sup>81</sup> These nanocrystalline oxide materials often comprise a number of phases and are characterised by a nonuniform particle size distribution, which is due to the difficulties of control of the experimental conditions in batch reactors. According to published data, the synthesis can take from a few minutes<sup>79</sup> to several days;<sup>72</sup> often, no explanation is given for the choice of a certain duration of the reaction.

To the best of our knowledge, current research on the synthesis of nanocrystalline oxide materials using subcritical and supercritical water in flow reactors is carried out at three research centres, namely, at the Tohoku University (Japan),<sup>8, 82–89</sup> at the University of Nottingham (United Kingdom)<sup>65, 90</sup> and at the M V Lomonosov Moscow State University (Russia).<sup>41–44</sup> Here, researchers developed methods of synthesis of many simple and complex oxide systems and demonstrated the possibility of carrying out one-step syntheses of supported nanocrystalline heterogeneous catalysts in flow reactors (Table 3). The majority of systems synthesised in flow reactors are characterised by a narrow particle

size distribution, a well-developed surface, and by being monophase. The synthesis takes a few seconds and the experimental conditions vary from 503 K and 25 MPa to 673 K and 35 MPa. The physicochemical properties of oxide nanosystems are governed by the synthesis conditions (temperature, pressure, duration) and by the composition and concentration of the reaction mixture.

##### 1. Mechanism of oxide formation

A research group from Japan headed by Prof. K Arai proposed a two-step mechanism of metal oxide formation under hydrothermal conditions.<sup>8, 83</sup> The first reaction stage involves fast hydrolysis of the metal salt solution to give corresponding hydroxides. In the second stage, dehydration of hydroxides results in the formation of oxides.



The overall rate of oxide formation is a function of the temperature, ionic product of water and dielectric constant of the medium. The ionic product of subcritical water is high; therefore, one can expect that in this case hydrolysis will proceed at a higher rate compared to the reaction in supercritical water. At the same time, dehydration of hydroxides and nucleation of oxides require a low dielectric constant of the medium. The solubilities of inorganic compounds in subcritical water are rather high; this hampers attainment of local supersaturations which is necessary for nucleation of crystalline oxides. Owing to the high dielectric constant of the medium, dehydration of hydroxides in subcritical water proceeds at a lower rate compared to the process in supercritical water. In this connection one should choose the experimental conditions with allowance for specific features of a particular system (namely, the tendency of the precursor towards hydrolysis and the solubility of the reaction products). In most cases the maximum rate of formation of nanocrystalline metal oxides under hydrothermal conditions is achieved using supercritical water. For instance, the synthesis of nanocrystalline  $\alpha\text{-Fe}_2\text{O}_3$  (particle size 20 nm) from ferric nitrate in supercritical water takes less than a second.<sup>8</sup>

##### 2. Choice of precursor

The properties of nanocrystalline oxides obtained by the hydrothermal method are to a great extent determined by the choice of precursor, all things being equal. For instance, hydrolysis of  $\text{Fe}(\text{NO}_3)_3$ ,  $\text{Fe}_2(\text{SO}_4)_3$  and  $\text{FeCl}_3$  in supercritical water results in  $\alpha\text{-Fe}_2\text{O}_3$ ; however, the reaction carried out under identical conditions with  $\text{Fe}(\text{NH}_4)_2\text{H}(\text{C}_6\text{H}_5\text{O}_7)_2$  as precursor gives mixed oxide  $\text{Fe}_3\text{O}_4$ .<sup>8</sup> The case in point is that in the latter case thermal decomposition of ammonium citrate leads to carbon monoxide, which reduces  $\text{Fe}^{3+}$  to  $\text{Fe}^{2+}$ .

Usually, nanocrystalline oxides are synthesised in flow reactors from true solutions of metal salts (nitrates, chlorides, sulfates, acetates). Multicomponent oxides are obtained using solutions that simultaneously contain a number of salts in stoichiometric ratios (see Table 3).

The use of solutions for the synthesis of multicomponent oxides in batch reactors is usually precluded owing to different hydrolysis rates of the salts of the metal constituents of the complex oxide because gradual heating of the autoclave leads to formation of individual simple oxides at different instants of time. Therefore, experiments in closed systems are carried out with gels or codeposited metal hydroxides as precursors. For instance, the oxides  $\text{Ce}_{1-x}\text{M}_x\text{O}_{2-\delta}$  ( $\text{M} = \text{Eu}, \text{Sm}, \text{La}$ ) were synthesised<sup>66–68</sup> in autoclaves loaded with gels prepared by coprecipitation of solutions of cerium nitrate and the second metal with ammonia at pH 10, while nanocrystalline solid solutions  $\text{ZrO}_2\text{--CaO}$  were synthesised from amorphous hydrated zirconia, freshly prepared  $\text{CaO}$  and alkali additives ( $\text{LiOH}$  or  $\text{NaOH}$ ).<sup>71</sup> However, synthesis involving alkali and other mineral additives is undesirable because they can contaminate nanomaterials.

**Table 3.** Synthesis conditions and characteristics of nanocrystalline oxide systems obtained under hydrothermal conditions.

| Oxide                                                                                          | Synthesis conditions |               |           | Precursor                                                                                                                                                 | Particle size /nm | Specific surface /m <sup>2</sup> g <sup>-1</sup> | Ref. |
|------------------------------------------------------------------------------------------------|----------------------|---------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|--------------------------------------------------|------|
|                                                                                                | <i>T</i> /K          | <i>P</i> /MPa | $\tau$ /s |                                                                                                                                                           |                   |                                                  |      |
| $\alpha$ -Fe <sub>2</sub> O <sub>3</sub>                                                       | 673                  | 35            | 120       | Fe(NO <sub>3</sub> ) <sub>3</sub>                                                                                                                         | ~ 50              | —                                                | 8    |
|                                                                                                | 673                  | 35            | 120       | Fe <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>                                                                                                           | ~ 50              | —                                                | 8    |
|                                                                                                | 673                  | 35            | 120       | FeCl <sub>2</sub>                                                                                                                                         | ~ 50              | —                                                | 8    |
| Fe <sub>3</sub> O <sub>4</sub>                                                                 | 673                  | 35            | 120       | Fe(NH <sub>4</sub> ) <sub>2</sub> H(C <sub>6</sub> H <sub>5</sub> O <sub>7</sub> ) <sub>2</sub>                                                           | ~ 50              | —                                                | 8    |
| Co <sub>3</sub> O <sub>4</sub>                                                                 | 673                  | 35            | 120       | Co(NO <sub>3</sub> ) <sub>2</sub>                                                                                                                         | ~ 100             | —                                                | 8    |
| AlOOH                                                                                          | 673                  | 35            | 120       | Al(NO <sub>3</sub> ) <sub>3</sub>                                                                                                                         | ~ 600             | —                                                | 8    |
| NiO                                                                                            | 673                  | 35            | 120       | Ni(NO <sub>3</sub> ) <sub>2</sub>                                                                                                                         | ~ 200             | —                                                | 8    |
| ZrO <sub>2</sub>                                                                               | 673                  | 30            | 120       | ZrOCl <sub>2</sub>                                                                                                                                        | ~ 10              | —                                                | 8    |
|                                                                                                | 653                  | 25            | 4.5       | ZrO(NO <sub>3</sub> ) <sub>2</sub>                                                                                                                        | 3–5               | 163–172                                          | 42   |
| TiO <sub>2</sub>                                                                               | 673                  | 30            | 120       | TiCl <sub>4</sub>                                                                                                                                         | ~ 20              | —                                                | 8    |
|                                                                                                | 673                  | 35            | 120       | TiSO <sub>4</sub>                                                                                                                                         | ~ 20              | —                                                | 8    |
|                                                                                                | 503                  | 25            | 8.5       | (CH <sub>3</sub> COO) <sub>x</sub> Ti(OPr) <sub>4-x</sub>                                                                                                 | 7–9               | 189–201                                          | 42   |
| CeO <sub>2</sub>                                                                               | 573                  | 30            | 20        | Ce(NO <sub>3</sub> ) <sub>3</sub>                                                                                                                         | ~ 300             | —                                                | 84   |
|                                                                                                | 673                  | 30            | 20        | Ce(NO <sub>3</sub> ) <sub>3</sub>                                                                                                                         | ~ 18              | —                                                | 84   |
|                                                                                                | 603                  | 25            | 6.8       | (NH <sub>4</sub> ) <sub>2</sub> Ce(NO <sub>3</sub> ) <sub>6</sub>                                                                                         | 6–7               | 110                                              | 42   |
| Ce <sub>1-x</sub> Zr <sub>x</sub> O <sub>2</sub><br>( <i>x</i> = 0–1)                          | 573                  | 25            | 5         | Zr(CH <sub>3</sub> COO) <sub>4</sub> ,<br>(NH <sub>4</sub> ) <sub>2</sub> Ce(NO <sub>3</sub> ) <sub>6</sub>                                               | 3–5               | 180                                              | 65   |
| Zr <sub>1-x</sub> Y <sub>x</sub> O <sub>2</sub><br>( <i>x</i> = 0.03–0.1)                      | 653                  | 25            | 4.5       | ZrO(NO <sub>3</sub> ) <sub>2</sub> ,<br>Y(CH <sub>3</sub> COO) <sub>3</sub>                                                                               | 4–5               | 147–161                                          | 42   |
| Zr <sub>1-x</sub> In <sub>x</sub> O <sub>2</sub><br>( <i>x</i> = 0.03–0.1)                     | 653                  | 25            | 4.5       | ZrO(NO <sub>3</sub> ) <sub>2</sub> ,<br>In(CH <sub>3</sub> COO) <sub>3</sub>                                                                              | 4–5               | 135–154                                          | 42   |
| Ce <sub>0.1</sub> Y <sub>x</sub> Zr <sub>0.9-x</sub> O <sub>2</sub><br>( <i>x</i> = 0.06, 0.1) | 653                  | 25            | 4.5       | ZrO(NO <sub>3</sub> ) <sub>2</sub> ,<br>Y(CH <sub>3</sub> COO) <sub>3</sub><br>(NH <sub>4</sub> ) <sub>2</sub> Ce(NO <sub>3</sub> ) <sub>6</sub>          | 3–4               | 115–164                                          | 42   |
| BaO·6 Fe <sub>2</sub> O <sub>3</sub>                                                           | 673                  | 30            | 60        | Fe(NO <sub>3</sub> ) <sub>3</sub> ,<br>Ba(NO <sub>3</sub> ) <sub>2</sub>                                                                                  | 50–1000           | —                                                | 85   |
| Al <sub>5</sub> (Y + Tb) <sub>3</sub> O <sub>12</sub>                                          | 653                  | 25            | 4.5       | Al(NO <sub>3</sub> ) <sub>3</sub> ,<br>Y(NO <sub>3</sub> ) <sub>3</sub> ,<br>TbCl <sub>3</sub>                                                            | 20–600            | —                                                | 89   |
| LiCoO <sub>2</sub>                                                                             | 673                  | 30            | 60        | LiNO <sub>3</sub> ,<br>Co(NO <sub>3</sub> ) <sub>2</sub>                                                                                                  | 40–400            | —                                                | 89   |
| Pd–Rh/ZrO <sub>2</sub>                                                                         | 653                  | 25            | 4.5       | ZrO(NO <sub>3</sub> ) <sub>2</sub> ,<br>Rh <sub>2</sub> (CH <sub>3</sub> COO) <sub>4</sub><br>Pd(CH <sub>3</sub> COO) <sub>2</sub>                        | 3–5               | 160–170                                          | 44   |
| Pd–Rh/TiO <sub>2</sub>                                                                         | 503                  | 25            | 8.5       | (CH <sub>3</sub> COO) <sub>x</sub> Ti(OPr) <sub>4-x</sub> ,<br>Rh <sub>2</sub> (CH <sub>3</sub> COO) <sub>4</sub><br>Pd(CH <sub>3</sub> COO) <sub>2</sub> | 7–9               | 190–210                                          | 44   |

### 3. Particle size and phase composition

By varying the synthesis conditions it is possible to vary the particle size and to change the morphology of the oxides obtained. An increase in the synthesis time causes an increase in the average particle size. A similar effect is also observed with increasing the concentration of reagent solutions.

There is no consensus of opinion as to the influence of the temperature of hydrothermal synthesis on the particle size. Taking TiO<sub>2</sub> as an example, it was shown that an increase in the reaction temperature from 503 to 653 K causes an increase in the particle size from 7–9 to 16–18 nm, respectively, and a decrease in the specific surface area of titania from 200 to 50 m<sup>2</sup> g<sup>-1</sup>, respectively (see Ref. 43). The reverse was observed for ceria, *viz.*, the CeO<sub>2</sub> particle size is 300 nm at 573 K and 18 nm at 673 K (see Ref. 84). Probably, these results could be explained with allowance for specific features of precursors and the ratio of the rates of hydrolysis, dehydration and crystal growth at various temperatures.

In spite of the short times for the synthesis of oxides in flow reactors, these substances are characterised by a high degree of crystallinity. Sometimes hydrothermal treatment leads to stabilisation of phases that are metastable under normal conditions. For instance, hydrolysis of zirconium nitrate in subcritical water results in a mixture of monoclinic and tetragonal ZrO<sub>2</sub> polymorphs.<sup>65</sup> The formation of the metastable tetragonal polymorph is most probably due to the size effect, namely, a decrease in the

particle size to a certain critical size causes preferred formation of the phases with higher symmetry of the crystal lattice.<sup>65,91</sup>

Depending on the composition of the solution used in the hydrothermal synthesis of the oxides Zr<sub>1-x</sub>M<sub>x</sub>O<sub>2</sub> (M = Ce, Y, In), it is possible to obtain systems with specified ratios of the monoclinic, tetragonal and cubic polymorphs. For instance, as the indium content in the system Zr<sub>1-x</sub>In<sub>x</sub>O<sub>2</sub> increases, the tetragonal-to-monoclinic ratio of ZrO<sub>2</sub> phases increases; nanocrystalline solid solutions Ce<sub>0.5</sub>Zr<sub>0.5</sub>O<sub>2</sub> and Ce<sub>0.1</sub>Y<sub>0.1</sub>Zr<sub>0.8</sub>O<sub>2</sub> obtained in supercritical water have cubic lattices.<sup>43</sup>

### 4. Control of the oxidation states of elements

Hydrolysis of metal acetates, formates and oxalates in supercritical water involves partial decomposition of acids formed to CO. At supercritical temperatures and pressures, carbon monoxide can be mixed with water in any proportion, thus forming a homogeneous reducing medium. By varying the experimental conditions one can control the oxidation states of the elements in nanocrystalline oxides and thus obtain systems with specified ratios of the phases containing the same element in different oxidation states.

In supercritical water (*T* = 658 K, *P* = 35 MPa) copper hydroxycarbonate decomposes into copper(II) oxide and oxalic acid decomposes into carbon monoxide. Carrying out these two reactions simultaneously in a batch reactor results in metallic copper, a mixture of copper and copper(I) oxide or a mixture of

copper(I) oxide and copper(II) oxide.<sup>43</sup> The content of each phase is governed by the amount of oxalic acid added and can be controlled with ease. This technique seems to be promising for the preparation of catalysts and magnetic materials with preset concentrations of paramagnetic centres.

Hydrocarbon ligands can also favour the formation of reduced nanocrystalline systems in supercritical water. In particular, hydrothermal treatment of copper(II) nitrate in the presence of hexane-1-thiol affords metallic copper with particle sizes lying between 1.5 and 30 nm (see Ref. 79).

The oxidation states of elements can also be controlled in the course of fabrication of nanocrystalline materials in subcritical and supercritical water using hydrogen, oxygen and hydrogen peroxide. For instance, hydrolysis of cobalt(II) salts under hydrothermal conditions in the presence of  $\text{H}_2\text{O}_2$  involves oxidation of  $\text{Co}^{2+}$  to  $\text{Co}^{3+}$ , which allows phases containing cobalt(III), *e.g.*,  $\text{LiCoO}_2$  to be synthesised.<sup>89</sup>

It should be noted that subcritical and supercritical water can be successfully used for the synthesis of not only oxides but also other nanocrystalline materials. For instance, carbon nanotubes can be obtained by hydrothermal treatment of amorphous carbon at a temperature of 1073 K and a pressure of 100 MPa.<sup>92</sup> The nanotubes are a few hundred nanometres long, have an outer diameter of 10 to 50 nm and contain no amorphous carbon impurities.

Nanomaterials can also be formed under hydrothermal conditions by the rapid expansion of supercritical water containing dissolved oxides and hydroxides (RESS process).<sup>93</sup> Nearly instantaneous transition from supercritical fluid to gas ( $< 10^{-5}$  s) causes the formation of nanocrystalline oxides. However, this is a low-performance technology because of the low solubility of inorganic substances in supercritical water. For instance, the solubility of  $\text{Co}(\text{OH})_2$  and  $\text{Ni}(\text{OH})_2$  in water at 653 K is only  $10^{-6}$  and  $10^{-8}$  mol  $\text{kg}^{-1}$ , respectively.<sup>94</sup> In this connection the RESS process is of limited use.

## V. Organic reactions in subcritical and supercritical water

To date, wide experience in carrying out various organic reactions under hydrothermal conditions has been accumulated.<sup>6,95–97</sup> Unfortunately, most studies are concerned with deep oxidation of organic substances in subcritical and supercritical water. These studies are undoubtedly of importance for solving problems of treatment of toxic industrial and municipal waste. However, water at elevated temperatures and pressures is first of all of interest as a unique solvent and reagent for fine organic synthesis.

Carrying out many organic reactions is preceded by the routine procedure of choosing a solvent with optimum physico-chemical characteristics. Many solvents are toxic, fire-hazardous and explosive, which present severe problems for the industrial application of these compounds. In the case of reactions involving subcritical and supercritical water the choice of solvent is replaced by 'tuning' the temperature and pressure in such a way that the properties of the medium (density, ionic product, dielectric constant, viscosity, *etc.*) be optimised for performing a particular organic reaction.

Differences between the physical properties of subcritical and supercritical water are responsible for the fundamentally different mechanisms of organic reactions proceeding in these media. Typically, acidic and basic catalyses involving charged intermediates proceed in subcritical water while free-radical processes proceed in supercritical water.<sup>98</sup> In the latter case the reactions are initiated by hydrogen atoms and hydroxyl radicals that form in the homolytic decomposition of water molecules. Primary free radicals can also be formed in the system by collisions between the reagent and solvent molecules or as a result of the reactions with  $\text{O}_2$  and  $\text{NO}_2$  molecules having unpaired electrons.

Generally, the organic reactions possible in subcritical and supercritical water are as follows: hydrolysis; hydration/dehydra-

tion; various rearrangements; elimination; formation and cleavage of carbon-carbon bonds; hydrogenation/dehydrogenation and oxidation.

Many of these reactions can proceed under hydrothermal conditions at rather high rates and yields in the absence of catalysts. As to other types of reactions, subcritical water is an efficient acid-base catalyst, which excludes the necessity of neutralisation of large amounts of salts traditionally used as Lewis acids in, *e.g.*, alkylation reactions.<sup>14</sup> Conventional oxide and metallic heterogeneous catalysts can also be employed; however, in this case particular attention should be paid to the stability of catalytic systems in subcritical and supercritical water.<sup>99</sup>

Below we will consider a number of organic reactions that proceed under hydrothermal conditions, are of greatest value for practical use and provide an idea of the features of transformations of organic compounds in subcritical and supercritical water.

### 1. Methanol oxidation

Methanol oxidation is one of the best studied reactions in supercritical water.<sup>100–108</sup> At present, most studies in the field are concerned with analysis of the available experimental data.

Methanol oxidation in supercritical water results in water and carbon dioxide as end products. A detailed kinetic model<sup>100</sup> for this reaction is in good agreement with the experimental data. The model includes one hundred and forty-eight reversible elementary radical stages and twenty-two types of reactive particles. Among the primary products of methanol oxidation is formaldehyde, which is more reactive than methanol under the reaction conditions (773–862 K, 24.6 MPa); therefore, eventually the yield of formaldehyde is at most 24%.<sup>101</sup> Kinetic studies revealed that methanol oxidation is a pseudo-first order reaction with respect to methanol and zero order reaction with respect to oxygen and has an activation energy of  $328 \pm 84$  kJ  $\text{mol}^{-1}$ .

Later,<sup>102</sup> it was shown that the kinetics of methanol oxidation in supercritical water can be correctly described using seventeen fastest radical reactions and fourteen types of reactive particles. The calculated overall rate constant for the reaction and the yields of various oxidation products were in agreement with those obtained using the more complex model (see Ref. 100).

Methanol oxidation under hydrothermal conditions can also be described using the ideal gas model.<sup>101, 102</sup> However, near the critical point of water the equation of ideal gas state is inapplicable owing to the infinite compressibility of the medium. The compressibility of supercritical water can be taken into account using, *e.g.*, the Peng–Robinson semiempirical cubic equation.<sup>103</sup>

### 2. Reactions involving hydrocarbons

The high stability of hydrocarbons at temperatures and pressures near the critical point of water opens great prospects for carrying out target organic synthesis under hydrothermal conditions. Here, methane oxidation reaction has been best studied (Refs 100, 106, 107, 109–112). Most studies were concerned with deep oxidation of methane in supercritical water to carbon oxides and water. The process is characterised by an activation energy of about 180 kJ  $\text{mol}^{-1}$  at  $T = 288–923$  K and  $P = 24.6$  MPa, being a first order reaction with respect to methane and a 2/3 order reaction with respect to oxygen.<sup>109</sup>

Methane oxidation in an excess of oxygen can be theoretically described using both traditional combustion models corrected for high pressure and the ideal gas model. In the latter case the inclusion of reactions involving the  $\text{HO}_2$  radical (probably, the main oxidant under supercritical conditions) has the strongest effect on the results of calculations.<sup>100, 110</sup>

Partial methane oxidation into methanol in subcritical and supercritical water is also possible.<sup>112, 113</sup> Methane conversion in a batch reactor ( $T = 622–754$  K,  $\rho = 150–350$  kg  $\text{m}^{-3}$ ) at a  $[\text{CH}_4]:[\text{O}_2]$  ratio of 10:26 is at most 6%, the greatest selectivity of methanol formation (75%) being attained at low methane conversions.<sup>112</sup> The maximum selectivity of methanol formation in a flow system in the temperature range 673–683 K at a pressure

of 25 MPa is 35%.<sup>113</sup> Among other oxidation products are carbon oxides and hydrogen. Raising the temperature and an increase in oxygen conversion reduces the selectivity. The activation energy for methane oxidation is 400 kJ mol<sup>-1</sup>, the process being a 1.3 order reaction with respect to methane and a 0.3 order reaction with respect to oxygen.

In the course of catalytic cyclotrimerisation of alkynes under supercritical conditions water behaves as a conventional organic solvent.<sup>114,115</sup> Hydration of hydrocarbons to give ketones proceeds only in the presence of acids.<sup>114</sup> In particular, treatment of hex-1-yne at pH 6 affords nearly 10%–14% yields of hexan-2-one in accord with Markovnikov's rule. In the case of salt catalysed ketone hydrolysis the product yields correlate with the acidity of the cation aqua complexes, namely, no hydrolysis proceeds in the presence of NaCl and CaCl<sub>2</sub> and a 100% selectivity of hexan-2-one formation is achieved in the presence of CuCl<sub>2</sub> and SnCl<sub>2</sub>.

Subcritical water (573–628 K) is suitable for selective oxidation of alkylaromatic hydrocarbons with molecular oxygen to the corresponding aromatic acids and carbonyl compounds in the presence of catalysts.<sup>116</sup> The best results were obtained using MnBr<sub>2</sub> and CoBr<sub>2</sub> as catalysts. Reactions in the presence of other salts or in the absence of catalysts are characterised by severe charring and formation of dimerisation products.

### 3. Dehydration of alcohols

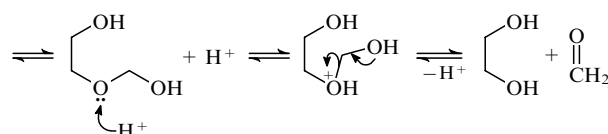
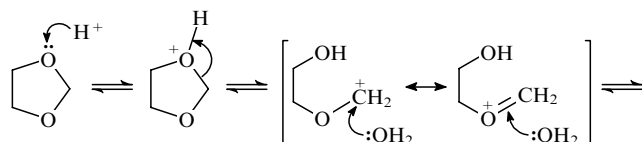
Dehydration of alcohols to give alkenes in subcritical water proceeds at high rates even in the absence of catalysts.<sup>6,117</sup> In the supercritical region, the reaction significantly slows down and the process can be accelerated only by adding mineral acids.<sup>98</sup> As a consequence, the selectivity decreases due to the reactions between the catalyst and alcohols. Formation of carbon oxides, methane and ethane in the ethanol dehydration in supercritical water points to a radical character of the reaction.

Subcritical water is a protic solvent; therefore, dehydration under subcritical conditions proceeds following the E2 mechanism with high selectivity.<sup>117</sup> The appearance of small amounts of by-products is due to alkene protonation to give carbocations that undergo rearrangements followed by isomerisation. For instance, dehydration of cyclohexanol results in cyclohexene, 1-methylcyclopentene and 3-methylcyclopentene.

### 4. Ether transformations

Supercritical water possesses no ionic properties; however, reactions catalysed by bases or acids that were added (or formed in the course of reaction) can proceed in this medium at high pressures and moderate temperatures. In particular, diphenyl ether decomposes into typical radical condensation products, diphenyl and phenoxydiphenyl, at a density of water of less than 300 kg m<sup>-3</sup> in the temperature interval 688–753 K.<sup>118</sup> However, as the critical density of water (~300 kg m<sup>-3</sup>) is attained, the conversion of diphenyl ether increases dramatically and only phenol is formed, a product of ether hydrolysis by the S<sub>N</sub>1 cationic mechanism. The reaction is catalysed by protons that appear during heterolytic dissociation of phenol; therefore, the process accelerates with time.

Hydrolysis of ethers in subcritical water has been well studied.<sup>98,119–122</sup> Note that in this case water can act as an efficient acid-base catalyst owing to a high dissociation constant.<sup>6,14</sup> For instance, hydrolysis of 1,3-dioxolane at 623 K and 34.5 MPa proceeds by the following acid-base mechanism:<sup>98</sup>



The degree of conversion is 99.8% and the end products are formaldehyde and ethylene glycol.

Decomposition of dibenzyl ether in supercritical water at 936–961 K and a density of water of 347 kg m<sup>-3</sup> results in benzyl alcohol, benzaldehyde, toluene and a number of by-products.<sup>123</sup> The proposed mechanism of the process includes eight main stages and is in good agreement with experimental data. The rate constant for pyrolysis of dibenzyl ether in supercritical water exceeds the rate constant for hydrolysis of this compound.

### 5. Acetic acid oxidation

The limiting stage of decomposition of various organic substances in supercritical water is oxidation of an intermediate product, acetic acid. Therefore, particular attention is paid to acetic acid oxidation under hydrothermal conditions.<sup>108,124–130</sup>

Depending on the reaction conditions, various products can be formed. For instance, oxidation with oxygen at 698–873 K and a pressure of 24.6 MPa (100% conversion at a residence time of 8 s) leads to the formation of carbon oxides, methane, hydrogen and trace amounts of propionic acid.<sup>124</sup> Oxidation in a batch reactor at long residence times results in carbon dioxide and water; however, in this case the conversion of acetic acid is at most 64% even in a five-fold excess of oxygen.<sup>125</sup> Hydrogen peroxide is a more efficient oxidant; here, the acid conversion increases to 97.7%.

Addition of transition metal cations favours the formation of large amounts of hydroxyl radicals and enhances the oxidising ability of H<sub>2</sub>O<sub>2</sub>. The efficiency of acetic acid oxidants in supercritical water ( $T = 673\text{--}733\text{ K}$ ,  $P = 27.5\text{--}35.0\text{ MPa}$ ) decreases as follows:<sup>126</sup> Cu–H<sub>2</sub>O<sub>2</sub> > Fe–H<sub>2</sub>O<sub>2</sub> > MnSO<sub>4</sub>–H<sub>2</sub>O<sub>2</sub> > H<sub>2</sub>O<sub>2</sub> > O<sub>2</sub>. In this case, the strongest acetic acid oxidant is potassium permanganate; however, its activity decreases in subcritical water.

Acetic acid oxidation reaction in a flow reactor is ~ 1/3 order with respect to oxygen and nearly first order with respect to acetic acid,<sup>124,128</sup> with an activation energy of about 180 kJ mol<sup>-1</sup>.

Acetic acid remains rather stable in supercritical water in the absence of oxidants, namely, the conversion of AcOH at 873 K and 24.6 MPa and a residence time of 8 s is only 35%.<sup>124</sup>

### 6. Phenol oxidation

The chemistry of phenol in supercritical media is interesting in regard to both the utilisation of toxic industrial waste and target organic synthesis, because phenolic type fragments are present in the structures of many organic molecules. A great body of experimental data and results of theoretical studies concerned with phenol transformations under hydrothermal conditions are available.<sup>131–140</sup> However, all of them were obtained for phenol oxidation only. At the same time phenol is rather stable in supercritical water in the absence of oxygen.<sup>135</sup> This suggests the possibility of carrying out more complex reactions involving phenol, such as formylation, sulfonation, amination, *etc.* under hydrothermal conditions.

The majority of the experimental data on phenol oxidation are consistent. The activation energy for this reaction is 100–125 kJ mol<sup>-1</sup> (see Refs 135 and 136). The rate of the reaction in supercritical water is proportional to the phenol concentration<sup>133–137</sup> and oxygen concentration to the 0.4–0.5 power.<sup>133,136</sup> It was experimentally proved that the rate of phenol oxidation is independent of the total pressure in the system, being dependent on the reagent concentrations<sup>135</sup>

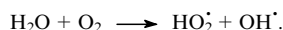
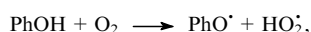
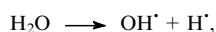
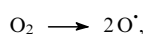
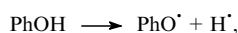
$$\frac{d[\text{PhOH}]}{dt} = -k \frac{[\text{PhOH}][\text{H}_2\text{O}]^{1.38}\chi}{2.89 + \chi}$$

where

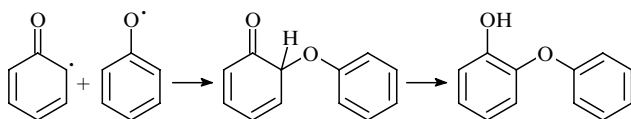
$$\chi = \frac{[\text{O}_2]}{[\text{PhOH}]}.$$

It is assumed that the mechanism of phenol oxidation involves two parallel reactions, ring opening and dimerisation.<sup>140</sup> The reaction results in carbon oxides as the end products; chain branching in the course of decomposition of an aromatic hydroperoxide and bimolecular initiation have the strongest effect on the kinetics of phenol oxidation. However, the reaction order with respect to oxygen, the activation energy and the rate constant for the reaction calculated using this model are overestimated compared to the experimental data.

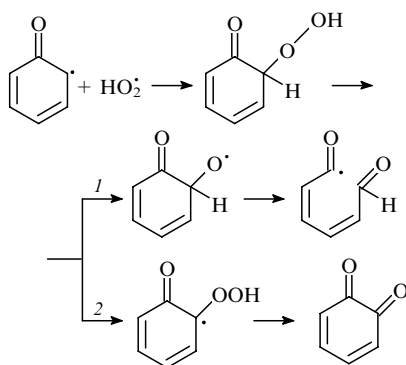
More complex kinetic models include the possibility for water to participate in the phenol oxidation as a reagent.<sup>135, 138</sup> Initially, the reaction system contains only phenol, oxygen and water; therefore, the oxidation can be initiated by three monomolecular and two bimolecular reactions<sup>138</sup>



The phenoxyl radical formed in the reaction can then undergo dimerisation, hydroxylation to give cresols and ring opening. Dimerisation leads to 2-phenoxyphenol, dibenzofuran, 4-phenoxyphenol and 2,2'-diphenol as the major products.<sup>138</sup> As an example, we will consider the formation of 2-phenoxyphenol.



Ring opening of the phenoxyl radical can proceed as follows:<sup>138</sup>



Only route 1 resulting in a substituted vinyl radical is possible for the radical bearing the unpaired electron in the *para*-position to the oxygen atom. Phenol dimers can also undergo similar transformations to give formic, glyoxylic, propionic, oxalic, succinic, maleic and acetic acids.<sup>136, 138</sup> Further oxidation of these carboxylic acids results in water and carbon dioxide.

## 7. Reduction of aldehydes and ketones

Reduction of the carbonyl group provides an example of a selective, environmentally safe reaction in subcritical water. Sodium formate reduces aldehydes and a number of ketones in the absence of catalysts and toxic solvents at 523–573 K and a pressure of 7.5 MPa.<sup>141</sup> Environmentally friendly carbon dioxide is produced as a by-product of the reaction. The selectivity of the reaction can be controlled by varying the reaction conditions. An increase in temperature gives higher yields of primary alcohols. In

most cases the reduction proceeds with high yield (up to 74%); only for acyclic ketones does the conversion remain low even at long residence times.

## 8. Diels–Alder reaction

The Diels–Alder reaction is a conventional method of synthesis of organic compounds containing six-membered rings in the chemical structure. However, a significant drawback of this reaction is its low rate. Sometimes, the reaction can take a few days. Raising the temperature accelerates the process; here, subcritical and supercritical water are excellent solvents.

It was established that the non-catalytic reaction of diethyl maleate with cyclopentadiene under hydrothermal conditions at 648 K results in a mixture of 2,3-diethoxycarbonyl-5-norbornene isomers in 86% yield.<sup>142</sup> The reaction time is at most one hour (*cf.* a few hours to a few days for the process in organic solvents under normal conditions).

Not only the rate but also the selectivity of the Diels–Alder reaction changes under hydrothermal conditions. In particular, the reaction of ethyl acrylate with cyclopentadiene in supercritical water results in a mixture of *endo*- and *exo*-isomers of 2-ethoxycarbonyl-5-norbornene in an equimolar ratio. Under normal conditions in the presence of the catalyst  $\text{LiClO}_4$  the yield of the *endo*-isomer is eight times higher. The change in the selectivity is associated with a weakening of hydrophobic interactions in supercritical water.<sup>143</sup>

## VI. Use of subcritical and supercritical water for solving environmental problems

Development of efficient and environmentally safe technologies for treatment of increasing amounts of various toxic inorganic and organic waste (products of anthropogenic activity) is among the most important problems of modern times. A possible way of solving this problem could be the use of subcritical and supercritical water for detoxification of these products. Being an environmentally safe solvent, water can be mixed with oxygen and organic compounds in any proportion near the critical point, it dissolves organic solid substances (but not inorganic salts), has high diffusion and mass transfer coefficients, is of low viscosity and zero surface tension.<sup>144</sup> It is these properties that must be possessed by a solvent appropriate for efficient treatment of industrial wastes.

Traditionally, organic waste detoxification methods involve combustion, liquid-phase oxidation or biodegradation.<sup>145</sup> Each technology has certain drawbacks and can only be used for particular concentration ranges of organic substances. For instance, combustion of highly concentrated organic waste produces toxic substances, *e.g.*,  $\text{CO}$ ,  $\text{NO}_x$ , dioxins and polyaromatic compounds that should be neutralised. Liquid-phase oxidation technology is applicable to moderate concentrations of organic waste. The process is limited by mass transfer phenomena and the solutions formed contain high concentrations of carboxylic acids and ammonia. Biodegradation is only used for neutralisation of waste containing up to 1 mass% of organic substances. This is a rather slow process and simultaneous biodegradation of large amounts of wastewater requires large surface areas.

The expedience of the use of supercritical water for detoxification of organic waste was assessed taking catalytic oxidation of pyridine as an example and this treatment technology was found to be efficient.<sup>145</sup> According to calculations, the amount of investment necessary to build a waste-disposal plant for treatment of pyridine-containing solutions in supercritical water is 1 650 000 US dollars. Building waste-disposal plants for combustion and liquid-phase oxidation treatment requires 1 920 000 and 2 350 000 US dollars, respectively. A plant for catalytic oxidation of pyridine in supercritical water is also cheaper than those employing combustion and liquid-phase oxidation treatment. In addition, supercritical water oxidation imposes almost no limitations on the concentration of the pyridine-containing solutions.

Thus, treatment of organic waste with subcritical and supercritical water could be an alternative to traditional methods.

Studies on the use of subcritical and supercritical water for the detoxification of waste were concerned with dechlorination and dearomatisation of organic solutions,<sup>53, 55, 131, 135, 146–162</sup> treatment of polymers and plastics,<sup>30, 144, 163–167</sup> oxidation of municipal and food waste,<sup>51, 168–173</sup> gasification of biomass,<sup>174–176</sup> oxidation of toxic naval waste,<sup>177</sup> hydrolysis of cellulose and lignin,<sup>3, 178–182</sup> treatment of industrial waste<sup>183</sup> and extraction of heavy-metal compounds from waste water.<sup>30, 49, 184–186</sup> A number of processes are considered below.

### 1. Phenol and heterocyclic compounds

Every year chemical and petroleum industries produce millions of tons of liquid waste containing aromatic and heterocyclic organic compounds and their halogenated derivatives. These substances are highly toxic and are often carcinogenic; however, they are irreplaceable in the production of various pharmaceuticals, vitamins, herbicides and pesticides. Here, dearomatisation, dechlorination and removal of heterocyclic compounds from waste water can be performed using subcritical and supercritical water.

The efficiency of hydrothermal detoxification of pyridine- and phenol-containing waste substantially increases when using heterogeneous catalysts.<sup>131, 151, 152, 159, 187–189</sup> For instance, a 99% conversion is reached in supercritical water oxidation of pyridine in the presence of catalyst (0.5% Pt/Al<sub>2</sub>O<sub>3</sub>).<sup>187</sup> The process is limited by the diffusion of reagents in the pores of the catalyst; it results in CO<sub>2</sub>, N<sub>2</sub>O and nitrate as the major oxidation products.

The use of CuO/Al<sub>2</sub>O<sub>3</sub> catalyst in supercritical water oxidation of phenol permits not only acceleration of the reaction but also reduction of the yield of undesirable polycyclic by-products.<sup>131</sup> Carbon-supported catalysts are more reactive in the phenol oxidations.<sup>151</sup> By reducing the partial pressure of oxygen down to 0.2 MPa it is possible to decrease the oxidation rate of this catalyst in the reaction medium. The use of catalytic systems MnO<sub>2</sub>/CeO<sub>2</sub>, V<sub>2</sub>O<sub>5</sub>/Al<sub>2</sub>O<sub>3</sub>, Cr<sub>2</sub>O<sub>3</sub>/Al<sub>2</sub>O<sub>3</sub> and V<sub>2</sub>O<sub>5</sub> in supercritical water oxidation of phenol provides 100% conversion of PhOH to carbon dioxide, the formation of by-products being suppressed.<sup>152, 153</sup> It should be noted that hydrothermal phenol oxidation is also possible at lower temperatures (308–338 K) in the presence of a bimetallic catalyst (20% Pt–5% Ru)/C with a high content of noble metals.<sup>156</sup> The rate of hydrothermal phenol oxidation depends on the temperature and reagent concentrations, being at the same time independent of the pressure in the system.<sup>135</sup>

### 2. Chlorinated organic compounds

Dechlorination in supercritical water is a promising environmentally safe method of decomposition of chlorinated organic compounds.<sup>53</sup> The efficiency of catalytic neutralisation of liquid waste containing chlorophenols increases in the presence of alkali metal and iron cations.<sup>154, 158, 190</sup> The presence of these metals favours chlorine fixation and suppresses the formation of by-products (*e.g.*, trichlorophenols, dibenzo-*p*-dioxin and polycyclic aromatic hydrocarbons).

Zeolite catalysts used for the supercritical water decomposition of chlorophenols do not react with the chlorine released; this was confirmed by X-ray photoelectron spectroscopy data.<sup>149</sup> The highest efficiency of the process is achieved using the CuO/ZSM-48 catalyst.<sup>149, 158</sup> Due to its two-dimensional channel structure, the catalyst ZSM-48 zeolite (in contrast to the ZSM-5 and Y zeolites) suppresses the formation of undesired by-products. Hydrothermal hydrodechlorination and hydroaromatisation of thirteen various chlorophenols under mild conditions ( $T = 298–353$  K,  $P = 0.3–0.5$  MPa) in the presence of industrial catalyst Ru/C was performed.<sup>146</sup> The complete conversion of contaminants into nontoxic cyclohexanol and sodium chloride was achieved.

3-Chlorodiphenol oxidation in supercritical water results in carbon dioxide, water and HCl.<sup>157</sup> Reactions carried out under

similar conditions ( $T = 673$  K,  $P = 30$  MPa, reaction time 72.7–101.7 s) with hydrogen peroxide and molecular oxygen as oxidants were characterised by substantially different conversions, 99.999% in the former and 14.3% in the latter case. The efficiency of hydrodechlorination of polychlorinated diphenyls considerably increases in the presence of methanol,<sup>161</sup> which initiates a radical decomposition of intermediate chlorine-containing products with the formation of diphenyl.

Methylene chloride decomposition in subcritical and supercritical water involves two stages. Initially, hydrolysis of methylene chloride yields hydrogen chloride, formaldehyde and methanol.<sup>55</sup> Then, HCHO and CH<sub>3</sub>OH are oxidised with oxygen to CO and CO<sub>2</sub>. A 99.9% conversion of methylene chloride is achieved if the reaction is carried out in the temperature range 723–873 K at a pressure of 24.6 MPa and residence times of 4 to 9 s. Here, hydrolysis is a first order reaction with respect to methylene chloride, being also the limiting stage. The decomposition rate of methylene chloride increases only slightly in the presence of sodium chloride and does not depend on the amount of oxygen added.<sup>160</sup>

### 3. Polymers and plastics

Production of polymers and plastics is increasing worldwide annually. The amount of polymeric and plastic waste also increases; therefore, the search for new utilisation methods is topical. Nearly 100 000 tons per year of printed circuit board waste are to be disposed of in Taiwan.<sup>144</sup> High bromine content in these wastes hampers utilisation by conventional methods. In supercritical water ( $T = 793$  K,  $P = 24$  MPa,  $\tau = 600$  s) the material printed circuits are made of is oxidised with hydrogen peroxide to water and CO<sub>2</sub>. The degree of conversion is 90% and the bromine released is efficiently bound by sodium cations.

Subcritical and supercritical water can also be used for treatment of other polymers. In particular, polyethylene terephthalate decomposes in supercritical water producing oligomers, ethylene glycol and terephthalic acid.<sup>30</sup> Hydrolysis of polycarbonate in the temperature range 503–703 K results in the formation of phenol, bisphenol A, *p*-isopropenylphenol and *p*-isopropylphenol.<sup>165</sup> Decomposition of polyethylene in supercritical water is characterised by higher conversion and the formation of hydrocarbons with shorter chains compared to pyrolysis in argon.<sup>164</sup> At the same time polyethylene degradation in supercritical water proceeds more slowly than thermal pyrolysis; however, the yield of liquid decomposition products in the former case is higher.<sup>166</sup>

### 4. Municipal and industrial wastes

Efficient treatment of excretory waste and biomass is a severe problem, especially in megalopolises. It could also be solved using subcritical and supercritical water. For instance, a flow reactor for oxidation of excretory and alcohol production waste with hydrogen peroxide in supercritical water (473–873 K) was designed.<sup>168</sup> Two major intermediate oxidation products are acetic acid and ammonia. Further oxidation of ammonia requires a higher temperature compared to the oxidation of acetic acid. The efficiency of ammonia oxidation to nitrogen can be significantly enhanced using heterogeneous catalysts, *e.g.*, MnO<sub>2</sub>/CeO<sub>2</sub>.<sup>191</sup>

Biomass and organic wastes can also be gasified under hydrothermal conditions to produce fuel gas.<sup>174</sup> At  $T = 873$  K and  $P = 25$  MPa, biomass is completely gasified in the presence of KOH and K<sub>2</sub>CO<sub>3</sub>, forming a hydrogen-rich gas containing CO<sub>2</sub> as the main carbon compound. Concentrations of CO, CH<sub>4</sub> and C<sub>2</sub>–C<sub>4</sub> hydrocarbons in the product gas are <1 vol.%, ~3 vol.% and <1 vol.%, respectively.

Surfactant concentrations in waste water can be rather high. These compounds are oxidised with hydrogen peroxide in supercritical water to low-molecular-mass fatty acids (formic acid and acetic acid), sulfur-containing aromatic substances and sulfates.<sup>192</sup>

Phenol-containing olive oil production waste water can be efficiently neutralised in the presence of oxygen or hydrogen

peroxide in the temperature range 653–773 K at a pressure of 25 MPa.<sup>171</sup> The major oxidation products are water and carbon dioxide.

Utilisation of municipal waste in supercritical water can be combined with liquefaction of low-rank coals to produce liquid fuel.<sup>175</sup> The use of organic solvents for liquefaction is inefficient because of the high cost. The physicochemical properties of supercritical water are similar to those of nonpolar organic solvents. Supercritical water can be mixed with liquefaction products in any proportion and provides an efficient separation from liquid fuel on cooling. However, liquefaction of coals in supercritical water produces fuel with high oxygen content compounds, which reduces the heat of combustion. This problem can be solved by adding a source of hydrogen (*e.g.*, excretory waste or cellulose) to water.

In megalopolises solid municipal waste is usually burned out. In the atmosphere, components of the ash formed produce up to 50% of all dioxin-containing contaminants. Ash treatment with supercritical water in the presence of hydrogen peroxide ( $T = 673$  K,  $P = 30$  MPa,  $\tau = 1800$  s) permits oxidation of up to 99.7% of all dioxins to produce non-toxic chemical compounds.<sup>173</sup>

As mentioned above, inorganic compounds are insoluble in supercritical water owing to the low dielectric constant of the medium. This property can be used successfully for detoxification of liquid waste containing inorganic substances. For instance, 96% of sulfates and chlorides are removed from waste at  $T > 773$  K and  $P = 29.8$  MPa.<sup>184</sup> Cobalt and other metals can also be extracted from low-level radioactive nuclear power plant waste under similar conditions.<sup>30, 185, 186</sup>

The possibility of simultaneous neutralisation of several components of industrial waste and waste water using subcritical and supercritical water should be pointed out. For instance, a compact plant was built for the oxidation of toxic naval waste simultaneously containing fuel, hydraulic liquids, lubricants, coolants, dyes and photographic materials.<sup>177</sup> The oxidant used was air; oxidation products obtained at  $T = 870$  K and  $P = 22.5$  MPa were  $\text{CO}_2$ , water, oxides and mineral acids. The plant is compact and can be placed on a ship's board.

## 5. Food waste

Oxidation of food waste (beef suet and carrots) with hydrogen peroxide in supercritical water involves two stages.<sup>169</sup> Fast hydrolysis of polysaccharides with the formation of glucose (in the case of carrots) or glycerides to give glycerol and carboxylic acids (in the case of beef suet) is followed by slow oxidation of the intermediates formed.

Hydrothermal treatment of various types of food waste can be combined with the production of valuable chemicals, *e.g.*, amino acids.<sup>51, 172</sup> For instance, shrimp shells usually contain 17% of chitin and 42% of proteins. Treatment with subcritical water permits extraction of up to 70 mg of valuable amino acids per gramme of dry shrimp shells.<sup>172</sup>

## 6. Cellulose and lignin

Cellulose is one of the most important organic substances on the Earth. At the same time large amounts of cellulose-containing waste have not been treated efficiently. Hydrolysis of various cellulose sources in supercritical water ( $T = 773$  K,  $P = 35$  MPa,  $\tau = 3 - 105$  s) allows one to obtain glucose and its derivatives.<sup>179</sup> The degree of cellulose conversion achieved is as high as in the treatment of corn starch under similar conditions. This result deserves particular attention because the time taken to attain the same conversion in the case of enzymic hydrolysis of cellulose is three orders of magnitude longer than in the case of corn starch. Probably, the water present in the structure of cellulose microfibres goes to a supercritical state at high temperatures and pressure, which appreciably accelerates hydrolysis.<sup>179</sup>

The rates of cellulose hydrolysis in subcritical and supercritical water were compared<sup>180</sup> with the rates of further decom-

position of glucose, fructose and various oligomers formed. Near the critical point the rate of cellulose hydrolysis abruptly increases by more than an order of magnitude; therefore, hydrolysis in supercritical water produces much higher yields of products compared to the process in subcritical water. At temperatures and pressures below the critical point parameters, saccharide decompositions dominate hydrolysis of cellulose. Hence, by varying the temperature and pressure it is possible either to obtain saccharides from cellulose (in supercritical water) or perform a deep treatment of cellulose waste (in subcritical water).

The mechanisms of cellobiose (a cellulose model compound) pyrolysis and hydrolysis in subcritical and supercritical water have been studied in detail.<sup>182</sup> Pyrolysis products are glycosylerythrose and glycosylglycol aldehyde, whereas hydrolysis gives glucose, erythrose and glycolaldehyde.

Gasification of a lignin–cellulose mixture in water at  $T = 623$  K and  $P = 25$  MPa produces hydrogen, methane and carbon dioxide.<sup>193</sup> The amount and composition of the product gas strongly depends on the lignin content; probably, cellulose is a hydrogen donor for lignin hydrogenation, which causes changes in the composition of the gas produced depending on the lignin/cellulose ratio.

## 7. Extraction processes

Such properties of supercritical fluids as low viscosity and zero surface tension open great prospects for the use of these substances in the extraction and impregnation of various materials. At elevated temperatures and pressures, water can be used instead of many toxic solvents such as dichloromethane and acetone traditionally used for the extraction of organics from various matrices. Subcritical and supercritical water was employed in extraction of toxic contaminants from soil,<sup>194–199</sup> sorbent regeneration,<sup>200</sup> impurity desorption from the surface of materials<sup>201</sup> and fuel quality improvement.<sup>202–204</sup>

Usually, detoxification of compounds in soil requires pre-extraction. Petrochemicals, chlorophenols, chloroanilines and methylanilines, nitrotoluene, alkylbenzenes, polychlorinated diphenyls, phosphonium acids and pesticides can be efficiently extracted from natural matrices with subcritical and supercritical water. Subcritical water extraction of polar contaminants (phenols and amines) proceeds at lower temperatures compared to nonpolar contaminants (polycyclic aromatic hydrocarbons).<sup>205</sup> By adding anionic surfactants to water it is possible to substantially shorten the hydrocarbon extraction time.<sup>196</sup>

The solubility of dioxins in subcritical water is 340 times higher than in water under normal conditions.<sup>199</sup> At 523 K, 30% to 100% of dioxins are extracted from soils depending on the type of the matrix; raising the temperature favours an increase in the extent of extraction.

Pesticides are nonpolar compounds well extractable with supercritical water, *i.e.*, at high temperature and pressure.<sup>195</sup> However, the addition of ethanol and some other solvents causes a substantial decrease in the polarity of subcritical water, which permits extraction of pesticides from soils under milder conditions.

In microelectronics, various contaminants must be removed from the surface of silicon. Compounds traditionally used to this end are acidic and basic solutions; as a consequence, utilisation of corrosive waste is required. Subcritical water is a good solvent for ionic inorganic compounds at temperatures below 373 K and for carbonaceous substances at higher temperatures.<sup>201</sup> Thus, subcritical water can be used instead of the corrosive solvents traditionally employed for cleaning the surface of silicon. Adding small amounts of carbon dioxide to water allows (at  $T = 373 - 443$  K and  $P = 1.03 - 13.8$  MPa) not only a silica film and hydrocarbons but also amorphous carbon insoluble in pure subcritical water to be removed from the surface of silicon.

Extraction of gaseous contaminants from air and treatment of waste water and drinking water are usually performed using activated carbon. This sorbent efficiently absorbs even very low



concentrations of toxic substances. However, the rather high cost of activated carbon requires its regeneration. In the case of thermal regeneration the loss of carbon is 5%–10%, bioregeneration is only applicable to biodegradable substances and chemical regeneration is too expensive a process.<sup>200</sup> Treatment of activated carbon with subcritical water ( $T = 573$  K,  $P = 12$  MPa) allows the adsorption properties of the material to be completely regenerated. The process is accompanied by removal of phenol, dyes and pesticides. The properties of carbon do not deteriorate after a few regeneration cycles.<sup>200</sup> Under more severe conditions ( $T = 873$ – $923$  K,  $P = 25.5$ – $34.5$  MPa) carbon reacts with water to give carbon monoxide and hydrogen; however, short-term gasification favours an increase in the specific surface area and improvement of the adsorption characteristics of activated carbon.<sup>206</sup>

Modified subcritical water can be used to improve fuel quality. For instance, treatment of coal with subcritical water containing nitric acid (4 vol.%) causes extraction of Al, Ca, Mg, Na, K and other ash-forming elements.<sup>207</sup> Subcritical water containing  $\text{HNO}_3$  and KCl can also be used for metal extraction from used industrial oils. After treatment of oil for 270 s up to 90% of Cu, V, Pb, Ni, Cd and Cr goes to the aqueous phase.

It should be noted that though traditional extraction techniques are much simpler to use compared to subcritical and supercritical water extraction, they are often of low selectivity. Extraction under hydrothermal conditions requires the use of complex equipment; however, in this case the process selectivity can be controlled by varying the temperature and pressure.<sup>208</sup>

## VII. Conclusion

Subcritical and supercritical water is finding increasing use as a reagent, acid-base catalyst and a unique environmentally safe solvent whose physicochemical properties can be varied over a wide range. In this review we have tried to demonstrate the possibilities and advantages of the use of subcritical and supercritical water for the synthesis of nanocrystalline materials, in organic synthesis and for solution of environmental problems.

Successful practical application of subcritical and supercritical water requires a deep insight into all features of the physicochemical interactions occurring under hydrothermal conditions on the molecular level. Production of efficient industrial plants requires the design of new materials that are corrosion stable under extreme conditions. Systematic basic and applied research on the possibility of use of subcritical and supercritical water for target organic synthesis and in heterogeneous catalysis should be carried out. In the latter case water at high temperatures and pressures should be considered not only as a medium appropriate for performing catalytic reactions but also as a reagent for the one-step synthesis of multicomponent nanocrystalline heterogeneous catalysts with specified properties. One should expect that, in contrast to traditional systems, catalytic systems prepared under nonequilibrium subcritical and supercritical conditions will be sufficiently stable for the operation in supercritical media.

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# Sorption preconcentration of microcomponents for chemical analysis

Yu A Zolotov, G I Tsysin, E I Morosanova, S G Dmitrienko

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**Abstract.** Data on the methodology of sorption preconcentration are surveyed and the key concepts and quantitative parameters are given. The approaches to the preconcentration are considered, and various sorbents are characterised. Examples of using cellulose, styrene–divinylbenzene sorbents with grafted complexing groups, polyurethane foams and non-covalently modified silica gels, including those prepared by the sol–gel strategy, for preconcentration of inorganic and organic substances and development of combined and hybrid methods of analysis are given. The bibliography includes 357 references.

## I. Introduction

Sorption, in particular, ion exchange, methods for the isolation, separation, and preconcentration of substances are widely used in the chemical and hydrometallurgical processes. The high efficiency of sorption processes in combination with high feasibility ensure the priority development of these methods. Sorption processes are also used on a large scale in analytical chemistry, for example, in chromatography. An essential place is occupied by sorption methods in solving problems of analytical preconcentration.

Preconcentration of microcomponents for determination is used, first of all, in those cases where the sensitivity of direct determination of these components is too low. Preconcentration is also necessary if the component is inhomogeneously distributed in the specimen. In addition, when physical methods of analysis are used, preconcentration makes it possible to manage without a large number of reference samples, in particular, standard samples, because preconcentration provides concentrates on a unified base, for example, in a carbon powder (in the case of atomic-emission analysis). During preconcentration, it is also convenient to introduce so-called internal standards if necessary. Therefore,

preconcentration methods play an exceptionally important role in analytical chemistry.

Development of preconcentration methods, especially during the last two decades, has demonstrated appreciable advantages of sorption preconcentration as a relatively non-laborious process ensuring high preconcentration factors of substances. In particular, of interest is the mobile version of this method, which eliminates the necessity of separating the phases after preconcentration and opens up the way for automation of the whole cycle of analysis including sample preparation.

Thousands of original publications have been devoted to the sorption preconcentration of trace amounts of inorganic and organic compounds. General aspects of this topic have been considered in a number of monographs.<sup>1–5</sup> The sorption preconcentration has been employed to develop combined and hybrid methods for the analysis of environmental objects and industrial, geological, and biological objects. However, the design of new sorbents with specified properties for quantitative recovery of substances from diverse objects remains a topical task. The search for new approaches to determination of compounds after the isolation by sorption, in particular, directly in the sorbent phase, and development of quick, sensitive and simple determination methods are equally important.

This review, based on published data and authors' research, covers the strategy of sorption preconcentration of inorganic and organic compounds and characteristic features of recovery of substances on various sorbents, discusses the approaches to rational coupling of preconcentration methods with methods used for the subsequent determination, and considers the use of sorption preconcentration in the analysis of diverse objects. The review is based on authors' studies carried out together with colleagues at the Preconcentration Laboratory of the Chair of Analytical Chemistry at the Department of Chemistry of the Moscow State University. The purpose of the review is to draw attention to modern sorption preconcentration techniques, to characterise promising sorbents and to reveal their advantages and drawbacks.

## II. Theoretical grounds of the selection of sorption systems for preconcentration under dynamic conditions

Some advantages of dynamic preconcentration have already been noted. To extend the scope of this method, one can also use non-equilibrium conditions for dynamic sorption. For example, the

Yu A Zolotov, G I Tsysin, E I Morosanova, S G Dmitrienko Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax (7-095) 939 46 75, tel. (7-095) 939 55 64, e-mail: zolotov@analyt.chem.msu.ru (Yu A Zolotov), tel. (7-095) 939 55 18, e-mail: tsysin@analyt.chem.msu.ru (G I Tsysin), tel. (7-095) 939 10 56, e-mail: e\_morosanova@mtu-net.ru (E I Morosanova), tel. (7-095) 939 46 08, e-mail: dmitrienko@analyt.chem.msu.ru (S G Dmitrienko)

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selectivity of the collection of a component may be increased by using kinetic features of its sorption and the preconcentration efficiency may be increased when non-equilibrium forms of components are recovered. Despite the good prospects offered by the last-mentioned approaches, they have been little developed as yet.

The last 15–20 years have seen vigorous development of flow analysis techniques which include the stage of dynamic sorption preconcentration (so-called on-line version). In this case, sorption, desorption and determination of components are performed in a cyclic mode, which implies repeated use of the sorbent without a change in its properties. However, not any determination method can be implemented in the on-line mode. Despite the attractive features of this approach, it cannot be applied, for example, for neutron activation or X-ray fluorescence determination of chemical elements. It is also noteworthy that the necessity of desorption leads inevitably to dilution of the concentrate and its dispersion in the flow on the way to a flow-type detector. In addition, the use of on-line preconcentration is expedient only provided that the preconcentration time is commensurable with the time of subsequent detection; otherwise, non-productive expenses related to the no-load running of the detector will increase. This is especially tangible when expensive equipment and valuable consumables, for example, inert gases, are used.

Thus, if on-line detectors are inapplicable, it is expedient to use the off-line version of flow preconcentration to attain high preconcentration factors. In this version, the preconcentration and determination steps are independent of each other and are separated in time. The off-line methods are difficult to automate; however, they possess certain advantages and their existence is thus justified. For example, many molecular-spectroscopic, atomic-spectroscopic and electrochemical methods impose similar requirements on the gross composition of the concentrate for determination of toxic elements (heavy metals) in the environmental objects and foodstuffs. In the preconcentration of the elements, it is necessary to separate the major matrix elements of the sample, first of all, alkali and alkaline earth metals, and organic substances, for example, fulvic acids. When effective sorbents are used in the off-line mode, preconcentration methods can ensure the development of unified sample preparation procedures. The practically facile off-line flow sorption preconcentration of water samples of various types, extracts from soils and plants, *etc.*, yields liquid or solid concentrates, which are suitable for long-term storage and transportation and which can be analysed by a variety of methods.

The use of the off-line and on-line options for preconcentration is determined by the sorbent properties or, strictly speaking, by the relationship between the properties of all components of the sorption system, which includes the sorbent, the solvent (most often, water), and the solutes including the trace component to be concentrated. In view of the sorbent inhomogeneity, the large numbers of components in solutions encountered in real-world tasks, and the diversity and complexity of the chemical and mass transfer processes that occur under non-equilibrium conditions of the dynamic preconcentration, one must admit that strict description of sorption systems is a highly complicated problem. However, without solving this problem, it is difficult to choose properly efficient sorbents and preconcentration systems. Most often, these are chosen empirically, taking into account the chemical properties of the functional group of the sorbent, the mechanical properties of the sorbent and other data. This is a labour-consuming procedure that requires screening of properties of sorption systems. This can be confirmed by tens of thousands of publications dealing with the use of various sorbents for the dynamic preconcentration of elements. Since most publications describe preconcentration of a small number of elements from a rather limited range of solutions, it can be stated that hundreds of variants have been proposed for the solution of similar tasks.

Meanwhile, in chromatography and chemical engineering — which have traditionally used sorption processes — mathematical

models have been developed that establish the relationship between the physicochemical properties of the sorbent, the microcomponent to be recovered, and other sorption parameters.<sup>6,7</sup> Vast experimental material on the physicochemical properties of sorption systems has been accumulated. The development of the theoretical grounds of the dynamic sorption preconcentration using these models has allowed researchers to minimise the amount of experimental studies needed to choose sorbents for preconcentration of elements, to outline the ways for the development (synthesis) of new efficient sorbents, and to propose computation methods for the optimisation of experimental conditions.<sup>8</sup>

## 1. Parameters of the dynamic sorption preconcentration

Like any other preconcentration technique, the dynamic sorption preconcentration is described by the following key parameters.<sup>1,4</sup>

1. Preconcentration factor  $K_{\text{conc}}$  defined as the ratio of the component (element) concentration in the concentrate to that in the initial sample. For the case where the sorbent phase functions as the concentrate,  $K_{\text{conc}} = c_s / c_{0\text{liq}}$  ( $c_s$  is the average concentration of microcomponent in the sorbent bulk,  $c_{0\text{liq}}$  is the starting concentration of the microcomponent in the solution).

2. Recovery of the microcomponent ( $R$ ) is the ratio of the amount of the substance in the concentrate  $m_s$  to that in the bulk of the initial solution  $m_{0\text{liq}}$  ( $R = m_s / m_{0\text{liq}}$ ). It is significant that the  $R$  values for preconcentration of a microcomponent from solutions with different compositions should remain constant; otherwise, when determining a component by a combined method including the preconcentration stage, it would be impossible to use calibration dependences plotted for 'pure' solutions.

3. Preconcentration rate. This value is determined by the time of preconcentration stage  $t_{\text{conc}}$ . In the ideal case,  $t_{\text{conc}}$  should not exceed the time of the subsequent instrument determination of the microcomponent. For the use of advanced instrumental methods of analysis, characterised by high sampling frequency (above 100 element determinations per hour), this parameter becomes not less important than the two previous parameters. In some cases, this value determines whether a system is suitable for dynamic preconcentration.<sup>9–14</sup>

4. Factors that describe the enhancement of the analytical signal. In flow analysis, sorption preconcentration is often characterised by parameters that reflect the growth of the analytical signal due to preconcentration, for example, the enrichment factor ( $EF$ ).<sup>9,14,15</sup> The  $EF$  is calculated as the ratio of the analytical signals obtained before and after preconcentration,<sup>16,17</sup> or as the ratio of the higher and lower concentrations of the analyte responsible for the same magnitude of the analytical signal without and after preconcentration.<sup>18</sup> It has also been proposed to define the  $EF$  as the ratio of the sensitivity coefficients of the determination method attained after and without preconcentration, respectively.<sup>19</sup> Note that in flow systems that include desorption and detection steps, the increase in the analytical signal is not determined by the preconcentration factor alone, being an integrated characteristics of the whole analytical cycle. In the last-mentioned case, the  $EF$  should be called more correctly the enhancement factor.<sup>9</sup>

The dynamic sorption preconcentration can also be characterised by an integral criterion, namely, preconcentration efficiency  $CE$ , which was defined as the product of the enrichment coefficient attained through preconcentration and sampling frequency ( $\text{min}^{-1}$ ).<sup>13,14</sup> According to this definition, the  $CE$  value is independent of the preconcentration or detection techniques and can be used to compare the efficiencies of various systems of flow analysis.<sup>9,14</sup>

The sorption preconcentration under dynamic conditions is characterised by a much higher  $CE$  value than that under static conditions. In the static mode,  $CE$  does not usually exceed  $4 \text{ min}^{-1}$ , whereas in flow analysis,  $CE$  reaches  $30–60 \text{ min}^{-1}$  or even more.<sup>9,14</sup> It has been noted<sup>9</sup> that with the use of advanced spectroscopic methods, the minimum  $CE$  value to justify the on-

line preconcentration compared to the off-line preconcentration from the economical standpoint is about 8 min<sup>-1</sup>.

Meanwhile, this definition of the *CE* does not allow one to distinguish the contribution of the proper preconcentration stage to the overall efficiency of the flow analysis. Moreover, *CE* does not take into account the recovery of the microcomponent. We proposed defining the *CE* value for preconcentration as the preconcentration factor attained per unit time at a specified microcomponent recovery.<sup>8</sup> Note that the preconcentration efficiency defined in this way is proportional to the ratio of the solution space velocity (*w*) to the volume of the sorbent layer (*V*<sub>sorb</sub>),

$$CE = \frac{Rw}{V_{\text{sorb}}} \quad (1)$$

Thus, the *CE* value actually characterises the effective productivity of the sorption preconcentration. Note that for a column with a constant cross-section area *S*, the ratio of the liquid phase space velocity to the volume of the sorbent layer is equal to the ratio of the linear velocity of the liquid phase *v* to the length of the sorbent layer *x*<sub>0</sub>. This can be easily seen if the numerator and denominator in expression (1) are divided by the column cross-section area *S*.

## 2. Comparison of the efficiency of sorption systems

For comparison of sorption systems under dynamic conditions and for elucidation of the optimal conditions of sorption, one should choose criteria describing the efficiency of such systems. This is done using a number of parameters, in particular, the preconcentration factor *K*<sub>conc</sub>, the recovery *R*, the dynamic capacity up to breakthrough, *t*<sub>conc</sub> and *CE*. These parameters are not independent;<sup>9</sup> therefore, efficient preconcentration systems and the optimal preconcentration conditions are usually chosen in the following ways.<sup>20</sup>

1. One parameter is varied, while the other are restricted. This method has found application in the design of low-output process units.

2. A unified optimality criterion is composed. In process engineering, this is an economical criterion that takes into account the contributions of all system parameters in terms of the cost per unit.<sup>20, 21</sup>

When elucidating the optimal conditions of the dynamic sorption preconcentration, variable parameters are also distinguished (usually, the length of the layer and the size of sorbent particles, the column diameter, and the solution flow rate). The preconcentration conditions are chosen by experimental or calculation methods proceeding from the particular task and imposing restrictions on most of the parameters. As in the static version of sorption, the first item is to choose the optimal values for the parameters responsible for chemical reactions in the system: functional groups of the sorbent, pH, composition of the solution, etc.<sup>9–14</sup> Equally important are the sorbent weight, the size and the shape of the sorbent layer, the flow rate of the solution (the optimal values of these parameters have been determined in numerous publications).

In flow sorption spectroscopic systems, the signal-to-noise ratio directly related to the *EF* is often used as the optimality criterion.<sup>9–12</sup> This criterion has been used to determine the optimal solution flow rate during the on-line preconcentration of cobalt on alumina modified by nitroso-R-salt;<sup>22</sup> seven elements on a cellulose sorbent with ethylenediaminetriacetic acid groups;<sup>23</sup> antimony on the CPG-8Q sorbent (glass with a controlled pore size and 8-hydroxyquinoline groups).<sup>24</sup> In the last-mentioned case, the recovery *R* provided an additional restrictive criterion. The optimal amount of the sorbent and the diameter of its layer at a constant length were determined for the on-line preconcentration of lead on basic alumina;<sup>25</sup> Cd, Cu, Ni and Pb on the Resin 122 sorbent;<sup>26</sup> the same elements as complexes with diethyldithiocarbamate on C<sub>18</sub> silica gel;<sup>27</sup> and Al, Cr(III), Fe(III), Ti(IV) and

V(IV) on the Muromac A-1 sorbent.<sup>28</sup> A significant contribution of hydrodynamic factors to the formation of the analytical signal has been noted.<sup>29</sup>

In a number of studies,<sup>30–38</sup> the efficiencies of systems with various sorbents under dynamic conditions have been compared using the microcomponent recovery *R*. However, this comparison is legitimate only provided that other conditions (the sorbent layer size and shape, the flow rate of the solvent, and the preconcentration ratio attained) are the same for all systems, which is far from being always the case.<sup>30, 31</sup>

When the efficiencies of dynamic sorption systems were compared as regards the microcomponent recovery, restriction was imposed on *K*<sub>conc</sub>. For example, the optimal flow rates of the samples were determined for the flow preconcentration of eight elements as complexes with 7-iodo-8-hydroxyquinoline-5-sulfonic acid on the BioRad AG MP 1 anion exchange resin;<sup>30</sup> with 8-hydroxyquinoline on Amberlite XAD-2;<sup>31</sup> or with bis(carboxymethyl)dithiocarbamate on Amberlite XAD-4;<sup>32</sup> ten elements on Chelex-100;<sup>33</sup> and Amberlite XAD-2 modified with 1-(2-thiasolylazo)-2-naphthol;<sup>34</sup> six elements from sea water as diethyldithiocarbamates on SiO<sub>2</sub>-C<sub>18</sub>, Amberlite XAD-2 and XAD-7;<sup>35</sup> Mo and W on the anion exchanger Amberlite IRA-93;<sup>36</sup> Pb on the Spheron-oxine sorbent;<sup>37</sup> Mn on the vinyl gel with immobilised 8-hydroxyquinoline.<sup>38</sup>

The microcomponent recovery has been used as the efficiency criterion in the choice of the optimal quantity of the sorbent and the column dimensions.<sup>31, 38</sup> Having determined the recoveries of several elements, the researchers compared the efficiencies of four sorbents under dynamic conditions.<sup>29</sup> This criterion was used to determine the optimal amount of the sorbent, the length and the cross-section of its layer for preconcentration of cadmium from soil extracts<sup>39</sup> and various forms of copper and lead from natural water as dithiocarbamates on SiO<sub>2</sub>-C<sub>18</sub>.<sup>27</sup>

The *R* value is related to the system capacity 'before breakthrough', which stands for the amount of the substance collected by the sorbent up to the instant where the recovery drops below a specified value.<sup>40</sup> For most tasks, it is taken that *R* = 0.95. The ratio of the average attained concentration of the microcomponent *a* to its equilibrium concentration *a*<sub>0</sub> in the solid phase characterises the fraction of the sorbent capacity that has been spent before the breakthrough (the dynamic sorbent capacity before the breakthrough). In other studies,<sup>40–44</sup> this parameter was used to compare the efficiency of different systems. The dynamic capacity before breakthrough depends, in particular, on the size and the shape of the sorbent layer, the solution flow rate (the pattern of this dependence was determined only in a few cases<sup>40</sup>). It has been noted that by using microcolumns with a great length-to-diameter ratio, one can attain fuller recovery of the microcomponent and a larger before-breakthrough capacity, especially at high *CE* values.<sup>40</sup>

The *CE* value was also used as the efficiency criterion; in this case, restrictions were imposed on *K*<sub>conc</sub> and *R*. Thus, the efficiencies of the Chelex-100, CPG-8Q and Resin 122 sorbents in the preconcentration of heavy metals were compared;<sup>45</sup> the optimal flow rate of the solution for gold preconcentration on Amberlite XAD-7 and XAD-8<sup>46</sup> and cobalt and cadmium preconcentration on CPG-8Q<sup>47</sup> were determined. In the latter case, the optimal amount of the sorbent and the layer shape were also found.

In a number of studies, computation techniques were used to optimise the geometric parameters and the hydrodynamic operating conditions of microcolumns-reactors meant for determination of physiologically active compounds based on the reaction products in flow-injection systems. The formation of the analytical signal in flow-injection systems was described using layer-by-layer models.<sup>48–51</sup> The analysis productivity served as the efficiency criterion, the degree of substance conversion served as the analogue of the recovery and the size of the analytical signal served as an approximate analogue of the preconcentration factor. The efficiency of operation of the reactor was estimated

from the magnitude of the analytical signal (determined by the degree of conversion of the analyte and the longitudinal dispersion of its zone); restrictions were imposed on the system productivity. The layer-by-layer model parameters determined experimentally were used to calculate the optimal volume and the inner diameter of the reactor, the grain diameter of the filler, and the solution flow rate.<sup>51</sup> By imposing additional restrictions on the hydrodynamic resistance, the optimal size and the length of the reactor, and the corresponding reagent and sample consumptions were determined. The calculated parameters were employed to compare the efficiency of reactors of different types.<sup>49</sup> The general principles of their construction were formulated.<sup>50</sup> The possibility of influence of the rate of chemical reactions<sup>48, 50, 51</sup> and the substantial contribution of the longitudinal dispersion to the formation of the analytical signal in these systems have been noted. When the analytical signal is used as the criterion of the efficiency for flow injection systems, the last-mentioned factor can become crucial. This indicates that not only the sorption preconcentration stage, but also the subsequent desorption should be considered separately and perhaps optimised.

Modelling of the sorption dynamics was also employed to calculate the amount of the sorbent and sorption time for the dynamic preconcentration of palladium and platinum on the POLIORGS XI-N sorbent<sup>52</sup> on the basis of previously determined physicochemical parameters. The required flow rate of the solution and recovery were specified for the calculation. Good agreement between the calculated and experimental parameters was noted.

Thus, the dynamic sorption preconcentration is characterised by a set of parameters that depend in an intricate manner on one another and on the physicochemical properties of the system. Therefore, when comparing the efficiencies of various dynamic sorption systems, these parameters should be considered together (this was done, in particular, by Fang<sup>9</sup>). The search for the optimal preconcentration conditions (the region of the highest efficiency of a sorption system) has been performed both empirically and using various theoretical models.

To elucidate the legitimate criteria for comparison of the efficiency of dynamic preconcentration sorption systems, we proposed the use of mathematical models of sorption dynamics.<sup>6–8</sup>

### 3. Mathematical models of sorption dynamics

The sorption under dynamic conditions is a complex heterogeneous process consisting of several successive stages:<sup>6, 7</sup> the transport of the substance in the solution to the sorbent surface; the transport of this substance in the sorbent phase to the point where the chemical reaction takes place; the chemical reaction between the substance and functional groups of the sorbent; the transport of the reaction products in the sorbent phase; the transport of the reaction products from the sorbent surface to the solution bulk. The full mathematical description of processes that occur in the system implies taking into account the contribution of each of these stages to the overall rate of mass transfer, which is a fairly complicated task. The mathematical models proposed for describing sorption include three equations: differential material balance and kinetic equations and the equilibrium equation (isotherm) with initial and boundary conditions.<sup>7</sup> Rather detailed models constructed in this way are called deterministic models. In many cases, these can be simplified by averaging the concentrations of the sorbed substance over some volume of the system. The models thus obtained are called aggregated.<sup>7, 20</sup> If the concentration of the microcomponent in the solution is averaged over some volume of the liquid phase, these models are called layer-by-layer ones.<sup>20, 53</sup> The layer-by-layer method is used to describe the dynamics of sorption of substance mixtures when combined allowance for all kinetic parameters is impossible.<sup>7, 20</sup> As applied to chromatographic systems, it is widely used under the name of the method of 'theoretical plates.'

Methods for the solution of sets of partial differential equations describing the dynamics of sorption are well developed and presented in a number of monographs.<sup>54, 55</sup> Analytical solutions have been obtained only for limiting cases, in particular, for linear and rectangular sorption isotherms, external- and internal-diffusion kinetics.<sup>54</sup> In more complicated cases, approximate and numerical methods are used.<sup>56, 57</sup> The developed algorithms have been implemented as software programs. By using them, it is possible to obtain solutions for any case of diffusion kinetics (external, internal and mixed diffusion).<sup>58–64</sup> The numerical solutions of the problem of external diffusion dynamics for the linear sorption isotherms are tabulated.<sup>64</sup>

### 4. The use of the mathematical model of sorption dynamics for description of preconcentration problems

Dynamic sorption is widely used for various purposes, first of all, for the isolation, preconcentration and separation of substances. However, the efficiency criteria of sorption systems differ appreciably in various applications, depending on the task to be solved. For example, in solving most of process engineering problems, the key criterion is represented by the 'specific reduced costs.' During dynamic preconcentration, it is important to quantitatively isolate the microcomponent from the solution using the smallest possible amount of the sorbent (*i.e.*, the capacity before breakthrough should be high) over the shortest period of time (*i.e.*, the flow rate of the solution should be high), which is especially important in flow systems. Thus, of the parameters describing dynamic preconcentration, the preconcentration efficiency *CE* and the preconcentration factor  $K_{\text{conc}}$  are most general.

Note that the *CE* does not reflect in any way the true value of the preconcentration factor  $K_{\text{conc}}$  or, in other words, the dynamic capacity of the sorbent. Thus, the problem of preconcentration, unlike technological problems, can be formulated as follows: in a sorption system, it is necessary to attain the highest possible *CE* value at a specified  $K_{\text{conc}}$  or, *vice versa*, the highest  $K_{\text{conc}}$  at a specified *CE* value. The former version rather applies to the solution of off-line problems where a microcomponent is to be collected from large solution volumes. The latter is more important in on-line systems where the dimensions of the column and the flow rate of the solution are restricted by the system design, the preconcentration being limited by column capacity. In any case, the *CE* and  $K_{\text{conc}}$  values considered simultaneously ensure a well-posed characterisation of the efficiency of the sorption system for preconcentration of the given microcomponent.

Let us consider the mathematical model of sorption dynamics.<sup>8</sup> Let the  $\eta$  value mean the fraction of the total sorbent capacity that has been used by the end of preconcentration,

$$\eta = \left[ \int_0^l a(x, t) dx \right] / \Gamma c_0,$$

where  $a$  is the concentration of the microcomponent in the bulk of the solid phase,  $t$  is time,  $\Gamma$  is a dimensionless distribution coefficient of the microcomponent ( $\text{ml ml}^{-1}$ ),  $\Gamma = K_{\text{conc}}/\eta$ ,  $c_0$  is its initial concentration in the solution. Note that within the bounds of the chosen and substantiated mathematical models, the  $\eta$  value can be calculated as a function of the dimensionless variables,  $X$  and  $T$  (the dimensionless sorption length and time), where  $X = \beta x/v$ ;  $T = \beta t/\Gamma$  ( $\beta$  is the effective mass transfer coefficient for the microcomponent in the solution,  $v$  is the linear velocity of the flow of the liquid phase).

For further calculations, it is convenient to represent  $\eta$  as isolines in the  $X-T$  plane (Fig. 1). The limiting value of  $\eta$  is 1, *i.e.*, the limiting value of  $K_{\text{conc}}$  is  $\Gamma$ . This provides the limitation for the sorbent capacity, namely, the  $\Gamma$  value cannot be lower than the required  $K_{\text{conc}}$ .

The second limitation is related to the allowable breakthrough level  $\chi$ . This means that the substance loss during sorption cannot be higher than a particular fraction of all substance that entered the layer, namely:

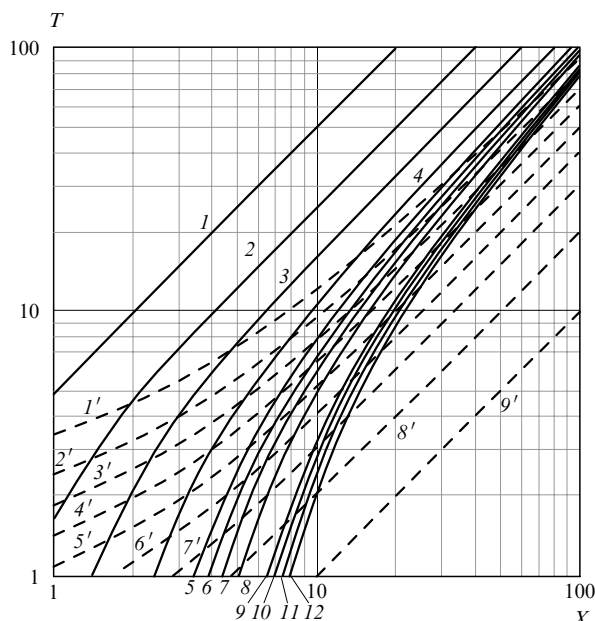


**Figure 1.** Theoretical function of the specific cumulative breakthrough  $\chi$  (continuous lines) and fractions of the sorbent used  $\eta$  (dashed lines) in the case of external diffusion dynamics and linear sorption isotherm in the  $X$ – $T$  coordinates used to determine the maximum attainable preconcentration efficiency.

$\chi$ : 0.8 (1), 0.6 (2), 0.4 (3), 0.2 (4), 0.1 (5), 0.07 (6), 0.05 (7), 0.03 (8), 0.01 (9), 0.007 (10), 0.005 (11), 0.003 (12);

$\eta$ : 0.9 (1'), 0.8 (2'), 0.7 (3'), 0.6 (4'), 0.5 (5'), 0.4 (6'), 0.3 (7'), 0.2 (8'), 0.1 (9').

$$\chi = \frac{m_{\text{liq}}}{m_{0\text{liq}}} = \frac{m_{0\text{liq}} - m_s}{m_{0\text{liq}}}.$$

Note that the  $\chi$  value is related to  $R$  by a simple relation  $\chi = 1 - R$ . It can also be calculated as a function of  $X$  and  $T$  for each type of kinetics and is represented as a series of theoretical curves.<sup>64</sup> Like the function  $\eta$ , this function is convenient to depict as isolines in the  $X$ – $T$  plane (see Fig. 1).<sup>8</sup>

The values of  $\eta(X, T)$  and  $\chi(X, T)$  found numerically using appropriate software are tabulated.<sup>64</sup>

A remarkable feature of this way of tackling the preconcentration problem (where it is necessary to attain a specified  $K_{\text{conc}}$  without losing more than  $m_{\text{liq}}$  of the microcomponent weight) is that the problem can be solved in terms of dimensionless variables with the restrictions already made. If metrological requirements have been specified as definite  $\eta$  and  $\chi$  values, the only  $X_{\text{opt}}$  and  $T_{\text{opt}}$  values corresponding to them can be found by a simple graphical operation, in particular, by matching two plots for  $\eta$  and  $\chi$  in the  $X$ – $T$  plane (Fig. 1).

Thus, in terms of dimensionless variables, we have a unique solution for the dimensionless length  $X_{\text{opt}}$  and the sorption time  $T_{\text{opt}}$ . The dimensional expressions for  $x_0$  and  $t_0$  are defined, in the case of external diffusion, by the relations

$$x_0 = \frac{X_{\text{opt}} v}{\beta}, \quad t_0 = \frac{T_{\text{opt}} \Gamma}{\beta}, \quad (2)$$

and for the internal-diffusion sorption kinetics, by the relations

$$x_0 = \frac{X_{\text{opt}} d^2 v}{4D\Gamma}, \quad t_0 = \frac{T_{\text{opt}} d^2}{4D}, \quad (3)$$

where  $d$  is the diameter of sorbent particles,  $D$  is the internal diffusion coefficient.

The  $X_{\text{opt}}$  and  $T_{\text{opt}}$  values determine the corresponding  $CE_{\text{max}}$ , i.e., the maximum preconcentration efficiency attainable in the system with specified  $K_{\text{conc}}$  and  $R$  (because  $\eta$  and  $\chi$  are specified).

Thus, we arrive at an important conclusion — in any sorption system and for specified preconcentration ratio and recovery of the microcomponent, one can calculate the maximum attainable preconcentration efficiency  $CE_{\text{max}}$ , which can serve as a universal criterion for comparison of the efficiency of dynamic sorption systems as regards their application for preconcentration of microcomponents.

The value of  $CE_{\text{max}} = T_{\text{opt}} \Gamma / X_{\text{opt}} t_0$  depends on  $t_0$ , which is determined by expressions (2) and (3); hence, it is related unambiguously to the  $v$ ,  $d$  and  $\Gamma$  parameters. It follows from (2) and (3) that the smaller the grain size of the sorbent and the higher the flow rate of the liquid phase, the higher the preconcentration efficiency. However, it is clear that  $v$  cannot be increased and  $d$  cannot be decreased infinitely if for no other reason than from hydrodynamic considerations.

For analysis of the reasons for different efficiencies of sorption systems in preconcentration processes, it is necessary to estimate the degree to which the thermodynamic and kinetic sorption parameters and the particle size of the sorbent influence the generalised efficiency criterion,  $CE_{\text{max}}$ , for specified  $K_{\text{conc}}$  and  $R$ . To solve this problem,  $CE_{\text{max}}$  values were calculated for various  $\Gamma$ ,  $\beta$ ,  $D$  and  $d$ .<sup>8</sup> The calculations were carried out for different kinetic mechanisms of sorption (Tables 1 and 2).

**Table 1.** Maximum attainable preconcentration efficiency  $CE_{\text{max}}$  ( $\text{s}^{-1}$ ) calculated for the external-diffusion mass transfer mechanism ( $K_{\text{conc}} = 1000$ ,  $R = 95\%$ ).

| $10^{-3} \Gamma$<br>/ml ml <sup>-1</sup> | $\beta$ /s <sup>-1</sup> |                       |                       |                       |                       |
|------------------------------------------|--------------------------|-----------------------|-----------------------|-----------------------|-----------------------|
|                                          | 0.01                     | 0.05                  | 0.1                   | 0.5                   | 1.0                   |
| 1.11                                     | $1.8 \times 10^{-4}$     | $9.1 \times 10^{-4}$  | $1.8 \times 10^{-3}$  | $9.1 \times 10^{-3}$  | $1.8 \times 10^{-2}$  |
| 1.25                                     | $3.89 \times 10^{-4}$    | $1.95 \times 10^{-3}$ | $3.89 \times 10^{-3}$ | $1.95 \times 10^{-2}$ | $3.89 \times 10^{-2}$ |
| 2.0                                      | $1.2 \times 10^{-3}$     | $6.0 \times 10^{-3}$  | $1.2 \times 10^{-2}$  | $6.0 \times 10^{-2}$  | $1.2 \times 10^{-1}$  |
| 5.0                                      | $2.4 \times 10^{-3}$     | $1.2 \times 10^{-2}$  | $2.4 \times 10^{-2}$  | $1.2 \times 10^{-1}$  | $2.4 \times 10^{-1}$  |
| 10 (see <sup>a</sup> )                   | $2.85 \times 10^{-3}$    | $1.43 \times 10^{-2}$ | $2.85 \times 10^{-2}$ | $1.43 \times 10^{-1}$ | $2.85 \times 10^{-1}$ |

<sup>a</sup> Here and in Table 2, obtained by extrapolation.

It follows from the data of Table 1 that in the case of external-diffusion sorption kinetics, an increase in the mass transfer coefficient by a factor of 10 results in an identical change in the  $CE_{\text{max}}$ , while the same increase in the distribution coefficient results in an approximately 16-fold increase in the  $CE_{\text{max}}$ , i.e., the thermodynamic sorption parameter impacts  $CE_{\text{max}}$  to somewhat a greater extent than the kinetic one.

In the case of internal-diffusion sorption kinetics,  $CE_{\text{max}}$  depends on the thermodynamic parameter to a markedly greater extent than on the kinetic one. Indeed, an 8-fold increase in  $\Gamma$  induces an increase in  $CE_{\text{max}}$  by more than two orders of magnitude; a similar change in the  $CE_{\text{max}}$  requires an increase in  $D$  (and  $1/d^2$ ) also by two orders of magnitude (Table 2).

The efficiency criterion of sorption systems for preconcentration ( $CE_{\text{max}}$  at specified  $K_{\text{conc}}$  and  $R$  values) and the method for its

**Table 2.** Maximum attainable preconcentration efficiency  $CE_{\text{max}}$  ( $\text{s}^{-1}$ ) calculated for the internal-diffusion mass transfer mechanism ( $K_{\text{conc}} = 1000$ ,  $R = 95\%$ ).

| $10^{-3} \Gamma$<br>/ml ml <sup>-1</sup> | $4D/d^2$ /s <sup>-1</sup> |                       |                       |                       |                    |
|------------------------------------------|---------------------------|-----------------------|-----------------------|-----------------------|--------------------|
|                                          | $1 \times 10^{-10}$       | $1 \times 10^{-8}$    | $1 \times 10^{-6}$    | $1 \times 10^{-4}$    | $1 \times 10^{-2}$ |
| 1.25                                     | $8.9 \times 10^{-8}$      | $8.9 \times 10^{-6}$  | $8.9 \times 10^{-4}$  | $8.9 \times 10^{-2}$  | 8.9                |
| 2.0                                      | $4.44 \times 10^{-7}$     | $4.44 \times 10^{-5}$ | $4.44 \times 10^{-3}$ | $4.44 \times 10^{-1}$ | 44.4               |
| 5.0                                      | $2.79 \times 10^{-6}$     | $2.79 \times 10^{-4}$ | $2.79 \times 10^{-2}$ | 2.79                  | 279                |
| 10 (see <sup>a</sup> )                   | $9.71 \times 10^{-6}$     | $9.71 \times 10^{-4}$ | $9.71 \times 10^{-2}$ | 9.71                  | 971                |



calculation allow a legitimate comparison of sorption systems. The following procedure was proposed for the selection of an efficient sorption system for dynamic preconcentration.<sup>8</sup>

1. Published data or experimental results (obtained, for example, by the method of dynamic breakthrough curves) are used to determine the kinetic sorption mechanism and the  $\Gamma$  (or the distribution coefficient  $K_d$ ),  $\beta$  or  $D$  values. This is done using mere matching of the theoretical and experimental curves.

2. Proceeding from the preconcentration factors  $K_{\text{conc}}$  needed to attain the specified detection limit in a combined method involving a sorption preconcentration stage, the required  $\eta$  value is calculated, the allowable breakthrough value  $\chi$  is specified (usually, it is equal to 0.05). Then the intersection point of the calculated  $X_{\text{opt}}$  and  $T_{\text{opt}}$  curves (corresponding to these  $\eta$  and  $\chi$ ) is found in the  $X$ – $T$  coordinates (Fig. 1). These values are used to calculate the maximum preconcentration efficiency  $CE_{\text{max}}$  attainable in this system. The sorption system that ensures the highest  $CE_{\text{max}}$  value, all other factors being the same, is the most efficient.

### III. Preconcentration of metal ions on polymeric sorbents with conformationally mobile aminocarboxyl groups

Complexing sorbents are often used for preconcentration of metal ions from solutions. Sorption in these systems is highly efficient if the solid-state metal compounds are stable and are formed at a high rate. When reacting with a metal ion, the sorbent acts as a ligand whose heteroatoms fill the metal coordination sphere either completely or partially. Various approaches to ensuring the efficiency and selectivity of these sorbents have been proposed and are successfully developing. These approaches are based, first of all, on the formation of a functional group required for optimal filling of the metal coordination sphere.

A traditional way is to design the sorbent taking into account the basicity of the heteroatoms of functional groups and the basicity of the species to be preconcentrated. In this case, the complexing groups are chosen on the basis of extensive knowledge accumulated in the field of monomeric analytical reagents. The geometric (spatial) factors are taken into account to a lesser extent.

#### 1. Development of new sorbents

Complexing sorbents of new types are developed deliberately, proceeding from the expected structure of the complex of an element with the monomeric ligand. The ability of the metal ion to form the optimal coordination polyhedron from a set of heteroatoms offered depends on the basicity of the donor atoms of the functional groups of the ligand and on the conformational mobility of these atoms, the latter being mainly determined by the possibility of bond angle and bond length distortions in these functional groups. Unlike solutions, the mobility of donor atoms in the complexing groups grafted onto a polymer matrix is restricted by both the conformational rigidity of the matrix and the length and the conformational mobility of the spacer, *i.e.*, the fragment that links the polymer matrix to the complexing group. The grafting density of the functional groups on the polymer is also important. (In the case where the polymer matrix is modified by polydentate ligands able to saturate the coordination sphere of the element, the requirement of high density of complexing groups and relatively long spacers become less stringent, because the complexation capacity is determined only by the conformational mobility of the grafted polydentate ligand.) The lower efficiency of interaction of metal ions with grafted groups compared to the corresponding monomeric reagents in solution is due, first of all, to the distortion of the resulting coordination polyhedron. In our opinion, an increase in the coordination mobility of the donor atoms incorporated in the functional groups of sorbents should

reduce the steric hindrance to the formation of the coordination sphere required for the given element.<sup>65</sup>

The complexation scheme considered<sup>65</sup> is not universal and has some limitations. In some cases, an increase in the number of donor atoms and in the spacer length can result in enhanced steric hindrance to complexation. However, generally, this scheme can show the way to the perfection of known and the development of new complexing sorbents.

Within the bounds of the proposed approach, sorbents based on polystyrene and poly(vinyl chloride) containing diethylenetri-aminetetraacetate (DETATA) groups were synthesised. The synthesis was carried out by condensation of chlorine-containing compounds with amines followed by treatment of the aminated products with monochloroacetic acid in an alkaline medium.<sup>66,67</sup> Gel-type chloromethylated polystyrene with a cross-linking degree of 2% (grain diameter 40–80  $\mu\text{m}$ ) and poly(vinyl chloride) fibre with a fibre diameter of 8–12  $\mu\text{m}$  were used. Cellulose-based sorbents were synthesised using a fibre (with a diameter of 10–20  $\mu\text{m}$ ) and ‘blue ribbon’ grade filter paper.

The results of experiments carried out under static conditions showed the advantage of sorbents with conformationally mobile groups over ‘usual’ aminocarboxyl sorbents, caused by the formation of stable coordinatively saturated complexes in the sorbent phase (Fig. 2).<sup>65,66</sup> Thus the equilibrium distribution coefficients  $K_d$  for the sorption of Mn(II), Ca, Co(II), Cu(II) and Zn on the polystyrene-based DETATA sorbent in the pH range most favourable for sorption are 1–1.5 orders of magnitude higher than those for the sorption of the same metals on the widely used Dowex A-1 sorbent (an analogue of Chelex 100) with iminodiacetate (IDA) groups. The dynamic capacity before breakthrough can serve as a criterion for comparison of dynamic sorption systems. As mentioned above, the use of this criterion is not completely legitimate<sup>8</sup> but fairly illustrative, for example, for the comparison of sorption filters (Table 3).<sup>66</sup> All other factors being the same (composition of the solution, solution flow rate, filter size), the capacity of DETATA filters is several times higher than that of the previously synthesised filters with IDA groups or EDTA-type groups in which one nitrogen atom is quaternary.

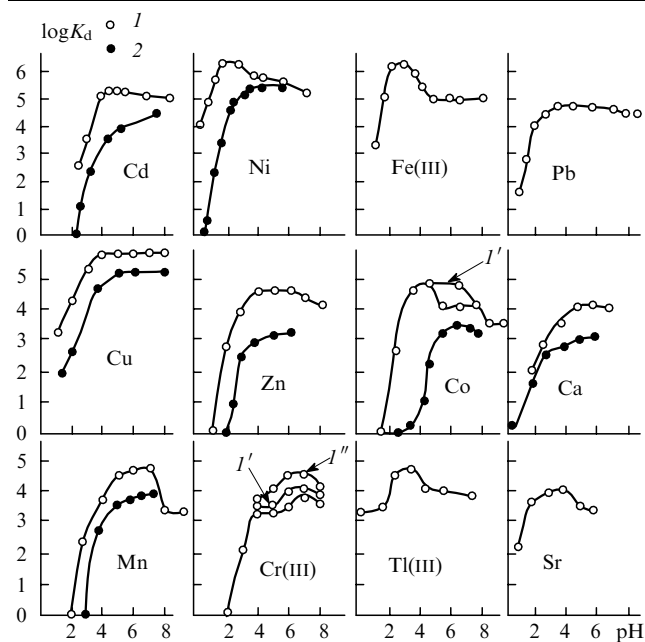


**Figure 2.** Distribution coefficients of some metals on aminocarboxyl sorbents.

(1) Polystyrene sorbent with DETATA groups; (2) Dowex A-1 sorbent;  $V_{\text{soln}} = 100 \text{ ml}$ ,  $m_{\text{sorb}} = 50 \text{ mg}$ ,  $20^\circ\text{C}$ ;  $t = 0.5$  (I, 2), 1 (I'), 3 h (I'').

**Table 3.** Capacity before breakthrough of some filters with aminocarboxyl groups ( $v = 1.0 \text{ ml min}^{-1} \text{ cm}^{-2}$ , pH 5.0).

| Filter | Before-breakthrough capacity of the filter<br>$/\mu\text{mol litre}^{-1} \text{ g}^{-1}$ |     |        |         |
|--------|------------------------------------------------------------------------------------------|-----|--------|---------|
|        | Co(II)                                                                                   | Zn  | Mn(II) | Fe(III) |
| EDTA   | 197                                                                                      | 209 | –      | 160     |
| IDA    | 171                                                                                      | 157 | –      | 109     |
| DETATA | 771                                                                                      | 671 | 445    | 340     |

## 2. Preconcentration of elements on DETATA sorbents

Under dynamic sorption conditions, sorbents are used most often in columns (columns, cartridges or cylinders) or as filters. The column version is preferred as regards the subsequent desorption because the dead volume of a column is much smaller than those of devices used for filter locking-up. In our studies, the elements were collected on microcolumns with a sorbent ( $d = 2-3 \text{ mm}$ ;  $l = 10-15 \text{ mm}$ ,  $V_{\text{col}} = 0.03-0.12 \text{ ml}$ ) and on cellulose filters with the same grafted groups (filter diameter, 25 mm; filter thickness, 0.15 mm, diameter of the filtering surface, 22 mm).<sup>68-71</sup>

A study of the mass transfer kinetics for metals during sorption on DETATA sorbents has shown<sup>72</sup> that high thermodynamic and kinetic sorption parameters and small size of sorbent grains and fibres ensure the quantitative recovery of metals even with exceptionally high flow rates of the solution. For example, it was found that Cd, Co, Cu, Fe, Mn, Pb and Zn (in a concentration of  $0.01 \mu\text{g ml}^{-1}$ ) are quantitatively recovered from 100 ml of a 0.1 M solution of ammonium acetate (pH 5) on a 0.03-ml column at a solution flow rate of up to  $20 \text{ ml min}^{-1}$  (see Ref. 73). An increase in the flow rate of the solution through a two-filter tandem to  $4 \text{ ml min}^{-1} \text{ cm}^{-2}$  ( $14 \text{ ml min}^{-1}$  through the filtering surface with  $d = 22 \text{ mm}$ ) does not lead to a loss in Cd, Co, Cu, Fe, Mn, Ni, Pb or Zn at the preconcentration stage ( $V_{\text{soln}} = 100 \text{ ml}$ ).<sup>74</sup> Thus, quick preconcentration of metals from large solution volumes is possible.

### a. Study of the effect of the major inorganic components of solutions on the sorption of heavy metals

It has been found that Cd and Pb are quantitatively collected on a column with a sorbent even in the presence of  $10 \text{ g litre}^{-1}$  of Ca and Mg and  $100 \text{ g litre}^{-1}$  of Na. Similar results have been obtained for Co, Cu, Ni and Zn. Some decrease in the recovery (down to 85%–90%) at high concentrations of alkali and alkaline earth metals was observed only for Mn sorption.<sup>73, 75</sup>

The recovery of Cd and Pb does not decrease either in the presence of iron (up to  $0.1 \text{ g litre}^{-1}$ ), whereas aluminium ( $0.05 \text{ g litre}^{-1}$ ) suppresses appreciably their sorption. With an iron concentration of  $10 \text{ g litre}^{-1}$ , the recovery of lead is equal to 96%. The pronounced influence of aluminium on the sorption of Cd and Pb may be due to the higher stability of complexes of the macrocomponent with respect to those formed by the microcomponents in the sorbent phase. Lead forms more stable complexes with functional groups than cadmium (and, apparently, iron), and is successfully recovered from solutions in the presence of this macrocomponent.<sup>75</sup>

A potential masking reagent for Al, Ca and Fe, namely, the citrate ion almost does not decrease the distribution coefficients or the recovery of Cd and Pb during sorption on DETATA sorbents and, therefore, it can be used to bind the macrocomponents when collecting these elements from solutions of complex composition.<sup>75</sup> For example, in the presence of citrate, the recovery of Cd and Pb from solutions with high contents of Al and Fe increases, quantitative extraction of microcomponents being observed when the citrate concentration is equimolar to the concentration of the macrocomponent.

In order to choose conditions for the preconcentration of lanthanides in the presence of the key matrix components of sedimentary rocks and elements creating noise in determination of

lanthanides by inductively coupled plasma atomic emission (ICP-AES), sorption of Al, Ba, Cr(III), Fe(III), Mo(VI), Sr, Ti(IV), V(V), W(VI) and Zr was studied. It was found that DETATA polymers do not exhibit high selectivity with respect to lanthanides. To reduce sorption of interfering elements, 5-sulfosalicylic acid was proposed as the masking reagent. In the presence of this reagent, sorption of other elements was suppressed and lanthanides can be recovered quantitatively over a broad pH range.<sup>76, 77</sup>

Chromium(III) is recovered quantitatively on the DETATA sorbent at pH 7, while chromium(VI), at pH 3; in addition, these pH values allow almost complete separation of these chromium forms. However, during sorption of this element, the equilibrium is attained slowly. The efficiency of chromium collection under both static and dynamic conditions increases when sorption is carried out in a microwave field.<sup>78</sup>

The sorption of Ag, Bi(III), In and Tl(III) from sea water on microcolumns with the DETATA-sorbent based on polystyrene has been studied under dynamic conditions. An increase in the content of alkali and alkaline earth metal salts in water to  $200 \text{ g litre}^{-1}$  does not decrease the recovery of the target elements.<sup>79</sup>

The experiments dealing with the effect of Na, K, Mg and Ca on the sorption of Cd, Cu(II) and Zn on DETATA filters were carried out over a broad range of concentrations of macrocomponents ( $0$  to  $100 \text{ mg litre}^{-1}$ ), which is fairly typical of the surface fresh water.<sup>74</sup> It was shown that potassium has a minor influence on sorption of copper and cadmium. In terms of their influence on the sorption of copper and cadmium, other macrocomponents can be arranged in the sequence  $\text{Mg} > \text{Ca} > \text{Na}$ .

The sorption of trace amounts of Mn(II) and Zn on DETATA filters as a function of the concentration of the same salt components in natural waters has been studied by the radio-isotopic tracer method.<sup>66, 70</sup> These elements are recovered quantitatively even when the concentrations of macrocomponents exceed markedly the natural level. Similar results have been obtained for the preconcentration of Bi, Cd, Co, Cu, Fe, In, Mn, Ni, Pb, Tl and Zn from sea water.<sup>74</sup> For increasing the recovery of heavy metals at high concentrations of inorganic components, it is better to use a tandem of two or three filters.

### b. Effect of some organic substances on the sorption of heavy metals

Fulvic acids are the major organic components of natural water and soil extracts able to affect the sorption of metals. In fresh water, they account for 60%–90% of the dissolved organic compounds, while in sea water, almost 100%. Fulvic acids are involved in complex formation mainly through the carboxy and hydroxy groups.<sup>74</sup>

The sorption of cadmium and lead on microcolumns with the DETATA sorbent from model solutions containing fulvic acids isolated preliminarily from river water has been studied.<sup>74, 75</sup> The presence of up to  $50 \text{ mg litre}^{-1}$  of fulvic acids barely influences the recovery of the target elements.

The dependence of the recovery of Cu(II) and Cd on filters on the colouring of model solutions caused by the presence of fulvic acids has been studied. The concentration of fulvic acids typical of the superficial land water has little influence on the recovery of Cu and Cd on DETATA filters.<sup>74</sup>

The high stability of heavy metal complexes in the DETATA sorbent phase suggests that these elements could be preconcentrated from juices or wines and other alcoholic beverages. It was found that a key complexing macrocomponent in these solutions, namely, citrate, does not influence the sorption of cadmium and lead on microcolumns up to a concentration of  $0.2 \text{ mol litre}^{-1}$  (Ref. 75). Similar results were obtained in the cadmium and lead preconcentration from tartrate-containing solutions.<sup>72</sup>

The conditions chosen for the dynamic preconcentration of Cd and Pb were applied to study the recovery of Co, Cu, Mn, Ni and Zn from various waters and solutions obtained after auto-clave digestion of some foodstuffs.<sup>80</sup> The recovery of all elements on a 0.03-ml microcolumn at a flow rate of  $6 \text{ ml min}^{-1}$  (200 sorb-

ent volumes per min) or on DETATA filters from solutions containing inorganic and organic macrocomponents amounts to 96%–99%. Quantitative recovery of Cd and Pb from solutions obtained after the autoclave digestion of soil (clay loam) is attained by adding  $0.02 \text{ mol litre}^{-1}$  of citrate.<sup>75</sup>

### 3. Methods for determination of elements that include dynamic preconcentration on DETATA sorbents

The techniques of the dynamic preconcentration of heavy metals have been used to develop highly sensitive combined methods for determination of these elements in various objects. The high efficiency of the chosen preconcentration systems ensured better metrological characteristics of these methods compared not only to direct methods but also to the methods proposed previously that involve sorption preconcentration.

#### a. Methods involving preconcentration and determination of the elements directly in the solid concentrate

The advantage of this combined approach is that high preconcentration factors ( $10^3$ – $10^4$  and more) are attained and, as a consequence, the detection limits are reduced compared to those attained in direct determination. However, the drawbacks of these combined methods are rather significant. As a rule, it is necessary to dry the concentrate and to transfer it from the preconcentration system into the system for determination. In the optimisation of the conditions for element determination by the combined method, it is necessary to take into account the influence of the solid matrix of the sorbent on the formation of the analytical signal; these effects can be more pronounced with solid concentrates than in the case of liquid ones. Methods that include determination of elements in solid concentrates usually cannot be fully automated. Some important analyses carried out by this method are considered below.

1. Sorption coupled with X-ray fluorescence determination of As, Cd, Co, Cr, Cu, Fe, Hg, Mn, Ni, Pb, Se, V and Zn in potable, natural and waste waters. X-ray fluorescence analysis (XFA) is known to be a widely used instrumental method for determining the elemental composition of natural and industrial materials, which is due to the simple instrumentation (especially in recent years), the possibility of multiple-element determination, high reproducibility and relatively low cost. However, until recently, this method has found only limited application for determination of minor concentrations of elements, in particular, in environmental objects due to low sensitivity.

For XFA determination of elements, it is useful to employ cellulose filters as substrates, as the fluorescence of the filter elements (C, H, N, O) does not fall in the spectral range covered and the small thickness and low density of the filters minimise the absorption and scattering of the primary and fluorescence emission. The data we obtained on the sorption of elements from solutions of complex composition on the DETATA filters were used to develop simple procedures involving sorption and X-ray fluorescence determination of a number of elements in potable, natural and treated waste waters and in urine.<sup>70, 71, 74, 81</sup>

When developing these procedures, three different spectrometers were used: an energy-dispersive spectrometer (a Si–Li semiconductor detector with a resolution of 180 eV at the  $\text{MnK}_\alpha$  line, a Kevex X-ray tube with an Ag anode and a Link Analytical spectrometer tract) and portable single-crystal diffraction Spark-1M and Spectroscan-001 instruments. The detection limits of elements in solutions were  $1$ – $5 \text{ } \mu\text{g litre}^{-1}$ , the relative standard deviation ( $s_r$ ) of the results did not exceed 0.06 over broad ranges of element concentrations.<sup>70, 74, 81</sup>

2. Determination of chromium forms in water by sorption coupled with atomic-absorption spectrometry (with electrothermal atomisation).<sup>78</sup> The procedure proposed for separate preconcentration of Cr(III) and Cr(VI) on the polystyrene-based DETATA sorbent made it possible to develop a procedure for determination of these species in river water. Chromium(III) and chromium(VI) were extracted from solutions at pH 3 and 7 on a

microcolumn with the sorbent (0.03 ml) placed in a microwave oven. Chromium was determined in solid and liquid concentrates by the atomic-absorption method with electrothermal atomisation at a wavelength of 357.9 nm, the background absorption being corrected based on broadening of the resonant absorption line. The detection limit of chromium (both in the case of determination in an aqueous suspension of the sorbent and after desorption with 6 M HCl) amounted to  $30 \text{ ng litre}^{-1}$  ( $K_{\text{conc}} = 100$ ). The method shows a high reproducibility; the  $s_r$  value did not exceed 0.05 in the region of chromium concentrations of  $0.2$ – $10 \text{ } \mu\text{g litre}^{-1}$ .

3. Determination of Ag, Bi, Cd, In, Pb and Tl in natural waters by sorption coupled with atomic-absorption spectrometry (with electrothermal atomisation).<sup>79, 82</sup> Two-chamber graphite atomisers of the crucible–cell type with independent heating of the vaporisation and atomisation zones, Saturn-2 and AAS-3 spectrometers and an experimental multichannel atomic-absorption/atomic-fluorescence setup were used. The atomiser crucibles with the bottom made of a porous graphite filter (disc) were employed as the microcolumns for dynamic preconcentration of elements. The dynamic preconcentration in the crucible/microcolumn with subsequent electrothermal atomic-absorption determination resulted in the following detection limits of elements:  $0.3$ – $1$  (Ag, Cd) and  $2$ – $10 \text{ ng litre}^{-1}$  (Bi, Pb, Tl). The relative standard deviation for a single determination of elements was  $0.1$ – $0.3$ , which complies with the goals of geochemical and ecological studies.

4. Determination of elements in waters by sorption coupled with neutron activation analysis. It has been demonstrated that the dynamic preconcentration of a broad range of elements can be easily combined with neutron activation determination.<sup>83</sup> For element preconcentration and determination, a special quartz cell acting as a microcolumn was used. The concentrates obtained were exposed to a neutron flux directly in these cells in an IR-8 reactor (the neutron flux density  $n \times 10^{14} \text{ n cm}^{-2} \text{ s}^{-1}$ ). The spectra were recorded using an HPGe detector (resolution 1.8 keV on the 1332.5 keV line) connected to a NUC-810 multichannel analyser. Two analysis protocols were used: (1) irradiation of the sorbent with the concentrate for  $5$ – $10 \text{ h}$ , storage the samples for a week after irradiation and determination of Au, Ba, Cd, Co, Cr, Eu, Fe, Hg, La, Mn, Sc, Sr and Zn; (2) irradiation of the sorbent with the concentrate for  $40$ – $60 \text{ s}$  for determination of Cu, In, Mn, V and some lanthanides.

#### b. Flow analysis for determination of elements involving preconcentration on sorbents with aminocarboxyl groups

A decrease in the proportion of human labour in performing analyses is a priority task in analytical chemistry. The extensive use of microprocessor-based units provided the possibility for the development of automated analytical systems characterised by high sampling frequency, good metrological characteristics and relatively low cost. Unfortunately, automated systems are still seldom used in the environment monitoring and quality control of foodstuffs where it may be necessary to take urgent measures on the basis of analysis of large series of samples.

It is relatively simple to automate analytical systems with flow detectors: atomic absorption, atomic fluorescence, inductively coupled plasma atomic emission, spectrophotometric, some electrochemical detectors and so on. A popular and rapidly developing way for automation of the sample preparation in the analysis of solutions is the use of flow-injection devices. Despite the relative simplicity of this equipment (usually this includes one or two peristaltic pumps, one to three injection valves and a simple electronic control device), its use not only ensured automation of numerous methods of analysis but also substantially increased the sampling frequency and improved the metrological characteristics, first of all, the sensitivity and reproducibility of the analysis.

In our opinion, for using sorption systems in flow methods of analysis, it is necessary and sufficient that the following conditions be met:<sup>84</sup>

— the microcomponent should be recovered quantitatively on a sorbent at a high flow rate of the solution (this ensures accumulation on the column of an amount of the analyte needed for reliable detection);

— the microcomponent is desorbed quickly and quantitatively by a desorbing solution suitable for detection; the sorption properties should not change after repeated sorption–desorption cycles;

— the capacity of the sorbent in the column should be sufficient for the recovery of the microcomponent from the solution under analysis in amounts exceeding the absolute limits of the subsequent detection;

— to decrease the dispersion of the concentrate zone in the stream, the dimensions of the column with the sorbent should be as small as possible;

— the sorbent should be sufficiently selective for the recovery of the target microcomponents in the presence of other components of the solution.

In flow analysis systems involving preconcentration, the analytical signal is formed under non-equilibrium conditions — when the concentrate zone resulting from the element desorption passes through the flow detector.<sup>84</sup> Attaining the maximum signal-to-noise ratio under the non-steady-state conditions existing in the flow system requires optimisation of the conditions for the desorption of metals from the column (the composition and concentration of the desorbing solution and the flow rate of this solution), conditions for analytical signal processing and some design factors of the flow system: flow distribution at various stages of the analysis cycle, some pipeline diameters, and the shape and dimensions of the column with the sorbent.

The sorption systems we proposed were chosen to ensure the highest efficiency, and they comply with most of the above requirements. The use of these systems in combination with flow detectors made it possible to develop automated highly sensitive flow techniques for determination of a large number of elements and to extend the range of objects suitable for analysis.

1. Flow sorption coupled with atomic absorption for determination of Cd, Co, Cu, Fe, Mn, Ni, Pb and Zn in potable, natural and waste waters, soil extracts and solutions obtained after digestion of soils and foodstuffs.<sup>75, 80, 84–86</sup> A set of procedures for determination of toxic elements in natural, potable and waste waters, soils and soil extracts, food raw materials, and foodstuffs have been proposed. The procedures were certified by Gosstandart of the Russian Federation. The procedures for determination of Cd, Co, Cu, Mn, Ni, Pb and Zn in potable, natural and treated waste waters and Cd and Pb in soils and soil extracts have been included in the Public Register of the Procedures Approved for the State Environmental Control (PND F 14.1:2:4.59-96 and PND F 16.14-97).

The limits of detection of elements by the flow sorption/atomic-absorption method (a KVANT AGA spectrometer) for preconcentration time of 1 min and atomisation in the propane–butane–air flame were 0.05 (Cd), 0.2 (Cu), 0.5 (Co, Mn, Zn), 1.0 (Pb), 2.0 (Ni)  $\mu\text{g litre}^{-1}$  (see Ref. 85). For the quantification of metals present in amounts 10 times as high as the detection limits, the relative standard deviation was 0.02–0.03. It should be noted that low detection limits of metals and high reproducibility of the results were attained with complete automation of the whole analysis cycle. The duration of the analysis cycle (with preconcentration for 1 min) was 95–105 s (depending on the time of column flushing), and the sampling frequency was up to 37 samples per hour. An increase in the preconcentration time results in lower detection limits of elements and better reproducibility of the determination results.

2. Flow sorption coupled with ICP AES for determination of Cd, Co, Cr, Cu, Fe, Mn, Ni, Pb, V and Zn in natural waters.<sup>69, 73</sup> The inductively coupled plasma atomic emission spectrometry (ICP AES) is a highly informational method for solution analysis. The use of a polychromator allows simultaneous determination of a large number of elements (up to 50) for sample consumption of

1–5 ml. In our studies, we have accomplished a combination of the flow sorption preconcentration on the DETATA sorbent and ICP AES determination of metals within a single automated cycle.

The non-stationary signals formed during flow determination by sorption coupled with atomic emission spectrometry of Cd, Co, Cr, Cu, Fe, Mn, Ni, Pb, V and Zn have been studied. It was found that desorption of all ten elements takes place simultaneously and requires the same period of time (equal signal widths).

The signal recording in the flow sorption coupled with ICP AES determination of elements requires identification of the zone of the concentrate which enters the spectrometer detector in the flow of the desorbing solution. The integration time of analytical signals determined by the size of the concentrate zone in the flow and the pre-integration time, which corresponds to the time it takes for the desorbing solution moving ahead of this zone to pass through the detector, are the key parameters for optimisation of the determination conditions. In the case of desorption of elements from the polystyrene-based DETATA sorbent, both parameters depend on the concentration of the acid in the desorbing solution and the flow rate of this solution. It was shown that all the ten elements can be desorbed with 2 M  $\text{HNO}_3$ . The optimal flow rate of the desorbing solution is 2  $\text{ml min}^{-1}$ . With this flow rate, the integration time for all the elements to be quantified is 20 s and the pre-integration time is 7 s.

Under the conditions chosen, the limits of detection of the elements in solutions by a flow method were 0.2–1  $\mu\text{g litre}^{-1}$  and the enhancement factors of the analytical signal due to preconcentration (*EF*) with respect to those in the direct ICP AES determination (after preconcentration for 1 min) were 17 (Cu), 15 (Cd, Zn), 14 (Co), 11 (Cr, Mn, Pb) and 10 (Fe, Ni, V). The relative standard deviation in the determination of elements present in concentrations of 10  $\mu\text{g litre}^{-1}$  was 0.02–0.06.

3. Flow sorption coupled with ICP AES for determination of rare earth elements in solutions of complex composition.<sup>76, 77</sup> To attain the highest signal-to-noise ratio, the composition and the flow rate of the desorbing solution were optimised. The range of quantifiable rare earth metal concentrations (for simultaneous determination) in solutions was  $1–1 \times 10^{-4} \mu\text{g ml}^{-1}$ .

4. Flow sorption coupled with voltammetry or with X-ray fluorescence for determination of metals in solutions ('stopped-flow systems'). Coupling of the dynamic sorption preconcentration with the electrothermal atomic absorption, inversion voltammetry and X-ray fluorescence implies a discrete analytical cycle. The specific feature of this approach is that the concentrate zone is identified in the flow of the desorbing solution and stopped in the area of analytical signal measurement. 'Stopped-flow systems' are promising, as they combine the advantages of the dynamic preconcentration and the determination methods involved. In the case where the preconcentration time is commensurable with the detection time, automation of the analysis cycle is expedient. It is especially convenient to combine preconcentration of a group of elements with simple and readily available methods of simultaneous multielement determination. Thus dynamic preconcentration of heavy metals on the DETATA sorbent can be coupled with their determination in the concentrates (solutions) by inversion voltammetry or XFA.<sup>87</sup>

X-Ray fluorescence analysis alone does not ensure determination of elements whose concentrations are at the MPC level. The time of measurement for the simultaneous determination of 9 elements using a Spectroscan spectrometer is about 15 min. A simple calculation shows that a 15-min preconcentration by forcing a solution through a DETATA microcolumn at a flow rate of 6–7  $\text{ml min}^{-1}$  ensures  $K_{\text{conc}} \approx 200$  (the volume of the desorbing solution is 0.5 ml). When the sorption technique is combined with the stopped flow, the time required for element determination remains the same (during the detection, the elements from the next sample are preconcentrated), while the detection limits markedly decrease. The following detection limits were attained for a frequency of 4 samples per h: 0.005 (Co, Ni); 0.02 (Cu, Fe, Mn, Pb, Zn); 0.05 (Cr) and 0.07 (V)  $\mu\text{g ml}^{-1}$  (see

Ref. 87). Owing to the high reproducibility of the results ( $s_r = 0.03-0.06$  over a broad range of element concentrations) and the stability of spectrometer operation with time, this method can be recommended for the monitoring of continuous industrial processes.

#### IV. Preconcentration on polyurethane foams

Polyurethane foams (PUF), an important product of the industrial organic synthesis, are of interest for the sorption preconcentration of substances. These sorbents are distinguished by high efficiency, versatility, chemical and mechanical stability, stability against organic solvents, relatively low cost and ready availability. The sorption properties of these synthetic polymeric materials are largely due to the combination of various hydrophobic (hydrocarbon, aromatic) and hydrophilic (urethane, amide, urea, ester, ether and terminal toluidine) groups, which allows the use of these materials for efficient sorption of both non-polar and polar compounds. A part of the solid phase in PUF is replaced by air,<sup>88</sup> which occurs in the polymer as numerous cells, thus forming an ordered system of solid quasispherical membranes. Owing to the system of cells, the sorbed substance can penetrate inside the sorbent. Thus, the substances are collected not only due to adsorption but also as a result of absorption; therefore, the capacity of PUF is fairly high. Polyurethane foams actually 'dissolve' sorbates in the membranes. This is a unique feature of PUF, which distinguishes them from many other sorbents.

Polyurethane foams have been used in analytical practice since the early 1970s.<sup>89-91</sup> At present, a large body of facts concerning sorption of organic compounds and elements on PUF have been accumulated. The publications generalised in a monograph<sup>92</sup> and reviews<sup>93-98</sup> discuss the reasons for the high efficiency of these sorbents, the factors that influence sorption and the ways of optimisation of the preconcentration and separation conditions of microcomponents. Below we consider (mainly, relying on our data) the characteristic features of sorption of various substances on PUF and discuss the potential of hybrid methods of analysis based on sorption preconcentration coupled with spectroscopic determination directly in the concentrate.

##### 1. Characteristic features of sorption on polyurethane foams

Development of combined and hybrid methods of analysis based on the use of PUF requires study of the laws of sorption processes and elucidation of sorption mechanisms. The knowledge of the chemistry of sorption of substances on PUF can facilitate the selection of practically important sorption systems and to explain (in favourable cases, even to predict) the conditions of sorption in systems not yet studied.

##### a. Effect of the sorbate hydrophobicity

Comparative estimation of the hydrophobicity of six industrial PUF samples based on ethers (PUF-ET) and esters (PUF-ES)<sup>99</sup> indicates that the surfaces of all these polymers are nearly equal in hydrophobicity. Their hydrophobicity proved to be higher than that of sorbents based on cellulose, cellulose triacetate, polyacrylate (Amberlite XAD-8), silicas (Diasorb-C<sub>4</sub>, -C<sub>8</sub>, -C<sub>16</sub>, -phenyl, -carboxyl) but lower than the hydrophobicity of the activated carbon AX-21.

Due to their hydrophobic properties, PUF efficiently sorb molecules containing hydrophobic fragments (for example, polycyclic aromatic hydrocarbons, PAH).<sup>100,101</sup> The distribution coefficients of PAH are linearly related to their hydrophobicity parameters, *i.e.*, the Hansch's parameters (the logarithms of the distribution constant in the *n*-octanol–water system,  $\log P_{ow}$ ), by correlation (4) (Table 4). The correlation equations (4)–(7) describe satisfactorily the sorption on PUF of not only PAH but also other aromatic hydrocarbons: the calculated and experimental distribution coefficients of benzene, toluene, acenaphthene, fluorene and fluoranthene are in good agreement with each other.<sup>101</sup>

**Table 4.** Types of correlations describing the sorption of various organic compounds on PUF.

| Class of compounds                                              | Correlation <sup>a</sup>                    | Correlation coefficient |
|-----------------------------------------------------------------|---------------------------------------------|-------------------------|
| PAH, aromatic hydrocarbons                                      | $\log K_d = a + b \log P_{ow}$ (4)          | 0.980–0.997             |
| Cationic surfactants of the alkyltrimethylammonium series       | $\log K_d = a + b n_C$ (5)                  | 0.970–0.989             |
| Phenols, phenol-carboxylic acids                                | $\log K_d = a + b \log P_{ow} - c pK_a$ (6) | 0.963–0.996             |
| Xanthene dyes, cationic metal chelates with 1,10-phenanthroline | $\log K_d = a + b \Delta H$ (7)             | 0.967–0.997             |

<sup>a</sup> *a*, *b*, *c* are constants.

The sorption of homologues of cationic surfactants of the alkyltrimethylammonium series increases with an increase in the chain length, which is indicative of an important role of hydrophobic interactions of the hydrocarbon parts of the cationic surfactant molecules with the PUF hydrophobic matrix and with one another.<sup>102</sup> The  $\log K_d$  values follow a linear dependence on the number of carbon atoms in the alkyl radical ( $n_C$ ) [relation (5) in Table 4].

For phenols with close  $pK_a$  values, differences in the sorption are also determined by the hydrophobicity difference. In the series phenol–3-cresol–1-naphthol,  $\log K_d$  values follow a linear correlation with the hydrophobicity parameter of the phenol on any of the PUF studied [relation (6) in Table 4].<sup>103,104</sup> Similar regularities are observed in the sorption of phenolcarboxylic acids.<sup>105</sup> The distribution coefficients, the limiting sorption values and the sorption constants of xanthene<sup>106</sup> and sulfophthalein dyes<sup>107</sup> increase with an increase in the hydrophobicity of their molecules in the following sequences: rhodamine 6G < rhodamine 3B < butylrhodamine, thymol blue < bromocresol purple < bromothymol blue < bromocresol green. An important role of hydrophobic interaction in the sorption of dyes was also pointed out in a study.<sup>108</sup>

The sorption of 4-nitrophenylazo derivatives of phenols increases with an increase in the hydrophobicity of the azo component on passing from phenol to 2-cresol and then to 1-naphthol.<sup>109</sup> For the associates formed by cationic surfactants of the alkyltrimethylammonium series with the bromothymol blue (BTB) anion<sup>110</sup> and with phenol and 1-naphthol 4-nitrophenylazo derivatives,<sup>111</sup> it has been shown that sorption increases with an increase in the hydrophobicity of the alkyl radical of the cationic surfactant in the sequence  $C_{10} < C_{12} < C_{14} < C_{16} < C_{18}$ . In the presence of cationic surfactants, the dependence of  $\log K_d$  of ion associates formed by 4-nitrophenylazophenol and 4-nitrophenylazo-1-naphthol on the number of carbon atoms in the alkyl radical of the cationic surfactant is described by linear equations (5) (Table 4).

##### b. The ability to form hydrogen bonds

As a rule, organic compounds containing a hydroxy group are sorbed more efficiently on PUF-ET, which, in the opinion of many researchers,<sup>104,105,112-116</sup> attests to the formation of a hydrogen bond (ether groups are known to be more prone to form hydrogen bonds than the ester groups). In the sorption of compounds containing hydrophobic fragments in addition to a hydroxy group, two factors should be taken into account, in particular, hydrophobicity and the ability to form intermolecular hydrogen bonds. It was shown that the logarithms of the distribution coefficients of phenols<sup>104,111</sup> and phenolcarboxylic acids<sup>105</sup> are related to their hydrophobicity parameters and the

$pK_a$  values by two-parameter correlation equations [relation (6) in Table 4].

### c. The concentration and the nature of the partner ion

Ionised compounds are most often sorbed on PUF as ion associates.<sup>117</sup> The concentration and the nature of the partner ion are important factors influencing their sorption. Typical dependences of the recovery of associates on the concentration of partner ions are curves with saturation.

The sorption of associates of xanthene dyes<sup>106</sup> and cationic metal chelates with 1,10-phenanthroline<sup>118, 119</sup> increases with an increase in the size and hydrophobicity of the anion in the sequence  $Cl^- < Br^- < NO_3^- < I^- < SCN^- < ClO_4^-$ . A linear correlation is observed between  $\log K_d$  and hydration energies of anions ( $\Delta H$ , kJ mol<sup>-1</sup>) [relation (7) in Table 4]. The distribution coefficients of the associates formed by 4-nitrophenylazophenols<sup>109, 111</sup> and sulfophthalein dyes<sup>107, 108, 119</sup> on PUF-ET in the presence of alkali metal ions increase in the sequence  $Li^+ < Na^+ < Rb^+ < K^+$  (the maximum value is observed for potassium). Similar dependences are observed for the sorption of anionic metal complexes (mainly thiocyanate complexes).<sup>120–123</sup> This means that the polyether units of PUF bind selectively alkali metal ions, especially potassium ions. The resulting positively charged fragments of the sorbent promote the recovery of anions.

### d. The structure of the PUF polymer unit

The influence of the structure of the PUF polymer unit shows itself in different ways for different groups of sorbates. The sorption of PAH<sup>100, 101</sup> and hydrophobic ion associates, for example, those of cationic surfactants with 4-nitrophenylazophenols,<sup>111</sup> is the same on PUF having different structures but identical hydrophobicities. As the sorbate hydrophobicity increases, the difference between the sorption properties of PUF differing in the structure of the polymer unit becomes less pronounced.<sup>124</sup> Conversely, the effect of the polymer base is essential when specific interactions are present in the system. As a rule, PUF-ET are more efficient for such compounds. In most cases, PUF-ET sorb more efficiently metal thiocyanate complexes,<sup>120–123</sup> heteropoly acids,<sup>125, 126</sup> singly and doubly charged anions of the sulfophthalein dyes,<sup>107, 108, 119</sup> anionic surfactants<sup>102, 119</sup> and 4-nitrophenylazo phenol derivatives.<sup>109, 111</sup> The recovery increases on passing from propylene oxide-based PUF to ethylene/propylene oxide-based PUF and then to ethylene oxide-based PUF.<sup>124</sup>

### e. The charge of ions, the composition of the aqueous phase and solution acidity

The sorption of ion associates depends on the charge of ions they contain. Doubly charged ions are sorbed less efficiently on any PUF than singly charged ions, all other factors being the same.<sup>117</sup>

The sorption of associates is influenced also by the solution composition and the pH. Depending on the pH, the compounds sorbed can exist as different species, either as singly or doubly charged species or as neutral molecules.<sup>106, 107, 127</sup> In addition, the sorption properties of PUF can change with the acidity and salt composition of the solution, as they can be modified by hydroxonium and alkali metal ions. It is known that PUF are protonated on contact with mineral acid solutions.<sup>124, 128</sup>

Let us consider some examples. The maximum recovery of phenols<sup>103, 104</sup> and phenolcarboxylic acids<sup>105</sup> is observed for  $pH \leq pK_a - 2$ , where the hydroxy group is not dissociated. As the pH increases to  $pK_a + 2$  and further, the recovery of phenol decreases almost to zero. Conversely, the sorption of PAH does not depend on the acidity of the initial solution over a broad pH range (from 4 M HCl to pH 13).<sup>100, 101</sup> The maximum recovery of the oxidised and reduced forms of heteropoly acids on PUF is attained in the range from 4 M HCl to pH 2, which coincide, on the one hand, with the stability region of the corresponding heteropoly anions in an aqueous solution, and on the other hand, with the pH of the maximum extraction of these compounds with oxygen-containing extractants.<sup>124, 125</sup> The quantitative

recovery of thiocyanate complexes is attained in the pH ranges of pH 2–3 (Cu), 5–1 M HCl (Co), pH 2–1 M HCl (Fe) and pH 1–2 M HCl (Ti), which coincides with the regions of quantitative extraction of these compounds with oxygen-containing solvents.<sup>124</sup>

## 2. Chemisorption of polyurethane foams

The chemisorption processes involving the functional groups of macromolecules of polyurethane foams and accompanied by the formation of intensely coloured products have been studied by diffuse reflectance and IR spectroscopy.<sup>129–134</sup> It was found that the terminal toluidine groups of PUF enter into heterogeneous chemical reactions typical of aromatic amines: diazotisation with sodium nitrite, azo coupling with 4-nitrophenyldiazonium tetrafluoroborate, the reaction with active chlorine, and condensation with formaldehyde. The chemisorption of the above-listed substances takes place under relatively mild conditions (aqueous solutions, room temperature, atmospheric pressure), the coloured products are formed rapidly and at rather low concentrations of the compounds in aqueous solutions. The main factors influencing these processes were elucidated, in particular, pH and the acid composition of the aqueous phase, the time of phase contact, the structure of the monomeric unit in the polymer and the concentrations of the reactants. The high efficiency of chemisorption preconcentration of free active chlorine and nitrite and nitrate ions, the intensive colour of the sorbent thus attained, the ready availability and the low cost of the sorbent proved to be attractive for the use of PUF as new polymeric reagents.<sup>129, 130, 133, 134</sup>

## 3. The state of sorbed molecules in the polyurethane foam matrix

Study of the state of the sorbed molecules in the polyurethane foam matrix is important for extension of the analytical potential of hybrid methods of analysis based on sorption coupled with spectroscopy. In a series of studies (Refs 100, 101, 109–111, 118, 119, 122–125, 127, 135) using the diffuse reflectance spectroscopy and luminescence, the spectroscopic characteristics of the coloured and luminescent sorbates have been studied. If hydrophobic (as in PAH)<sup>100, 101</sup> or electrostatic (as in thiocyanate metal complexes) interactions are the predominant type of intermolecular interactions in the sorbed compounds, no pronounced changes in their spectroscopic characteristics take place.<sup>122–124</sup> The normalised fluorescence, fluorescence excitation, absorption and diffuse reflectance spectra for these groups of compounds incorporated in a PUF matrix or occurring in solution are shifted with respect to each other by not more than 10 nm.

For other groups of sorbed compounds, the changes in the spectral characteristics can be more pronounced. For example, the maxima of the diffuse reflectance spectra of oxidised forms of heteropoly acids as sorbates are shifted bathochromically by 55, 45 and 65 nm for molybdosilicic, molybdophosphoric and molybdovanadophosphoric acids, respectively, with respect to the absorption spectra of aqueous solutions, which is indicative of strong interaction between the heteropoly anion and the polymeric matrix.<sup>125</sup>

The diffuse reflectance spectra of 4-nitrophenylazo phenol derivatives<sup>109, 111</sup> or sulfophthalein dyes<sup>119</sup> as sorbates are shifted bathochromically with respect to those in the absorption spectra of aqueous solutions by 50–60 nm, which may be due to the change in the nature of the ionic bond in the associates caused by ionisation processes taking place in the PUF phase and resulting in the separation of ion pairs to give solvated ions. As shown in a study,<sup>136</sup> PUF membranes contain polar microregions in addition to the hydrophobic ones. Similar structural changes have been observed previously for the ion pairs formed by alkali metal ions with hydrophobic anions in the presence of crown ethers.<sup>137</sup>

On storage of some sorbates, for example, 4-nitrophenylazophenols<sup>111</sup> or acridine yellow,<sup>127</sup> in air, the diffuse reflectance spectra change, in particular, the amplitude decreases or new bands appear. Most often, these processes are reversible and are

related to acid–base interactions taking place in the PUF matrix upon the contact of sorbed compounds with acid or ammonia vapour present in the laboratory air. A method for stabilisation of the colour of 4-nitrophenylazo phenol derivatives as sorbates consisting of treating the material with a solution of tetrabutylammonium hydroxide has been proposed.<sup>111</sup>

In some cases, reactions that are impossible in solutions take place in the PUF matrix. Thus the diffuse reflectance spectrum of Cu(II) thiocyanate sorbed on PUF-ET exhibits a broad band with a maximum at 480 nm, which is shifted bathochromically by 130 nm compared to that in the absorption spectrum of the aqueous solution. The Cu(II) thiocyanate complexes in an aqueous solution and in the PUF matrix were compared by EPR. The hyperfine splitting constants and the *g*-factors for aqueous solutions and sorbates were determined. It was shown that the  $\text{Cu}(\text{NCS})_4^{2-}$  complexes in which copper is coordinated by four equivalent nitrogen atoms predominate in aqueous solutions, whereas the PUF matrix incorporates mainly  $\text{Cu}(\text{NCS})_3^-$  complexes whose inner coordination sphere contains one oxygen-containing group of the polymer.<sup>124</sup>

The product formed in the reaction of PUF-immobilised diphenylcarbazide with chromium(VI) in the presence of tetraphenylborate ions  $\text{BPh}_4^-$  differs in spectral characteristics from the product formed in the presence of other anions.<sup>122, 123</sup> In the presence of  $\text{BPh}_4^-$  in highly acidic media (1.5–4.5 M  $\text{H}_2\text{SO}_4$ ), the diffuse reflectance spectra of the sorbate exhibit a bathochromic shift (40 nm) and a hyperchromic effect (~5-fold). The formation of intensively coloured compounds on the PUF surface in the presence of  $\text{BPh}_4^-$  is also typical of other potent oxidants ( $\text{O}_2$ ,  $\text{MnO}_4^-$ ,  $\text{S}_2\text{O}_8^{2-}$ ), which may be used for their combined determination at a level of  $10^{-8}$  mol litre<sup>-1</sup>, the detection limit of chromium being decreased by almost an order of magnitude.

Comparative analysis of the fluorescence spectra of the PAH sorbates allows one to classify all these compounds into two groups.<sup>100, 101</sup> One group includes naphthalene, phenanthrene, acenaphthene and fluorene, for which the fluorescence excitation wavelength ( $\lambda_{\text{ex}}$ ) is smaller than 310 nm. The fluorescence spectra of these compounds coincide with the fluorescence spectrum of PUF; therefore, it is difficult to quantify them by the solid-phase luminescence technique. The second group includes anthracene, pyrene, fluoranthene and 3,4-benzpyrene, for which  $\lambda_{\text{ex}}$  is greater than 310 nm. These compounds develop intensive fluorescence in the PUF matrix in the region where no sorbent fluorescence is observed. The characteristics of the luminescence spectra of binary and ternary mixtures of the PAH sorbates were studied. It was found that the presence of feebly fluorescing naphthalene, phenanthrene, fluorene and/or acenaphthene molecules (even in a 100-fold amount) in the PUF phase together with intensively fluorescing anthracene, fluoranthene, pyrene and 3,4-benzpyrene has virtually no influence on the emission intensity from the latter group. By changing the excitation wavelength, it is possible to distinguish between PAH present as binary or ternary sorbate mixtures in comparable amounts and to identify them on the basis of characteristic bands in the spectrum.<sup>100, 101</sup>

For all the coloured and luminescent compounds, the change in the sorbate concentration does not change either the positions of peaks in the diffuse reflectance or fluorescence spectra or the spectral patterns. Within the linear sections of sorption isotherms, there exists a linear correlation between the Kubelka–Munk function values or the fluorescence intensity and the concentration of the compounds being sorbed in an aqueous solution, which is the reason why these polymers can be used to develop hybrid methods of analysis based on coupling of sorption with photometry or luminescence measurements.<sup>100, 109, 110, 118, 122–124</sup>

#### 4. The technique of preconcentration on polyurethane foams

The technique of preconcentration of elements and organic compounds on PUF differs from that with other sorbents. The sorption preconcentration and separation of PUF can be accomplished in either static or dynamic mode.

The static sorption is performed by two ways. A traditional method is based on shaking (stirring) of the solution under analysis with a known amount of the sorbent, from which air bubbles have been removed. Usually PUF are used as cubes, cylinders, cylindrical discs (tablets) cut or stamped out from a polymer sheet. The PUF cubes or discs occurring in the solution should be squeezed at intervals either manually (for example, by means of the bottom of a glass measuring cylinder) or using special automatic devices.

The dynamic version of sorption implies passing of the solution under analysis through chromatographic column filled with PUF cubes or cylinders. A number of methods for packing of these columns have been developed; a vacuum method is the most popular among them. Yet another specific mode of preconcentration on PUF called the method of ‘pulsating column’ is implemented by pumping the solution through a sorbent layer situated in a glass or plastic medical syringe. Owing to the sorbent elasticity, the cylindrical core of polyurethane foam can be easily compressed and released by movement of the syringe piston. The pulsating column technique suits perfectly for process automation in the sorption–desorption mode. More detailed information concerning various modes of sorption on PUF from aqueous solutions can be found in monographs<sup>92</sup> and reviews;<sup>93, 94</sup> these publications also describe various types of samplers used for sorption preconcentration of organic compounds in air.

The efficiency of preconcentration on PUF can be increased by increasing the sample volume (Table 5), decreasing the sorbent weight within reasonable limits or by performing successive sorption.<sup>138, 139</sup> In the last-mentioned case, the same sorbent tablet is successively brought in contact with fresh portions of the solution to be analysed. Due to the presence of linear sections on sorption isotherms, high recovery values and the ease of separation of the sorbent from the solution, this method provides efficient preconcentration of compounds from dilute solutions. The absolute amount of the substance that has passed to the PUF phase is equal, to a good approximation, to  $nqR$  (*n* is the number of successive sorptions, *q* is the absolute amount of the substance in the sample, µg), and *R* is the recovery.

**Table 5.** Recoveries and preconcentration ratios for the ion associate formed by 4-nitrophenylazo phenol derivative with cetyltrimethylammonium (4-NPA ... CTMA)<sup>138</sup> and for pyrene<sup>139</sup> and sorption time of these compounds from different volumes of aqueous solutions on polyurethane foams.

| <i>V</i> /ml | 4-NPA ... CTMA |                           |               | Pyrene       |                           |               |
|--------------|----------------|---------------------------|---------------|--------------|---------------------------|---------------|
|              | <i>R</i> (%)   | $10^{-2} K_{\text{conc}}$ | <i>t</i> /min | <i>R</i> (%) | $10^{-2} K_{\text{conc}}$ | <i>t</i> /min |
| 25           | 95             | 7.3                       | 40            | 99           | 4.5                       | 10            |
| 50           | 95             | 16.1                      | 50            | 98           | 8.7                       | 15            |
| 100          | 95             | 27.6                      | 60            | 99           | 17.0                      | 20            |
| 200          | 73             | 45.0                      | 90            | 98           | 33.0                      | 30            |
| 250          | –              | –                         | –             | 98           | 41.0                      | 40            |
| 500          | –              | –                         | –             | 96           | 81.0                      | 60            |

The sorbent capacity, *i.e.*, the greatest amount of the preconcentrated component per unit weight of the sorbent is an important parameter as regards the subsequent isolation of the preconcentrated substances in reasonable amounts. Here the advantages of PUF are obvious, as the preconcentration takes place throughout the whole sorbent volume. The sorption capacities with respect to anionic metal complexes vary from 0.2 to 2 mmol per gramme of the sorbent, *i.e.*, they reach 10% of the sorbent weight.<sup>89, 140–146</sup> Taking into account the sorption sites and the limiting sorption values for pyrene and heteropoly acids, the areas occupied by these compounds in the PUF phase have been calculated.<sup>100, 124, 125</sup> They were found to exceed the specific surface area of PUF by factors of 10 to 340.

It has been noted in a number of publication that PUF have a number of advantages over other polymeric sorbents and carbons for preconcentration of polychlorobiphenyls,<sup>147–150</sup> PAH,<sup>139, 150–152</sup> phenols,<sup>113, 114, 138</sup> organophosphorus and chlorinated acaricides and organophosphorus insecticides<sup>153, 154</sup> from waters.

### 5. Polyurethane foams in sorption spectroscopic and test methods of analysis

The methods of analysis combining sorption and spectroscopic determination are based on the sorption preconcentration of the component to be quantified on PUF, the formation of a coloured or luminescent product on the PUF surface, and its subsequent determination directly in the sorbent matrix by measuring the optical density, diffuse reflectance, luminescence intensity or chromatic characteristics. The sorption preconcentration combined with measurement of the analytical signal on the sorbent surface decreases the limit of detection of the target components by several orders of magnitude, while the use of sorbents modified by specific analytical reagents increases the selectivity of analysis.

Depending on the way of measurement of the analytical signal, the methods based on sorption coupled with spectroscopy can be classified into solid-phase spectrophotometry, sorption photometric and sorption luminescence methods and chromaticity measurements.

The solid-phase spectrophotometry is based on direct measurement of light absorption by the sorbent after it has collected the target component.<sup>155–161</sup> To this end, a thin parallelepiped with dimensions matching the cell dimensions ( $2 \times 1 \times 0.1$  cm) is cut out of a PUF plate, a coloured compound is sorbed on it, the sorbent is transferred into the cell filled by an organic solvent and the optical density is measured. The solvent serves as the immersion liquid which decreases light scattering. Methods have been developed for determination of bismuth as the iodide complex,<sup>155</sup> cobalt as the thiocyanate,<sup>156</sup> phosphate ions as the reduced molybdophosphoric heteropoly acid,<sup>157</sup> zinc and bismuth<sup>158</sup> and Hg(II) chloride and phenyl chloride<sup>159</sup> as dithizonates, chromium as blue peroxychromic acid and as the diphenylcarbazide complex.<sup>160, 161</sup> These methods are characterised by a rather narrow ranges of linearity of the calibration plots and relatively low reproducibility of the results.

In the method of analysis where sorption is coupled photometry, the appearance or change of the sorbent colour due to sorption of the component under analysis on its surface can be recorded by measuring the diffusion reflectance (Refs 109–111, 119, 121–124, 129, 130, 133, 135, 162–172). The method involving sorption and luminescence measurement is based on preconcentration of the component by a solid substrate followed by determination directly in the sorbent phase using luminescence spectroscopy.<sup>100, 173–175</sup> The procedural aspects of the quantitative measurement of diffuse reflectance and luminescence intensity for the sorbates on PUF have been considered.<sup>176</sup> The key characteristics of the analysis of organic compounds, anions and elements based on sorption coupled with photometric determination or with luminescent determination are summarised in Table 6.

In the chromaticity measurements, colour coordinates serve as the analytical signal determined in the sorbent matrix. A method including chromaticity measurements and numerical estimation of the colour intensity of substances sorbed on PUF by means of an office scanner and computer software for digital image processing has been proposed.<sup>177</sup>

Test methods of analysis are quick, simple and cheap techniques for detection and determination of substances that do not require any essential sample preparation, the use of complex instrumentation, complex laboratory equipment or highly qualified personnel.<sup>178</sup> The analytical signal used in test methods is the appearance or a change of the sorbent colour upon collection of the analyte on its surface as a coloured analytical form. Most often, this change is detected by sight, although in some cases,

**Table 6.** Characteristics of determination methods of organic compounds, non-metals and metal ions based on sorption on polyurethane foams and spectroscopy.

| Analyte                          | Quantifiable concentration range /mg litre <sup>-1</sup> | Detection limit /mg litre <sup>-1</sup> | Ref.           |
|----------------------------------|----------------------------------------------------------|-----------------------------------------|----------------|
| Diffuse reflectance spectroscopy |                                                          |                                         |                |
| Phenol                           | 0.01 – 0.8                                               | 0.003                                   | 109, 111       |
| 1-Naphthol                       | 0.01 – 1                                                 | 0.003                                   | 111, 163       |
| Gallic acid                      | 0.1 – 10                                                 | 0.04                                    | 164            |
| CTMA <sup>a</sup>                | 0.2 – 3                                                  | 0.04                                    | 110, 119       |
| CP <sup>b</sup>                  | 0.8 – 8                                                  | 0.2                                     | 110, 119       |
| DDC <sup>c</sup>                 | 1.2 – 50                                                 | 0.30                                    | 118, 119, 165  |
| Si(IV)                           | 0.008 – 0.04                                             | 0.003                                   | 166            |
| Nitrite ions                     | 0.1 – 4                                                  | 0.02                                    | 129, 133, 134  |
| Nitrate ions                     | 2 – 50                                                   | 0.5                                     | 133, 134       |
| Free active chlorine             | 0.2 – 15                                                 | 0.07                                    | 130, 134       |
| Fe(III)                          | 0.004 – 0.6                                              | 0.001                                   | 121 – 123, 167 |
| Co(II)                           | 0.07 – 6                                                 | 0.02                                    | 121 – 123, 168 |
| Cu(II)                           | 0.2 – 10                                                 | 0.05                                    | 124            |
| Ti(IV)                           | 0.008 – 0.5                                              | 0.002                                   | 123            |
| Sn(II)                           | 0.2 – 4                                                  | 0.08                                    | 124            |
| Ascorbic acid                    | 0.3 – 2.4                                                | 0.1                                     | 169            |
| Ascorbic acid <sup>d</sup>       | 0.6 – 4                                                  | 0.2                                     | 135            |
| Ni(II)                           | 0.04 – 4                                                 | 0.01                                    | 121 – 123, 170 |
| Cr(VI)                           | 0.001 – 0.2                                              | 0.0004                                  | 122, 123, 172  |
| Luminescence spectroscopy        |                                                          |                                         |                |
| Anthracene                       | 0.02 – 0.7                                               | 0.006                                   | 100, 101       |
| Pyrene                           | 0.001 – 0.1                                              | 0.0003                                  | 100, 101       |
| 3,4-Benzpyrene                   | 0.001 – 0.06                                             | 0.0004                                  | 100, 101       |
| Ru(IV)                           | 0.002 – 0.1                                              | 0.0004                                  | 174            |
| Se(IV)                           | 0.001 – 0.1                                              | 0.0003                                  | 174, 175       |
| Cr(VI)                           | 0.01 – 0.4                                               | 0.008                                   | 173            |

<sup>a</sup> CTMA is cetyltrimethylammonium bromide, <sup>b</sup> CP is cetylpyridinium chloride, <sup>c</sup> DDC is sodium dodecyl sulfate, <sup>d</sup> the reduction was performed in a microwave field.

recording by simple instruments is also possible.<sup>178</sup> The possibility of using PUF in test methods of analysis was first noted in 1974.<sup>179</sup> Determination was performed after preconcentration of elements on chromofoams (the term was proposed by Braun<sup>179</sup>), i.e., PUF modified by photometric reagents. On contact of these foams (as small cubes) with the solution to be analysed, the initially white polymer acquires a colour typical of the given photometric reaction. These reactions are highly sensitive. The detection limits for sorption under static conditions and for a sample volume of not more than 1 to 2 ml are tenth or even hundredths of a µg (as, for example, for Co,<sup>179</sup> Cu,<sup>179–181</sup> Cd,<sup>180</sup> Pd,<sup>181</sup> Pb,<sup>179</sup> Cr,<sup>182</sup> Mo<sup>183</sup>).

A different way of using PUF in test methods that does not require the preparation of modified PUF has also been proposed. In a number of studies,<sup>110, 118, 129, 130, 138, 163, 164, 184</sup> tablets of non-modified PUF in combination with tubes containing a reagent solution were used as test systems. The reproducibility of the results ( $s_r$ ) of visual determination against a colour scale varies from 0.1 to 0.5. Test systems based on PUF for determination of Co, Ni, Fe(III), nitrite ions, active chlorine, the total content of phenols and anionic and cationic surfactants have passed the metrological certification procedure at the Urals Research Institute of Metrology of the Russian Federation Gosstandart, have been included in the register of test system types and are now manufactured commercially by the ecological and analytical association Ekoanalitika. The test kits based on PUF are easily manufactured, reliable in operation and can be used to determine environmentally toxic compounds in various types of water



including potable and mineral water, soil extracts and juices. If necessary, the test form can be preserved and analysed in a laboratory using diffuse reflectance spectroscopy or (after desorption of the compounds) by HPLC.<sup>138, 139</sup>

## V. Preconcentration on non-covalently modified silicas

Silicas differ favourably from other inorganic and organic sorbents: they do not tend to swell, ensure a rather high mass exchange rate, possess chemical stability and mechanical strength, and in some cases, also fairly high hydrolytic stability.<sup>185–188</sup> On the basis of silica, a large number of diverse modified materials that possess chemical features of the immobilised compound and the properties of silica as a solid have been produced.<sup>185–192</sup> Covalently and non-covalently modified silicas can be distinguished.

For preconcentration and determination of metal ions, a number of chemically modified silicas have been prepared and studied, the chemical modification being performed by mono-, di-, tri- and tetramines,<sup>185, 193–195</sup> eriochrome black T,<sup>196</sup> naphthoquinone,<sup>197</sup> carbazides,<sup>194</sup> purpurogallin,<sup>198</sup> nitrogen-containing heterocycles (1,10-phenanthroline, 2,2'-bipyridine, 8-hydroxyquinoline, *etc.*),<sup>199</sup> iminodiacetic,<sup>185, 200</sup> aminophosphonic<sup>201</sup> and carboxylic<sup>202</sup> acids.

Yet another approach is non-covalent immobilisation of analytical reagents on silicas. Depending on the chemical nature and the structure, analytical reagents can undergo electrostatic, donor-acceptor, hydrophobic and other types of interaction with the silica surface groups and thus become attached to the surface.<sup>203</sup> It has been proposed to use immobilisation both to improve the chemicoanalytical properties of the reagents and to design new organic reagents.<sup>204</sup> The non-covalent modification of silochromes and other silica gels by complexing analytical reagents has been studied fairly comprehensively.<sup>205–235</sup>

Terada *et al.* have prepared and described silica gels modified by 2-mercaptobenzothiazole,<sup>205–207</sup> 2-mercaptobenzoimidazole, 2,5-dimercapto-1,3,4-thiadiazole,<sup>207</sup> thionalide,<sup>208, 209</sup> *p*-dimethylaminobenzylidenerhodanine<sup>210</sup> and 1-nitroso-2-naphthol.<sup>211</sup> Ukrainian researchers immobilised on silica gels dodecylaminoethyl- $\beta$ -triiodoammonium iodide, high-molecular-mass quaternary ammonium salts,<sup>212, 213</sup> 1,10-phenanthroline,<sup>214, 215</sup> dithizone and zinc dithizonate,<sup>216</sup> 1-(2-thiazolazo)-2-naphthol<sup>217</sup> and other reagents<sup>218–221</sup> and found that a substantial contribution to the retention of reagents is made by the formation of hydrogen bonds between the donor atoms of the reagents and the silanol groups on the silica gel surface.<sup>212, 217</sup> For attaching of readily water-soluble organic complexing reagents such as nitroso-R-salt,<sup>222</sup> eriochrome black T,<sup>223</sup> calcion,<sup>224</sup> titanium yellow<sup>225</sup> and zincon<sup>226</sup> to silica gels, Kocjan *et al.* have proposed that the reagent to be fastened should be preliminarily extracted into chloroform as an ionic associate with methyltriethylammonium chloride (Aliquat 336) and, after treatment of silica gel, chloroform was removed by evaporation. Heterocyclic azo compounds were immobilised on silica gels of various brands through sorption from aqueous and water-organic solutions.<sup>227–235</sup> Ivanov and co-workers prepared and characterised silica gels modified by 4-(2-pyridylazo)resorcinol (PAR),<sup>228, 229</sup> 1-(2-pyridylazo)-2-naphthol (PAN),<sup>228–232, 234</sup> 4-(2-thiazolylazo)resorcinol,<sup>233</sup> 2-(5-bromo-2-pyridylazo)-5-diethylaminophenol (5-Br-PAAP),<sup>234, 235</sup>

Complexing sorbents based on non-covalently modified silica gels are often used for preconcentration under static conditions to determine metal ions, including radioactive ones.

The few papers dealing with non-covalently immobilised redox reagents show that the redox properties change upon immobilisation.<sup>236–239</sup> Examples of the practical use of redox sorbents are virtually missing. We have prepared and studied a number of complexing and redox sorbents. Diverse analytical reagents were immobilised in two ways, either sorbed on the surface of modified silicas containing hydrophobic and ion

exchange groups or incorporated into xerogels of silicic acid using the sol-gel process.

## 1. Preparation and characteristics of modified silicas

### a. Hydrophobised silicas and capillary columns modified with complexing reagents

In the mid-1990s when we started our studies, only a few examples of non-covalent modification of hydrophobised silicas were known.<sup>240–245</sup> We have studied immobilisation, on reverse-phase silica gels with alkyl (SG-C<sub>1</sub>, SG-C<sub>8</sub>, SG-C<sub>16</sub>), nirtile (SG-CN) and phenyl (SG-P) groups and in capillary columns with hydrophobic inner surface, of the following reagents: hydroxyquinolines [2-methyl-8-hydroxyquinoline (MOx),<sup>246, 247</sup> 8-hydroxyquinoline (Ox),<sup>246–248</sup> 5-phenylazo-8-hydroxyquinoline (PAOx),<sup>246, 247</sup>]; oximes [nioxime (NIO),<sup>246, 247</sup> dimethylglyoxime (DMGO),<sup>246, 247</sup> salicylaldehyde (SAO),<sup>246, 247</sup>];  $\beta$ -diketones [benzoylacetone (BA),<sup>246, 247</sup> thenoyltrifluoroacetone (TTA),<sup>246, 247</sup> 1-phenyl-3-methyl-4-benzoylpyrazolone-5 (PMBP),<sup>246, 247, 249</sup>]; bis(2-ethylhexyl) hydrogen phosphate (BEHHP),<sup>246, 247, 249</sup> azo compounds [PAR,<sup>246, 250</sup> PAN,<sup>246, 251–253</sup> sulfochlorophenolazorhodanine (SCPAR),<sup>246, 250</sup> 1-(6-bromo-2-benzothiazolylazo)-2-naphthol (BBT),<sup>246, 250</sup> lumogallion (LG),<sup>246</sup> cadion (CD),<sup>246, 250, 251</sup> hexaoxacycloazochromium (HOCAC),<sup>246, 253</sup> pyrogallol and bromopyrogallol red,<sup>246, 252</sup>]; triphenylmethane and xanthane derivatives [xylanol orange (XO),<sup>246, 251, 252, 254</sup> crystal violet (CV),<sup>246, 250</sup>]; N,O,S-macrocyclic compounds<sup>246, 255–257</sup> and octaethylporphyrin (EEP),<sup>246, 255</sup> sodium diethyldithiocarbamate (DDTC),<sup>246, 249, 252</sup> sodium rhodizionate,<sup>246, 252</sup> 1-nitroso-2-naphthol (NN),<sup>246, 249, 252, 258, 259</sup> 4-dimethylaminobenzylidenerhodanine (DMABR),<sup>246</sup> 2,2'-dipyridine (D),<sup>246, 252, 258</sup> 1,10-phenanthroline (P),<sup>246, 252, 258</sup> diphenylcarbazone (DPCone),<sup>246</sup> diphenylcarbazide (DPCide),<sup>246</sup> quinalizarin (QL),<sup>246, 260</sup>

We proposed capillary columns with a hydrophobic inner surface for the on-line sorption preconcentration and separation of metal ions. For this purpose, the inner surface of quartz capillary tubes (internal diameter 0.45–1.1 mm, length 1–10 m) was chemically etched and then modified *in situ* with organosilicon compounds (dimethyldichlorosilane S-C<sub>1</sub>, methylhexyldichlorosilane S-C<sub>6</sub>, diphenyldichlorosilane S-P) and their polymeric analogues (S-polyC<sub>1</sub>, S-polyC<sub>6</sub>, S-polyP).<sup>257, 253, 260</sup> It was found that the major contribution to the retention of reagents on hydrophobised surfaces is made by the distribution mechanism, which determines the behaviour of the reagents in organic solvent-water extraction systems. As the reagent and surface hydrophobicities increase, for example, with an increase in the number of atoms in the carbon chain, C<sub>1</sub> < C<sub>8</sub> < C<sub>16</sub>, the capacity increases. All the reagents we studied are strongly held on 'phenyl' hydrophobic surfaces, apparently, due to non-specific  $\pi$ - $\pi$ -interactions between the aromatic systems of the reagents and the surface. In the sorbents we studied, the interaction between the donor atoms of the reagents and the surface silanol groups does not make a substantial contribution to the retention of the reagents (apparently, due to the high density of grafting of hydrophobic groups).<sup>246, 247, 250–253, 260, 261</sup>

The strongest retention of the reagents is observed in slightly acidic and neutral media in which the molecular forms of the reagents predominate.<sup>246–261</sup> In the presence of non-ionic surfactants (Triton X-100 and Bridge 35), the capacity of a hydrophobic surface markedly increases.<sup>246, 262</sup> Probably, a hydrophilically hydrated reagent becomes hydrophobically hydrated in micellar media, which enhances the hydrophobic interactions.<sup>263</sup>

The service life of complex-forming sorbents (the reproducibility of the retention times of metal ions) prepared based on hydrophobised silicas is rather long: for example, the Ox/SG-C<sub>16</sub> sorbent can be used 30 times in the sorption-desorption mode<sup>248</sup> and sorbents based on PAOx, diaza-18-crown-6 (DAC) and OEP withstand up to 100 cycles.<sup>246</sup>

The modification of hydrophobised surfaces under dynamic conditions allows one to obtain complex-forming sorbents within

several minutes. Conditions for modification–regeneration of packed micro and capillary columns in an automated mode have been selected; after modification for 30–120 s, capillary columns can be used in continuous flow analysis systems for up to 15 h.<sup>246, 249, 251, 260</sup>

Dynamic sorption of Ca, Mg, Al, Mn(II), Fe(III), Co(II), Ni, Cu(II), Zn, Cd, Pb and Ag(I) on modified silica gels and capillary columns has been studied in the off-line and on-line modes.<sup>246–261</sup> The key factors affecting the sorption behaviour of metals include the nature of immobilised complexing reagent (first of all, the set of donor atoms) and the sample pH and flow rate.

The conditions for quantitative sorption of metals are virtually the same as the optimal conditions for the reactions of these metals with free reagents in solutions.<sup>246–261</sup> Therefore, the enormous body of data accumulated on the complexation of metal ions with analytical reagents in solutions (in particular, for solvent extraction) can be utilised to design sorbents with specified properties.<sup>246</sup>

To increase the selectivity of sorption, the most selective complexing reagents have been immobilised; mixed sorbents<sup>246, 248, 261, 264, 265</sup> and exchange sorption<sup>249</sup> have been used. Sorbents containing at least two sorts of functional groups (complexing, ion exchange, and so on) are referred to as mixed sorbents. If the compound to be sorbed reacts with both sorts of group, its retention can be smoothly controlled by varying their ratio.<sup>264</sup> Mixed sorbents are used in chromatography to enhance the separation of organic substances<sup>266–269</sup> or metal ions.<sup>270</sup> Examples of modification of the substrate simultaneously by hydrophilic and hydrophobic reagents have been reported.<sup>268, 269</sup> Mixtures of ion exchangers have been used for simultaneous determination of cations and anions from the same sample;<sup>271</sup> and mixed metal hydroxides and phosphates have been used for selective sorption preconcentration of Ca, Mg, Sr and Ba.<sup>272</sup> We have proposed preparing mixed sorbents by modification of hydrophobised surfaces with mixtures of complexing reagents with different sets of donor atoms. The sorption behaviour of metals can be controlled (for example, to ensure that a required metal is eluted first) by mere variation of the ratio of complexing reagents in the modifying solution.<sup>246, 248, 261, 264</sup> Mixed sorbents have been used to increase the selectivity of sorption preconcentration,<sup>246, 248, 261, 265</sup> including that in the on-line mode,<sup>261</sup> and for TLC separation.<sup>264</sup>

Exchange sorption is also employed to increase the selectivity of the sorption process. The immobilised complexing reagent is loaded with a metal ion and then used to recover another metal ion.<sup>249</sup> It is obvious that this approach resembles exchange solvent extraction; however, the sorption version does not require the presence of an organic solvent and implies a much lower consumption of the reagent; this version is faster and can be more easily automated. The metal ion-loaded complexing sorbents based on non-covalently modified hydrophobised silicas ensured a record selectivity of the sorption preconcentration of Cu(II) and Fe(III).<sup>249</sup>

Non-covalently immobilised complexing reagents have been used to develop hybrid methods for metal determination that combine sorption preconcentration and separation.<sup>246–261, 265, 273</sup>

#### b. Hydrophobised silicas and ion exchangers modified by redox reagents

The immobilisation of quinone imines (2,6-dichloroindophenol, 2,6-dibromoindoguaiacol, indophenol blue, Bindschedler's green, variamine blue, phenol blue), thiazine dyes (methylene blue, toluidine blue), *N,N*-diethyl-*p*-phenylenediamine (DPPDA) and benzidine on Silochrome S 80 (SG), reverse-phase silica gels (SG-P, SG-C<sub>16</sub>, SG-CN) and ion exchange resins with sulfo groups (SG-SO<sub>3</sub><sup>−</sup>) and tetramethylammonium groups (SG-TA) has been studied.<sup>274–278</sup> In addition, benzidine was grafted covalently to silica gel and cellulose<sup>278</sup> and quinone imine was immobilised on ion exchangers obtained by modification of SG-CN by solutions of cationic and anionic surfactants.<sup>277</sup>

The retention of reagents depends substantially on the nature of the sorbent and the solution pH. Silica gels retain strongly thiazine dyes (methylene blue, toluidine blue) and DPPDA (apparently, due to the formation of hydrogen bonds between the amine and imine nitrogen atoms of the reagents and the silanol groups of the substrate surface).<sup>274, 275</sup> In weakly acidic and neutral media (when molecular species predominate), quinone imine derivatives are firmly held on SG-P. Indophenols are held on an anion exchanger (SG-TA) in an alkaline medium where indophenolates predominate. The protonated forms of indamines and benzidine are held on cation exchangers (SG-SO<sub>3</sub>H).<sup>276, 277</sup>

The redox equilibrium involving non-covalently immobilised reagents is attained within a few minutes.<sup>276, 278</sup> In the mode of successively repeated oxidation–reduction cycles, indophenol- and indanine-based sorbents are almost completely reversible. Non-covalently immobilised 2,6-dichloroindophenol can be used in 50 cycles and 2,6-dibromoindoguaiacol and Bindschedler's green, in 20 cycles.<sup>277</sup>

The nature of substrates has a pronounced influence on the acid–base and redox properties of the reagents. Whereas sorption on reverse-phase silica gels does not change the acid–base properties, sorption on cation exchangers markedly enhances the acidic properties of reagents.<sup>277</sup> Indophenols and indamines have been used as examples to elucidate the influence of non-covalent immobilisation on the redox properties of reagents. For Bindschedler's green, the greatest difference between the formal redox potentials in a solution and on a sorbent surface was found in the case of SG-P.<sup>277</sup>

The redox sorbents considered were used to develop hybrid methods for determination of sulfur-containing reducing agents, ascorbic acid, free active chlorine and aniline.<sup>274–278</sup>

#### c. Xerogels of silicic acid modified by analytical reagents

The sol–gel process is now widely used to obtain materials with specified properties. Sol–gel materials are characterised by high strength and high thermal and light stabilities, many of these being optically transparent. Using sol–gel process, it is possible to modify materials by various substances, in particular, analytical reagents.<sup>187, 279–285</sup>

Sol–gel materials based on silica (xerogels, XG) are used most often for analytical purposes. The sol–gel process is performed in the presence of catalysts. The porosity and the specific surface area of xerogels depend substantially on both the conditions of the sol–gel process (the composition of the mixture subjected to hydrolysis, the nature of the catalyst, and the pH) and on the drying conditions.<sup>279–284</sup>

Modified sol–gel materials can be prepared either by using functionally substituted alkoxysilanes containing alkyl, amino, vinyl, epoxy, mercapto and other groups<sup>187, 280, 285–287</sup> or by adding the compound to be grafted at the sol formation stage.<sup>286–323</sup> The latter approach is obviously more versatile and has an almost infinite potential, because in this case, retention is mainly provided by the mechanical capture of substances by the network silica structure formed during the gelation.

The immobilisation of an analytical reagent (rhodamine 6G) on a sol–gel material was first accomplished in 1984.<sup>289</sup> However, intensive research along this line started only in 1990 when Avnir and co-workers<sup>290</sup> concluded, based on the data accumulated at that time, that substances incorporated in sol–gel materials can participate in chemical reactions. The materials now obtained include silica-based monoliths and films modified by acid–base indicators (azo, phthalein and sulfophthalein compounds and by porphyrins),<sup>291–295</sup> complexing organic reagents (ethylenediamine, tetraacetic acid, 1,10-phenanthroline, alizarin, quinalizarin, 1-nitroso-2-naphthol, dimethylglyoxime, sodium rhodizonate, hydroturbic acid, cuproin, galloycyanin, morin, eriochrome cyanine, diphenylcarbazine)<sup>286, 290, 296–303</sup> and metal salts.<sup>290</sup> Sol–gel process is a convenient way of immobilisation of biological molecules (proteins, enzymes, antibodies); interesting data concerning this issue have been reported in reviews.<sup>304–306</sup>

The protolytic reactions involving acid–base indicators incorporated in sol–gel materials have been studied fairly comprehensively.<sup>292, 294</sup> Complexation reactions have been less investigated [only the nickel–dimethylglyoxime,<sup>286</sup> iron(II)–1,10-phenanthroline,<sup>287</sup> aluminium–morin,<sup>300</sup> copper(II)–eriochrome cyanine (ECC) systems have been studied in detail].<sup>300</sup> It has been noted that the retention of complexing reagents and their interaction with metal ions depends appreciably on the material porosity.<sup>286, 300</sup>

The sol–gel materials modified by analytical reagents have been used for determination of metal ions by solid-phase spectroscopy<sup>298–300</sup> and by test methods (indicator tubes),<sup>287, 296, 297</sup> for the design of spectroscopic<sup>301–317</sup> and electrochemical sensors<sup>318, 319</sup> and as sorbents.<sup>187, 286, 320–323</sup> A study of affinity sorbents — sol–gel materials modified by polyclonal antibodies — has demonstrated a better selectivity of the antigen–antibody interaction.<sup>322, 323</sup> A substantial limitation hampering the extensive use of sol–gel materials in analysis is the long time it takes for sorption equilibrium to be established (in some cases, up to several days).

Good results have been obtained in gas and liquid chromatography used to separate organic compounds on capillary columns modified by ion exchange or hydrophobic sol–gel films.<sup>324–328</sup> The use of capillary columns containing sol–gel monoliths has been proposed.<sup>327</sup>

Our studies<sup>246, 250, 273, 329–344</sup> have promoted extensive introduction of sol–gel materials modified by analytical reagents into the chemical analysis practice in Russia. We have developed a new method for the preparation of silicic acid xerogel powders with specified physicochemical properties (specific surface area, pore diameter, concentration of the immobilised reagent).<sup>329</sup> These were used to immobilise analytical reagents promising for preconcentration, separation and determination of metal ions, anions and a number of organic compounds including those whose immobilisation had been studied on hydrophobic surfaces: hydroxyquinolines [Ox,<sup>246</sup> 5,7-dibromo-8-hydroxyquinoline (5,7-dibromo-8-Ox)<sup>246, 342</sup>]; azo compounds [PAN,<sup>246, 250, 331, 332</sup> PAR,<sup>246, 250, 333</sup> 4-(2-thiazolylazo)-2-naphthol,<sup>246</sup> SCPAR,<sup>246, 250</sup> BBT,<sup>246, 250</sup> LG,<sup>246</sup> CD,<sup>246, 250</sup> HOCAC,<sup>246</sup> sulfarsazene (SA)<sup>246</sup>]; triphenylmethane and xanthone derivatives [chromazurol (CAZ),<sup>246, 334, 335</sup> sulfochrome (SC),<sup>334</sup> ECC,<sup>246, 334</sup> XO,<sup>246, 331, 336</sup> CV<sup>246, 250</sup>]; 1,10-phenanthroline,<sup>246</sup> bathophenanthroline (BP),<sup>246</sup> DPCide,<sup>246, 335</sup> DPCone,<sup>246, 336</sup> morin,<sup>246</sup> chrompyrazol I (CP I),<sup>246</sup> copper(II),<sup>246</sup> cobalt(II),<sup>246, 337</sup> iron(III),<sup>246, 338</sup> molybdophosphoric acid and its ammonium salt, Vavele reagent (VR) (a mixture of 12- and 18-row molybdophosphoric acids),<sup>246, 339–341</sup> aromatic hydroxy compounds [1- and 2-naphthols, 2,7-dihydroxynaphthalene, *N*-(1-naphthyl)ethylene-diamine, *p*-hydroxydiphenyl],<sup>246, 342</sup> 4-aminoantipyrine (4-AAP),<sup>246, 343</sup> disodium 4,4'-dithiobis(8-chloro-1-hydroxy-2-phenylazonaphthalene)-3,6-disulfonic acid (BAS) and butyrylthiocholine (BTCI).<sup>344</sup> Methods for the synthesis of modified sol–gel materials with a specified concentration of an analytical reagent, in particular, those modified by mixtures of reagents [a complexing reagent and a surfactant,<sup>333, 334</sup> molybdophosphoric heteropoly compound and copper(II),<sup>246, 341</sup> and BAS and BTCI] have been developed.<sup>344</sup>

Data on the thermodynamics and kinetics of heterogeneous reactions involving immobilised analytical reagents have been obtained. It was shown that inclusion of complexing reagents of various classes or 1-naphthol and 4-aminoantipyrine into silicic acid xerogel powders enhances the acid–base properties of the reagents.<sup>246</sup> Apparently, this is due to the reaction of active hydrogen atoms of immobilised compounds with the silanol groups in the bulk of the xerogel matrix. The formation of complexes in xerogels of silicic acid is possible upon immobilisation of both a complexing reagent and a metal ion. Complexes with a metal : reagent ratio of  $\leq 1 : 3$  are formed in the xerogels. The equilibrium constants of heterogeneous reactions vary in parallel with the stability constants of complexes in solutions,

which makes it possible to predict the analytical properties of reagents incorporated in xerogels of silicic acid.<sup>246</sup> Xerogels modified by molybdophosphoric heteropoly compounds (HPC) withstand at least 30 oxidation–reduction cycles. It was found that the oxidative ability of molybdophosphoric HPC is enhanced upon their inclusion into xerogels of silicic acid.<sup>339–341</sup> Various reactions can take place in xerogels of silicic acid: azo coupling, diazotisation–azo coupling and oxidative condensation.<sup>246, 342, 343</sup> For example, in xerogels modified by aromatic hydroxy compounds (the best results were attained with 1-naphthol), reactions with diazotised anilines yield azo dyes.<sup>246, 342</sup> The xerogel modified by a mixture of sulfanilic and chromotropic acids reacts with nitrite ions (diazotisation–azo coupling reactions).<sup>246</sup> The selectivity of oxidative condensation of phenolic compounds in 4-aminoantipyrine substantially increases in xerogels.<sup>246, 343</sup>

The conditions of interaction of choline esterase with BAS and BTCI contained in a xerogel have been selected: first, enzymic hydrolysis of BTCI takes place and then the resulting thiocholine reacts with BAS, which is accompanied by a sharp colour change.<sup>344</sup>

In two publications,<sup>246, 330</sup> reactions of inorganic and organic compounds with modified xerogels have been considered from the standpoint of the general mass transfer theory as sequences of the following processes: diffusion of a reactant from the bulk to the surface of modified xerogel particles (external diffusion), diffusion inside the pores (internal diffusion) and the proper chemical reaction with immobilised reagents. The rate-limiting steps were established and the rate constants for diffusion processes were determined.<sup>246</sup>

Interesting data on the effect of microwave radiation and ultrasound on the rate of heterogeneous processes involving sol–gel materials have been obtained. The microwave radiation intensifies all stages of the heterogeneous process. The time it takes to attain the equilibrium decreases three- to four-fold, while the rate constants for diffusion processes are almost doubled. It was shown that it is expedient to use 200–600 W microwave radiation.<sup>246, 330</sup> To accelerate the processes whose duration is determined by external diffusion, ultrasonic treatment was used. The high intensity of stirring, and apparently cavitation phenomena markedly accelerate heterogeneous reactions by intensification of, most of all, the external diffusion (the rate constants for external diffusion increase by a factor of almost three).<sup>246, 330</sup>

In powders of sol–gel materials, heterogeneous reactions proceed much faster than in monolithic structures: whereas the complexation of copper(II) with the monolith modified by eriochrome cyanine requires 48 h,<sup>300</sup> the reaction with a powder modified with the same reagent (pore diameter 40 Å) takes place over a period of 5 min.<sup>334</sup> An increase in the average pore diameter in the powders from 20 to 200 Å (which can be easily attained by using the method for the preparation of xerogels we developed) results in a higher rate of internal diffusion, which almost halves the time required to reach the equilibrium.<sup>246</sup>

To accelerate the reactions between molybdophosphoric HPC immobilised on xerogels and reducing agents, we synthesised xerogels containing simultaneously molybdophosphoric HPC and copper(II) as the catalyst for their reduction. The results indicate a substantial acceleration of the heterogeneous reaction, *i.e.*, a catalytic reaction takes place.<sup>341</sup>

## 2. The use of non-covalently modified silicas in analysis

Due to the simplicity of preparation of silicas non-covalently modified by analytical reagents with a high concentration of firmly attached reagents and to the high rate of sorption, these materials can be regarded as promising sorbents. They have been used for sorption preconcentration and separation of metal ions, including that in the on-line mode,<sup>246–252, 255, 257, 259–261, 265</sup> and for the solid-state spectroscopic and test determination of metal ions, anions, reducing agents, oxidants and organic compounds.<sup>246, 254, 258, 274–278, 330–344</sup>

### a. Determination of metal ions by sorption coupled with atomic absorption spectrometry or photometry

The sorption preconcentration of metal ions on reverse-phase silica gels and xerogels of silicic acid non-covalently modified by complexing reagents results in high preconcentration factors (up to  $5 \times 10^3$ ). The capacities before breakthrough of the complexing sorbents with respect to metal ions are rather high ( $5\text{--}100\text{ }\mu\text{mol g}^{-1}$ ). The high preconcentration efficiency is determined by rather high flow rates of the sample: from  $3\text{--}4\text{ ml min}^{-1}$  (for complexes) to  $20\text{ ml min}^{-1}$  (for ion associates).<sup>246–248, 250–253, 259, 273</sup>

An obvious advantage of complexing sorbents based on modified silicas is the high selectivity attained by immobilisation of selective complexing reagents, choice of appropriate conditions and by using mixed sorbents<sup>246, 255, 261, 265</sup> or exchange sorption.<sup>246, 249</sup>

For sorption preconcentration of metal ions, the use of cartridges filled with hydrophobic silica gels modified by complexing reagents (XO, PAN, CD, Ox and DMABR) has been proposed. If necessary, modification can be carried out under field conditions on the sampling site.<sup>246, 248</sup>

The procedures proposed for determination of Ag, Cd, Cu(II), Fe(II), Mn(II) and Pb using sorption preconcentration coupled with atomic absorption or photometry allow the use of serial, readily available and cheap spectrophotometers and flame atomic absorption spectrometers to determine traces of metals in natural, potable and waste waters, atmospheric precipitates and industrial solutions at the MPC level (Table 7). The sorption–atomic absorption procedure for determination of Cd, Pb and Zn in atmospheric precipitates or natural and waste water using preconcentrating cartridges filled with reverse-phase silica gel SG-P non-covalently modified by XO has passed the state metrological certification procedure (PND P 14.1:2.81-96) and was approved for the use in the state ecological monitoring.<sup>246</sup>

### b. Continuous flow analysis

Flow analysis of samples has a high sampling frequency and good reproducibility and requires small amounts of samples and

**Table 7.** Characteristics of metal determination by sorption on non-covalently modified silicas ( $n = 3$ ,  $p = 0.95$ ) coupled with atomic absorption spectrometry and photometry.

| Sorbent                                   | Analyte | Quantifiable concentration range /mg litre <sup>-1</sup> | Detection limit /mg litre <sup>-1</sup> |
|-------------------------------------------|---------|----------------------------------------------------------|-----------------------------------------|
| Atomic absorption spectrometry            |         |                                                          |                                         |
| N <sub>4</sub> /SG <sup>a</sup>           | Co(II)  | 0.025–0.15                                               | 0.02                                    |
|                                           | Cu(II)  | 0.020–0.12                                               | 0.01                                    |
| DMABR/SG-C <sub>16</sub>                  | Ag(I)   | 0.002–0.1                                                | 0.001                                   |
| Ox/SG-C <sub>16</sub> (see <sup>b</sup> ) | Cd      | 0.0009–0.06                                              | 0.0003                                  |
|                                           | Pb      | 0.06–0.2                                                 | 0.03                                    |
| CD/SG-P                                   | Cd      | 0.006–0.1                                                | 0.002                                   |
| QO/SG-P <sup>c</sup>                      | Cd      | 0.0005–0.01                                              | 0.0002                                  |
|                                           | Pb      | 0.001–0.1                                                | 0.0006                                  |
|                                           | Zn      | 0.01–0.1                                                 | 0.004                                   |
| Ox/SG-C <sub>16</sub> + Cu                | Fe(III) | 0.38–3.61                                                | 0.25                                    |
| BEHHP/SG + Zn                             | Fe(III) | 0.03–1.70                                                | 0.02                                    |
| PMBP/SG + Co                              | Cu(II)  | 0.06–0.85                                                | 0.03                                    |
| BBT/XG                                    | Cd      | 0.006–0.1                                                | 0.002                                   |
| Spectrophotometry                         |         |                                                          |                                         |
| PAN/SG-P                                  | Mn(II)  | 0.0006–0.01                                              | 0.0003                                  |
| QO/SG-P                                   | Fe(III) | 0.001–0.03                                               | 0.0005                                  |
| (DDTC) <sub>2</sub> Pb/SG                 | Cu(II)  | 0.13–3.20                                                | 0.02                                    |
| CV/XG                                     | Cd      | 0.01–0.34                                                | 0.002                                   |

<sup>a</sup> N<sub>4</sub> is the tetraaza analogue of dibenzo-18-crown-6; <sup>b</sup> joint determination of Cd and Pb; <sup>c</sup> joint determination of Cd, Pb and Zn.

reagents. Currently, the development of flow analysis is related to the possibility of performing sorption preconcentration and separation and solid-state detection under dynamic flow conditions (often, on a micro scale).<sup>345</sup>

The reasonable efficiency ( $CE = 5\text{--}95$ ) and high selectivity of complexing sorbents based on non-covalently modified silicas determine the success in using them for the on-line sorption preconcentration and separation of metal ions.

A study<sup>273</sup> describes a flow distribution system for automated photometric determination of  $0.009\text{--}0.3\text{ mg litre}^{-1}$  of aluminium in waters and beverages including the on-line sorption preconcentration on a microcolumn filled with xerogel of silicic acid modified by chromazurol (50 samples per hour).

We developed a universal flow distribution system for determination of metal ions. The system core is a sorption column. This can be either a microcolumn packed with reverse-phase silica gel or a capillary column with a hydrophobic inner surface, which is modified alternately by various complexing reagents that ensure the retention of different metal ions (Fig. 3). The system allows automated sorption separation of metal ions, preconcentration of one ion and separation of the interfering metal ions; hence, a number of analytical problems can be solved. Automated highly productive procedures for determination of traces of metal ions [Cd, Pb, Co(II), Cu(II), Fe(III)] or for simultaneous determination of two metal ions [Ca–Mg, Co(II)–Fe(III), Pb–Fe(III)] in atmospheric precipitates have been developed. The high selectivity of the flow photometric determination of metal ions with on-line sorption preconcentration is ensured by the appropriate choice of the sorbent and by the sorption–desorption and photometric detection conditions. Advantages of capillary columns over packed microcolumns include higher sampling frequency and better metrological characteristics of the determination. The main reason is the decrease in sample diffusion in the case of capillary columns (Table 8).<sup>246, 251, 259–261</sup>

For determination of Pb(II), Co(II), Mn(II) and Fe(III) traces in natural waters, the versatile gas distribution system was supplemented by a block for on-line sample preparation (destruction of the metal complexes with humic and fulvic acids) in a microwave field (see Fig. 3).<sup>346</sup>

The flow distribution systems for the simultaneous determination of cadmium and zinc, aluminium and manganese(II) have been developed on the basis of on-line sorption separation on

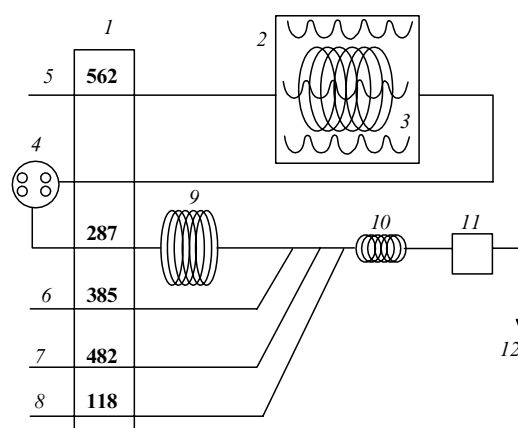


**Figure 3.** Flow distribution system for photometric determination of metals in natural waters.

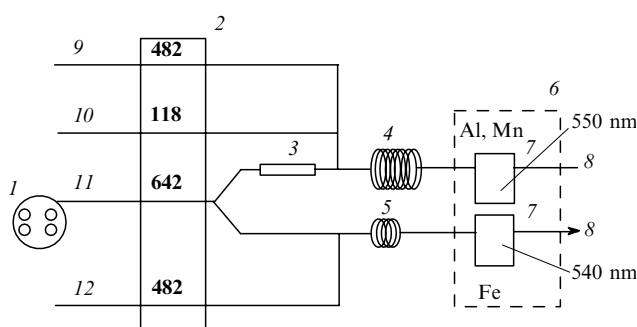
(1) Peristaltic pump, (2) microwave oven, (3) reaction helix, (4) sampler, (5) inlet of the modifying solution, the sample and the rinsing solution, (6) inlet of the photometric reagent, (7) inlet of the buffer solution, (8) air inlet, (9) capillary column, (10) mixing helix, (11) flow photometer, (12) discharge.

The values typed in bold in this and in the next Figure are the corresponding flow rates in  $\mu\text{l min}^{-1}$ .

**Table 8.** Characteristics of flow photometric determination of metals with the on-line sorption preconcentration and separation on microcolumns (SG-P) and capillary columns (S-P).

| Analyte                    | Modifying reagent | Column | Quantifiable concentration range /mg litre <sup>-1</sup> | Sampling frequency, samples per h |
|----------------------------|-------------------|--------|----------------------------------------------------------|-----------------------------------|
| One-component systems      |                   |        |                                                          |                                   |
| Copper(II)                 | PAN               | SG-P   | 0.006–0.06                                               | 19                                |
|                            | PAN               | S-P    | 0.003–1.5                                                | 19                                |
| Cobalt(II)                 | QO                | SG-P   | 0.005–0.05                                               | 18                                |
|                            | QO                | S-P    | 0.003–0.9                                                | 18                                |
| Iron(III)                  | QO                | SG-P   | 0.02–1.0                                                 | 17                                |
|                            | QO                | S-P    | 0.005–3.0                                                | 17                                |
| Lead                       | HOCAC             | S-P    | 0.01–1.0                                                 | 17                                |
| Two-component systems      |                   |        |                                                          |                                   |
| Zinc + iron(III)           | QO                | SG-P   | 0.5–6.5                                                  | 30                                |
|                            | QO                | S-P    | 0.3–1.7                                                  | 60                                |
| Copper(II) + manganese(II) | PAN               | SG-P   | 0.06–4.0                                                 | 30                                |
|                            | PAN               | S-P    | 0.3–1.7                                                  | 51                                |
| Calcium + magnesium        | Quinalizarin      | S-P    | 2–32                                                     | 55                                |
|                            |                   |        | 0.1–2                                                    |                                   |

mixed sorbents.<sup>246</sup> For automation of routine agrochemical analyses, a flow distribution system for simultaneous photometric determination of three components — manganese(II), aluminium and iron(II)<sup>261</sup> — has been developed; the system combines the on-line sorption separation on a mixed sorbent with twice repeated flow detection (23 samples per hour) (Fig. 4).

**Figure 4.** Flow distribution system for simultaneous photometric determination of Mn(II), Al and Fe(III) with the on-line sorption separation and double detection.

(1) Sampler, (2) peristaltic pump, (3) microcolumn, (4, 5) mixing helices, (6) flow photometer, (7) flow cells, (8) discharge, (9) inlet for the solution of XO in a buffer solution, (10) air inlet, (11) inlet of the sample and the rinsing solution, (12) inlet of a XO solution in 0.1 M nitric acid.

### c. Solid-state spectroscopy and test methods

Due to the simplicity and high sensitivity of the determinations, the title methods are now attracting considerable attention of researchers. The determination is based on a chromogenic heterogeneous reaction carried out under static conditions (as a result of sorption of pre-synthesised coloured compounds by appropriate sorbents or the reaction of the analyte with immobilised chromogenic reagents) and measurement of the spectroscopic characteristics of the solid phase. The spectroscopic characteristics of the indicator powders are recorded, after the sorption equilibrium has

been established, by diffuse reflectance spectroscopy, solid-state spectrophotometry or chromaticity measurements.<sup>347, 348</sup>

When the colour can be estimated by sight or portable instruments can be used, test versions of these methods can be developed.<sup>178, 349</sup>

Solid-state spectroscopy has found the most extensive application for determination of metal ions. To this end, ion exchange resins,<sup>348</sup> fibrous materials and fabrics with ionogenic groups filled by ion exchangers,<sup>350–352</sup> cellulose sorbents,<sup>348</sup> silochromes<sup>212–221, 228–235</sup> and sol–gel materials (monoliths and films)<sup>298–300</sup> have been used.

The high porosity and optical transparency of silicas modified by analytical reagents and the possibility of implementation of various heterogeneous reactions in the solid phase ensured further development of methods based on solid-state spectroscopy. Highly sensitive and simple procedures for determination of Mn(II), Cu(II), Zn, Mo(VI), Cd, Pb; nitrate, nitrite, fluoride and phosphate ions; the total content of sulfur-containing anions, ammonium ions, anionic surfactants, ascorbic acid, hydrazines, asymmetric dimethylhydrazine, anilines, phenols, naphthols and esters have been developed (Table 9, 10). The procedures are fairly quick; it takes only 5–20 min to attain the sorption equilibrium.<sup>246, 274–277, 330–343</sup>

Quantification by these procedures does not imply the use of expensive instrumentation and can be performed by portable photometers and reflectometers; in the test version, this is also done using colour scales. The procedures proved useful in analysis of field samples: water, industrial process solutions, foodstuffs, pharmaceuticals and biological liquids.<sup>246</sup>

Test systems based on indicator powders have passed metrological certification procedure at the State Metrological Scientific Centre based on Urals Research Institute of Metrology; they have been included in the register of test system types, approved for the use and are now manufactured commercially by the limited liability company MedEkoTest (Moscow).

**Table 9.** Characteristics of solid-state spectrophotometric determination of inorganic and organic substances using modified silicas ( $n = 3$ ;  $p = 0.95$ ).

| Analyte              | Indicator powder                      | Quantifiable concentration range /mg litre <sup>-1</sup> | Detection limit /mg litre <sup>-1</sup> |
|----------------------|---------------------------------------|----------------------------------------------------------|-----------------------------------------|
| Ag                   | SCPAR/XG                              | 0.5–8.0                                                  | 0.1                                     |
| Cd <sup>a</sup>      | BBT/XG                                | 0.02–0.2                                                 | 0.01                                    |
|                      |                                       | 0.005–0.2                                                | 0.005                                   |
|                      |                                       | 0.002–0.2                                                | 0.001                                   |
| Cu(II)               | ECC/XG                                | 0.002–0.2                                                | 0.001                                   |
| Zn                   | PAR + CP/XG                           | 0.4–10                                                   | 0.2                                     |
| Mn(II)               | PAN/XG                                | 0.5–5.0                                                  | 0.5                                     |
| Mo(VI)               | LG/KG                                 | 0.2–6.0                                                  | 0.2                                     |
| Pb                   | CP 1/XG                               | 0.01–4.0                                                 | 0.005                                   |
| F <sup>-</sup>       | QO/XG                                 | 0.5–10.0                                                 | 0.3                                     |
| Cl <sup>-</sup>      | DPCone/XG                             | 1.0–30.0                                                 | 0.5                                     |
| Free active chlorine | DPPDA/SG-SO <sub>3</sub> <sup>-</sup> | 0.02–0.8                                                 | 0.01                                    |
| Hydrazines           | PB + Cu(II)/XG                        | 0.2–2.0                                                  | 0.1                                     |
| Ascorbic acid        | PB + Cu(II)/XG                        | 1–50                                                     | 0.3                                     |
| Naphthols            | Co(III)/XG                            | 0.1–4.0                                                  | 0.05                                    |
| Esters               | Fe(III)/XG                            | 17–450                                                   | 11                                      |
| Aniline              | 1-Naphthol/XG                         | 0.05–10                                                  | 0.02                                    |
|                      |                                       | 0.1–10 <sup>a</sup>                                      | 0.05 <sup>a</sup>                       |
| Phenols              | 4-AAP/XG                              | 0.03–0.5                                                 | 0.01                                    |

<sup>a</sup> Determined by diffuse reflectance spectroscopy.

### d. The method of indicator tubes

This method is based on the direct proportionality between the length of the coloured segment of the indicator powder located in the tube and the concentration of the analyte. The main advantage

**Table 10.** Characteristics of test systems based on modified silicas for determination of inorganic and organic compounds.

| Analyte                                               | Quantifiable concentration range /mg litre <sup>-1</sup> |
|-------------------------------------------------------|----------------------------------------------------------|
| <b>Indicator powders</b>                              |                                                          |
| Manganese(II)                                         | 0.5 – 5.0                                                |
| Copper(II)                                            | 0.001 – 0.1                                              |
| Zinc                                                  | 0.1 – 10                                                 |
| Molybdenum(VI)                                        | 0.2 – 60                                                 |
| Silver                                                | 0.5 – 80                                                 |
| Cadmium                                               | 0.001 – 0.01                                             |
| Lead                                                  | 0.01 – 1.0                                               |
| Nitrate ions                                          | 0 – 1                                                    |
| Nitrite ions                                          | 0.01 – 10                                                |
| Fluoride ions                                         | 1.0 – 10                                                 |
| Asymmetric <i>N,N</i> -dimethylhydrazine <sup>a</sup> | 0.2 – 50                                                 |
| Aniline                                               | 0.05 – 10                                                |
| Phenolic index                                        | 0.0005 – 0.1                                             |
| Naphthols                                             | 0.1 – 4.0                                                |
| Esters                                                | 40 – 450                                                 |
| Anionic surfactants                                   | 0.1 – 50                                                 |
| <b>Indicator tubes</b>                                |                                                          |
| Mixture of heavy metals <sup>b</sup>                  | (0.001 – 1) × 10 <sup>-3</sup> (see <sup>c</sup> )       |
| Tin(II)                                               | 10 – 200                                                 |
| Copper(II)                                            | 0.1 – 65                                                 |
| Iron                                                  | 0.05 – 50                                                |
| Aluminium                                             | 0.3 – 3.0                                                |
| Chromium(VI)                                          | 0.5 – 50                                                 |
| Cobalt(II)                                            | 0.06 – 6.0                                               |
| Cadmium                                               | 0.3 – 3.0                                                |
| Nickel                                                | 0.2 – 30                                                 |
| Nitrate ions                                          | 0.5 – 20                                                 |
| Nitrite ions                                          | 0.1 – 5                                                  |
| Chloride ions                                         | 0 – 2000                                                 |
| Iodide ions                                           | 100 – 800                                                |
| Free active chlorine                                  | 0.05 – 3.0                                               |
| Ascorbic acid                                         | 3.0 – 330                                                |
| Aniline                                               | 0.02 – 2.5                                               |
| Anionic surfactants                                   | 0.1 – 150                                                |
| Cationic surfactants                                  | 10 – 150                                                 |

<sup>a</sup> The test system has passed the state metrological certification procedure, registered under the number TS-224.01:11/008-2004 and approved for the use by the Problem Commission of the RF Ministry of Health; <sup>b</sup> the test system has passed the state metrological certification procedure and is registered under the number TS-224.09/009-2004; <sup>c</sup> in mol litre<sup>-1</sup>.

of this approach is the possibility of reliable test determination based on the easily measurable stain length rather than on the degree of colour or tint change (as in most test methods). The method is widely used to analyse gases and aerosols, in particular, in military chemistry.<sup>353</sup>

We have applied the indicator tube method for analysis of solutions (environmental objects, waste waters, foodstuffs and beverages, biological liquids).<sup>246, 252, 254, 258, 274–276, 331, 336, 339, 344</sup> For the preparation of indicator powders, analytical reagents were either non-covalently immobilised on reverse-phase silica gels and silica gel-based ion exchangers directly in the indicator tube<sup>246, 252, 254, 258, 274–276, 354</sup> or incorporated in xerogels of silicic acid.<sup>246, 331, 332, 335, 336, 339, 344</sup>

On the basis of studies of the dependence of determination sensitivity on the physicochemical characteristics of the indicator powders, the flow rate and the mode of supply of the analyte solution to the tube, and the tube length and internal diameter, requirements to the selection of indicator reactions and analysis protocols have been formulated. To ensure high accuracy of determination, the time of passage of the solution through the tube should be 10–20 times longer than the characteristic time of the chemical reaction.<sup>355</sup>

Two modes were employed to feed analyte solutions to the indicator tubes: rising of the liquid due to capillary forces (the 'sinking' mode) and pumping the solution through the tube, for example, by means of a medical syringe (the 'passing' mode). The former mode markedly facilitates and accelerates the procedure of analysis, while the latter ensures a higher determination sensitivity due to the larger solution volume.<sup>246, 254, 258, 274–276, 331, 332, 335, 336, 339, 344, 354</sup>

Indicator tubes for determination of heavy metal mixtures, Al, Cr(VI), Fe, Co(II), Ni, Cu(III), Cd and Sn(III); nitrate, nitrite, chloride and iodide ions; the total content of sulfite, thiosulfate and sulfide ions, ascorbic acid, free active chlorine, cationic and anionic surfactants, sulfur-containing reducing agents, aniline and hydrazines; and the choline esterase activity have been developed (see Table 10). The indicator tubes have been used to analyse environmental objects, industrial process solutions, food-stuffs (after the appropriate sample preparation), beverages, and biological liquids.<sup>246, 254, 258, 274–276, 331, 332, 335, 336, 339, 344, 354</sup>

The metrological characteristics of indicator tube analyses are comparable to those for instrument methods. The relative standard deviation for determination using indicator tubes is 0.02–0.15 and the analysis time is 2–10 min.

Test systems based on indicator tubes have passed metrological certification procedure at the State Metrological Scientific Centre based on the Urals Research Institute of Metrology; they have been included in the register of test system types, approved for the use and are now manufactured commercially by the limited liability company MedEkoTest (Moscow).

Test systems for determination of nitrate, nitrite and chloride ions and Cu(II) and Fe in natural waters have passed state inter-branch tests. The test system for determination of asymmetrical dimethylhydrazine ensures reliable quantification of this toxic substance in soils and in special rinsing solutions.

Indicator tubes are used to determine Sn(II) in the reagents for the preparation of radiopharmaceuticals by the <sup>99m</sup>Tc generator. The test system for determination of nitrate ions is used for clinical urine and blood serum analyses. The indicator tubes for determination of chloride ions in sweat and the choline esterase activity in biological liquids have been recommended for detection of mucoviscidosis in babies and general intoxication in patients.

Thus, non-covalent immobilisation on the surface-modified silicas and incorporation into xerogels of silicic acid has imparted new analytical properties to the fixed analytical reagents, which determined their use in the practice of chemical analysis. In our opinion, silicas modified by analytical reagents can be successfully used to develop flow methods of analysis, in particular, electro-injection<sup>356</sup> and sequential injection analyses and analysis with particle injection.<sup>357</sup> Of particular interest is the design of micro-electrodes and microanalytical systems on microchips.

## VI. Conclusion

The information presented in the review demonstrates the substantial achievements in the development of sorption preconcentration techniques aimed at solving topical tasks of chemical analysis. First, this is the pronounced increase in the number of sorbents that allow quantitative and in some cases fairly selective recovery of trace amounts of metal ions (including complex ions), various ionised and non-ionised organic compounds and simple inorganic anions. Second, this is the appreciable progress attained in the quantitative description of sorption processes, in the investigation of the interaction mechanism, in the development of the strategy for the *a priori* estimation of the sorption conditions and even in the deliberate selection of sorbents for particular purposes. Third, fundamental research has resulted in the development of a large number of combined and hybrid methods for the analysis of diverse objects, including environmental objects. Some of these methods are routinely used in chemical analysis.

A prominent place in the approaches and methods considered belongs to dynamic sorption preconcentration and flow preconcentration. This provides a way to automation of the analysis; numerous examples of automated analyses are currently known, mainly represented by flow injection analysis. A significant contribution to the development of analytical sorption preconcentration was made by the researchers of the Department of Chemistry of the Moscow State University.

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<sup>a</sup> — *J. Anal. Chem. (Engl. Transl.)*

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<sup>c</sup> — *Russ. J. Coord. Chem. (Engl. Transl.)*

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<sup>h</sup> — *Chem. Phys. Rep. (Engl. Transl.)*

<sup>i</sup> — *Chem. Dokl. (Engl. Transl.)*

<sup>j</sup> — *Colloid. J. (Engl. Transl.)*

<sup>k</sup> — *Herald Russ. Acad. Sci. (Engl. Transl.)*

# Catalytic sites of hydrolases: structures and catalytic cycles

S D Varfolomeev, I A Gariev, I V Uporov

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**Abstract.** The applications of various bioinformatics methods and databases to the analysis and classification of proteins and search for active sites of enzymes are considered. The published data on the structures of active sites and mechanisms of action of hydrolases are analysed. It is emphasised that all of the known hydrolases can be divided into four groups according to the types of catalytic site which differ in the mechanisms of water activation. The mechanisms of water activation by catalytic groups in the active sites of hydrolases are discussed and the schemes of catalytic cycles characteristic of classical types of active sites of these enzymes are considered. Using glycosyl hydrolases and serine hydrolases as examples, it is demonstrated that different proteins possess common catalytic sites and mechanisms of action. The role of aspartic acid and histidine in the activation of hydrolase substrates and the role of structure-forming acids (glycine, proline, cysteine) in the structural organisation of the catalytic sites are considered. The bibliography includes 195 references.

## I. Introduction

Considerable progress achieved in the study of enzymes in recent decades is caused by the profound fundamental interest in enzymes as highly efficient catalysts of chemical reactions, on the one hand, and by continuously expanding areas of their applications aimed at the solution of numerous practical tasks, on the other hand.<sup>1–13</sup>

The large amount of information on the structures of enzymes has been accumulated over recent years, considerable progress has been observed in the development of concepts of the principles of formation of active sites of enzymes and their mechanisms of action. Tremendous amounts of information concerning amino

acid sequences and spatial structures of protein molecules have been amassed in numerous computer databases. This information demands analysis, systematisation and interpretation from the standpoint of the chemistry of catalytic processes. This review is devoted to applications of bioinformatics methods and databases in the analysis of enzymes and search for their active sites.

Hydrolases, *i.e.*, enzymes catalysing hydrolysis of various compounds, were chosen as the subjects of investigation. This choice was determined by a number of circumstances. Hydrolases constitute about one third of all currently known enzymes (approximately 1100 out of 3700 in the Enzyme Classification). The functional groups in the active sites of many hydrolases that effect their catalytic cycles have been determined. The mechanisms of action of all hydrolases include activation of water by a limited array of functional groups. The fact that many structural elements in the active sites of hydrolases are present in enzymes pertaining to other classes is of no less importance for enzymatic catalysis at large.

## II. Databases of amino acid sequences and three-dimensional structures of enzymes

A considerable body of information on the primary and spatial structures of biopolymers has been accumulated to date. Information on amino acid sequences of enzymes is widely used for their classification, *i.e.*, belonging to one or another family,<sup>†</sup> determination of conserved amino acids and their positions within the families, studies of translated sequences of proteins derived from decoded genomes, *etc.* Spatial structures of enzymes are used for the studies of enzyme-catalysed chemical transformations, rationalisation of substrate specificities, site-directed mutagenesis of enzymes aimed at conferring specific functions on them, *etc.*

Databases containing amino acid sequences or spatial structures of proteins are referred to as primary. Secondary databases comprise elements of the primary databases classified according to their specific features, *e.g.*, databases on alignments of amino acid sequences of proteins or hierarchical databases of protein structures.

S D Varfolomeev, I A Gariev, I V Uporov Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax (7-095) 939 54 17, tel. (7-095) 939 35 89, e-mail: sdvarf@enzyme.chem.msu.ru (S D Varfolomeev), tel. (7-095) 939 34 07, e-mail: gariev@hotmail.com (I A Gariev), e-mail: iuporov@rabbit.chem.msu.ru (I V Uporov)

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<sup>†</sup> The terminology used by different authors may differ.



The Swiss-Prot/TrEMBL (EMBL stands for 'European Molecular Biology Laboratory' database),<sup>14</sup> which further developed into the knowledgebase UniProt,<sup>15</sup> is one of the most popular primary databases of protein sequences. The non-commercial database Swiss-Prot is supported by several research institutes in Europe (e.g., the Swiss and European Institutes for Bioinformatics) and the USA and is accessible through Expasy (Expert Protein Analysis System), the proteomic server of the Swiss Institute for Bioinformatics (<http://www.expasy.org>). Information deposited therein is available through servers in many other countries, which ensures rapid responses to the users' queries.

By the time of writing of this paper (June 2004), the latest version of the Swiss-Prot 43.5 database contained information about 153 017 annotated amino acid sequences with the overall length of 56 301 572 amino acids retrieved from 116 894 publications. It is noteworthy that this database contains only annotated sequences, i.e., sequences of the proteins (including enzymes) with well-established functions. The database TrEMBL, which comprises translated protein sequences, is a supplement to the Swiss-Prot database. The translation is carried out automatically from the nucleotide sequences deposited with the EMBL Nucleotide Sequence Database.<sup>16</sup> For the protein sequences deposited in the database TrEMBL, only the sources are known. The conclusion about their putative functions is made on the basis of their similarities to the sequences of the studied (annotated) proteins. The latest version of the database TrEMBL contained information about 1 062 416 sequences with the overall length of 332 514 237 amino acids. Special mention should be made of a nearly tenfold difference between the number of protein sequences in the databases Swiss-Prot (annotated) and TrEMBL (translated). As a result of their investigation, the proteins from the database TrEMBL pass into the database Swiss-Prot, where they supplement the arrays of sequences of the annotated proteins. The number of sequences in the database Swiss-Prot/TrEMBL increases nearly exponentially with time.

The data deposited with the database Swiss-Prot/TrEMBL encompass several fields; their content can be illustrated by the following example. The amino acid sequence of formate dehydrogenase from *Pseudomonas* sp. strain 101 has the primary accession number P33160 (a unique identifier of this sequence in the Swiss-Prot) and the entry name FDH\_PSESR (the second unique identifier of this particular sequence having a definite semantic meaning): FDH is abbreviated from Formate DeHydrogenase, while the abbreviation PSESR indicates the source, viz., *Pseudomonas* sp. Using the accession number or the entry name, one can obtain available information about the amino acid sequence.<sup>‡</sup> The accession number and the entry name (if it exists) are followed by chronological information (database entry date, latest modification date, annotation modification date, etc.); name(s) of the protein [official, synonyms, Enzyme Classification (EC) number]; origin and taxonomic data; references to the literature sources of the sequence or its corrections; comments on enzyme-catalysed reactions and data on the quaternary structure and relatedness to a protein family. Other information includes cross-references to the corresponding entries of other databases. For formate dehydrogenase used as an example, there are references to the entry in the protein structure database PDB (Protein Data Bank, 2NAC identifier) and two entries in the Protein families database (Pfam).<sup>17</sup> It is of note that the number of cross-references varies for different sequences and depends on the level of investigation of a protein. The cross-references are succeeded by the field 'Features', which provides information about the domain structure and secondary structure elements based on the spatial structure of a protein (if any) and, finally, the amino acid sequence itself.

‡ It is of note that the primary accession number and entry name for each amino acid sequence deposited with the database TrEMBL coincide, since their functions are unknown and the conferment of names reflecting their function or classification is unjustified.

For the overwhelming majority of protein sequences deposited in the database Swiss-Prot, the set of fields is not that big, since the spatial structures are known only for a limited number of proteins including well-studied ones. For protein sequences deposited with the database TrEMBL, the set of fields is even smaller: it is only the sequence source (gene), references and the sequence itself that are reliable. It is of note that the access to the database Swiss-Prot/TrEMBL permits the use of different kinds of search and the user's interface is well thought-out, which significantly facilitates the work.

The Protein Data Bank (PDB)<sup>18</sup> (<http://www.rcsb.org>) represents a primary database of spatial structures of biopolymers. This data bank is supported by the Research Collaboratory for Structural Bioinformatics which comprises three research centres in the USA. By June 2004, this data bank comprised information about 25 882 biopolymer structures (including 23 429 peptide and viral structures) established by X-ray diffraction analysis and multidimensional NMR.<sup>§</sup> It is of note that the number of structures deposited with PDB increases exponentially and so does the volume of data banks of the primary sequences. However, in contrast to amino acid sequence data banks, the structure data bank includes different structures of the same biopolymer obtained under different conditions (e.g., pH) or as a complex with different molecules (e.g., with inhibitors), etc. Some protein structures look very similar. If such 'similar' structures are omitted, the remaining ~ 5 000 structures will differ, in one degree or another, in the fold of their polypeptide chains, the increase in the number of new folding types being far from exponential. It is noteworthy that the difference in the growth rates of the bank of primary sequences and the bank of spatial protein structures makes the simulation of protein structures based on their amino acid sequences a topical task. The development of methods for simulation is progressing rapidly.<sup>19</sup>

Every structure deposited with the PDB is presented as a text file, which includes the coordinates of all of its heavy atoms (these coordinates are read by molecular graphics programs or are used as the starting information for calculations). Some proteins possess spatial elements (groups of atoms) manifesting high lability (these include disordered structures situated on the surface of protein globules or several amino acid residues nearest to the N-/C-ends). The impossibility of determining their coordinates leads to the appearance of gaps in the polypeptide chains or a lack of structural data on the side chains of amino acid residues.

In addition to the atom coordinates, PDB files contain references to the papers with the protein structures, experimental procedures and subsequent processing of the results obtained, amino acid sequences and secondary structures of proteins. High accuracy of determination of spatial structures of enzymes makes quantum-chemical methods applicable to simulation of enzymatic catalytic processes.<sup>20</sup>

The interface of the PDB database allows text searching in different fields. In our opinion, the database PDBsum (<http://www.biochem.ucl.ac.uk/bsm/pdbsum/>) developed and supported by researchers of the European Institute for Bioinformatics is the most convenient tool for object searching.<sup>21–23</sup> This database is secondary according to our classification and contains references to PDB files ordered according to specific features. For example, it allows a rapid search for protein structures on the basis of their EC numbers, determination of all structures containing a specific ligand or a prosthetic group (e.g., heme or NAD) and retrieval of a list of biomolecules isolated from any particular organism. In addition to a large number of cross-references, this database provides a graphical presentation of the secondary structure of a protein with the indication of its conserved amino acids.

§ The term 'biopolymer (particularly, protein) structure' stands for a set of Cartesian coordinates of heavy atoms (of all atoms with the exception of hydrogen atoms) constituting the given biopolymer.

Two databases, *viz.*, CATH (<http://www.biochem.ucl.ac.uk/bsm/cath/>),<sup>24–25</sup> and SCOP (<http://scop.mrc-lmb.cam.ac.uk/scop/>),<sup>26–28</sup> comprise a hierarchical classification of protein structures. The structural domains of the proteins deposited with these databases are clustered according to the fold of the polypeptide chain. The hierarchical nature of these databases is manifested in the stepwise introduction of similarity levels of protein structures. Thus the structures in the database CATH are first combined into homologous superfamilies (Homology), the families are united into topologies (Topology), which form the topology architectures (Architecture); the latter, in turn, form classes (Class). A knowledge of the index of a structure in the database classification allows a rapid search for structural ‘neighbours’ and determination of the qualitative degree of similarity between different protein structures.

The database HSSP (Homology-derived Secondary Structures of Proteins)<sup>29</sup> available at the address <http://www.sander.ebi.ac.uk/hssp/> is a database linking structural information to sequence information. This database comprises pairwise alignment of the amino acid sequence of a protein deposited with the data bank PDB and homologous sequences with the degree of identity of 30% and higher from the data bank Swiss-Prot/TrEMBL. This information can be used for the construction of spatial structure models of proteins using homologous simulation.<sup>19</sup> The database HSSP also contains information about the conservation of the constituent amino acids in the amino acid sequences.

The aforementioned database Pfam is the only secondary database of protein sequences that deserves special consideration.<sup>17</sup> This database comprises multiple alignments of protein sequences from the database Swiss-Prot/TrEMBL, united into families according to the similarity of their amino acid sequences. The protein families deposited with the version 14.0 of this database (June 2004) cover 95% of all known protein sequences. The database Pfam is available at the address <http://www.sanger.ac.uk/Software/Pfam/>. Multiple alignments of protein sequences have made it possible to single out domains manifesting the highest degree of similarity. The amino acid sequence of a real protein may contain several domains. It is therefore important to discriminate between the structural domains of the proteins deposited with the databases CATH and SCOP and the amino acid sequence domains. The former are derived from similar folding of the peptide chains of proteins with the known spatial structures, while the latter were established by multiple alignments of an array of protein sequences. Very often, the boundaries of structural and amino acid sequence domains coincide.

Multiple alignments in the database Pfam were built by the program HMMER (<http://hmmer.wustl.edu>) based on the Hidden Markovian Model.<sup>29</sup> The alignment of sequences by the HMM method is characterised by an extremely high sensitivity in the determination of homologies between evolutionary distant proteins. This method is based on the concept according to which every position in a sequence is determined by a random Markovian process, which results in the generation of an amino acid. In this approach, conserved positions generate only one type of amino acid, while less conserved positions generate two or three such types. In mathematical terms, this fact can be described by the introduction of probabilities of generation of amino acids in all positions. Moreover, it is necessary to introduce probabilities of a transition from one position to another, gap probabilities and so on. The set of such probabilities and the HMM architecture constitute the main principle of the HMM method for the given protein family. Some efficient methods for the determination of a set of probabilities by sequential iteration have been devised. The main advantage of the HMM method over traditional alignment methods is that the penalty of the sequence gap is not an external parameter, but rather is established in a self-consistent mode in the course of HMM construction and varies on going from one position to another. The HMM method is successfully used for predicting structures and hypothetical functions of protein

sequences in the genome annotation.<sup>30</sup> In addition to HMM parameters, the database Pfam contains the multiple alignment itself and the corresponding dendrogram (a phylogenetic tree), *i.e.*, a schematic presentation of the spatial structure of the given domain (if a family comprises at least one domain with a known spatial structure) and a histogram of probabilities of amino acid generation in each position of the protein domain (the higher the column height, the higher the conservation of the given position). This information is extremely important in designing site-directed mutagenesis of enzymes, since it allows rapid localisation of the most significant amino acid residues for the tested sequence.

The list of the aforementioned databases of protein sequences and structures is far from being complete. We have mentioned and discussed only some of these databases which, in our opinion, comprise important information about amino acid sequences and spatial structures of enzymes. This information is displayed in a convenient form and is extremely useful in the different steps of an investigation.

### III. Methods for identification of groups constituting the catalytic site

Information about the involvement of one or another group in the catalytic site and in the catalytic process at large can be derived from different (often complementary) sources. An essential role in the development of concepts on the structure of active sites is played by the methods of chemical modification of amino acid residues, especially if a modifier can be incorporated into a substrate or an inhibitor to be further directed to the active site of the enzyme.<sup>4,11</sup> The use of site-directed mutagenesis with replacement of one or several amino acids in the polypeptide chain of the enzyme enables reliable identification of participants in the catalytic process. This methodological approach is very popular.<sup>31–36</sup> The design and progress in the development of methods for the studies of spatial structures of proteins has provided this branch of enzymology with abundant and highly reliable structural information.<sup>37–40</sup> At the same time, this information is insufficient for identification of groups constituting the active site. It is necessary to isolate a fragment directly involved in the catalytic process. The approaches to the solution of this task are discussed below.

Owing to the decoding of DNA sequences of individual genes and entire genomes, the number of proteins with established amino acid sequences exceeds 1 000 000. However, this diversity is rather apparent, since different organisms often contain similar (homologous) proteins derived from the same evolutionary progenitor. Their amino acid sequences are characterised by an extremely high degree of identity. In the case of enzymes, they possess similar catalytic sites, mechanisms of action, cofactors and inhibitors. Therefore, the bioinformatics methods are often employed to classify enzymes based on the analysis of their primary structures and to unite them into homologous protein families. It should be noted that methods of comparison (alignment of amino acid sequences and detection of the degree of their identity) are fairly well-developed and automated; therefore, this approach allows operation with large amounts of information in an automatic mode. The two main databases using this approach for classification of hydrolases are MEROPS<sup>41–50</sup> and CAZY.<sup>51–59</sup>

The database MEROPS<sup>41–50</sup> (<http://merops.sanger.ac.uk/>) comprises information about peptidases and their inhibitors. Two enzymes are united into a family, if the degree of identity of their amino acid sequences exceeds 30%. In turn, the families are united into clans, *viz.*, groups of families where protein homology cannot be established by analysis of their amino acid sequences, although there is some indirect evidence (*e.g.*, the fold of the polypeptide chains and the sequence order of the active site residues in amino acid sequences), which suggests a relationship between these proteins. The clans are united into classes according to the type of their catalytic mechanisms. For example, serine, thiol, aspartyl

and metal-dependent proteases are known; the serine proteases are divided into 10 clans which in turn are divided into 25 families that comprise altogether 6886 proteins.

The database CAZY<sup>51–59</sup> (<http://afmb.cnrs-mrs.fr/CAZY/>) contains information about glycosidases, glycosyl transferases and other enzymes catalysing the formation and cleavage of the glycosidic bond. Based on the results of analysis of identity of their amino acid sequences, all glycosidases are divided into 14 clans which unite 96 families.

An analysis of identities of amino acid sequences was also employed in the construction of the database Catalytic Site Atlas<sup>60,61</sup> (<http://www.ebi.ac.uk/thornton-srv/databases/CSA/>), although inclusion of enzymes into homologous protein families was not their main goal. The base designers have chosen about 300 most well-studied enzymes with established three-dimensional structures. The data on the amino acid residues constituting the active sites and a list of proteins with amino acid sequences with high degree of identity are given separately for each enzyme.<sup>¶</sup>

The bioinformatics methods of analysis of amino acid sequences and determination of protein functions considered above have become very popular owing to abundant original structures obtained by translation of their nucleotide sequences. However, the functional potentials of proteins are determined primarily by their three-dimensional (rather than primary) structures. Although high degree of identity of amino acid sequences underlies the similarity of spatial structures of active sites of enzymes, in the general case the converse is wrong. Thus the catalytic triad Ser-His-Asp is characteristic of both trypsin and subtilisin. These proteins possess non-homologous amino acid sequences, they differ in the order of amino acid residues within the active site and the fold of the protein globule. Mammalian trypsin and bacterial subtilisin provide examples of convergent evolution of enzymes where enzymes derived from different proteins acquire similar (in all probability, optimum) structures of catalytic sites in the course of evolution. However, a comparison of primary amino acid sequences of such proteins does not allow one to establish a similarity of their catalytic sites.

The methods for analysis of three-dimensional (3D) structures of proteins allow one to cope, in principle, with evolutionally non-related proteins; however, they are much less developed than the methods for the analysis of amino acid sequences and are still at the stage of development rather than at the wide-scale application stage. First, this is due to the complexity of the systems under study and, second, to the lower level of the original data (since proteins with established three-dimensional structures are far less numerous than proteins with established primary structures). It can be assumed that in future the methods of analysis of three-dimensional structures of proteins will play a more significant role, since the number of structures in the database PDB is steadily increasing and so is the accuracy of prediction of the 3D-structures of proteins based on their amino acid sequences. Some methods aimed at a search for functional sites on the basis of structural data have been reviewed.<sup>63</sup>

A convenient method for classification of active sites of enzymes and substrate-binding sites (ligands or cofactors) according to the three-dimensional structure of proteins has been developed.<sup>64</sup> Considering that the active sites of 70% of enzymes are localised in the largest cavity of the protein globule,<sup>65</sup> one can restrict oneself to the analysis of the amino acid sequences of the protein that form the cavity surface. Such residues can be found automatically. The search can culminate in the physicochemical 'image' of the cavity, *viz.*, spatial arrangement of charges, the groups serving as potential donors or acceptors of the hydrogen bond as well as hydrophobic and hydrophilic sites on the protein surface. The presentation of the cavity as a graph with the atoms as vertices and the distances between them as edges allows a

comparison of two proteins irrespective of their amino acid sequences as well as a search for the greatest common elements using an algorithm for the search of the largest common subgraph. This approach was used for identification of substrate-binding sites in subtilisin, trypsin and chorismate isomerase isolated from different sources with the degree of identity of the amino acid residues of < 20%, as well as NADH-binding sites in several non-related oxidoreductases.

Although this method is applicable to the study of substrate-binding sites, it does not seem to be suitable for the search for the catalytic sites themselves. For instance, it is only the serine residue in serine hydrolases with the catalytic triad Ser-His-Asp that is localised on the surface of the protein globule, while histidine and aspartic acid residues are embedded inside the protein.

The so-called method of geometrical invariants was suggested for classification of proteins according to the presence of clusters built of several amino acid residues with similar spatial distributions.<sup>66</sup> All possible combinations of several amino acid residues are sorted out for each protein; the geometrical invariants, *i.e.*, the parameters dependent on the coordinates of the appropriate atoms, but independent of translations and frame rotations are calculated. These include the distance between two atoms, the volume of a tetrahedron formed by four atoms, *etc.* For each group of residues, there is a single point in the *n*-meric space (*n* is the selected number of invariants) and a set of such points for each protein. By applying this procedure to all proteins, one can obtain several domains in the *n*-meric space where the points corresponding to different proteins are concentrated. All these proteins are characterised by a similar arrangement of amino acid residues within the protein structure. This method has made it possible to determine the active site residues for many enzymes including cysteine proteases, xylanases and  $\beta$ -lactamases. The advantage of this method is that it permits an automated search for common structural elements for different proteins and does not require preliminary elucidation of common elements of the tested proteins. Besides, it enables the detection of common elements even in the sites where their occurrence was thought to be hardly probable.

In yet another approach, which is based on expert knowledge and analysis of the published data, a desired spatial arrangement of amino acid residues or individual atoms,<sup>†</sup> which corresponds, *e.g.*, to the active site of the enzyme, is preset, and the search routine finds the corresponding proteins in the structure database.

The graph-theoretic approach based on the use of templates for the classification of proteins has been suggested.<sup>67,68</sup> Each amino acid residue is represented by a vector between two atoms depending on the type of the amino acid residue. The reciprocal spatial arrangement of two vectors is determined by the distances between their initial, final and central points. A template represents an array of the vectors and a matrix of triples of distances between them plotted as a graph; each graph vertex corresponds to an amino acid residue and each edge is a set of distances between the vectors of the residues. One graph isomorphism search algorithm is used as a template in a search for protein structure coincidence. This method has been realised in the program ASSAM, which was successfully used for a correct search of the catalytic triad Ser-His-Asp, the zinc-binding site of thermolysin (and related enzymes) and a great number of other functional sites of proteins.

The transition from the presentation of an amino acid residue as a vector (which imparts an additional degree of axial symmetry to the amino acid residue) is an obvious route to further perfection of the method. This approach was realised in the programs TESS and JESS.<sup>69–71</sup> The coordinates of the atoms from the primary database PDB of amino acid residues with established functional

¶ The search for the appropriate proteins was carried out using the BLAST method (Basic Local Alignment Search Tool).<sup>62</sup>

† The set of limitations for the types of amino acid residues or atoms and their reciprocal spatial distributions is usually referred to as a template, although the terminology used by different authors may differ.



significance were used as templates. This approach resulted in the construction of the database PROCAT<sup>70</sup> (<http://www.biochem.ucl.ac.uk/bism/PROCAT/>), which comprises the data on the active sites in protein structures.

The aforementioned methods make use of the data only on three-dimensional structures of proteins. They seemed opposed to the methods based only on the primary structures data. In actual research practice, both approaches are used to determine the functional significance of amino acid residues.

The Evolutionary Trace method<sup>72</sup> consists of the search (usually automated, employing the BLAST method) of a set of homologous proteins, their alignment and construction of a dendrogram (a tree) from the alignment data obtained. Each terminal node in the tree corresponds to a real protein and each intermediate node corresponds to a certain hypothetical protein called 'evolutionary precursor'. In the sequence of the latter, only that part of the amino acid sequence is known which is common for all the proteins of the daughter nodes. Therefore, the amino acid residues of the starting protein can be ranged from the most conserved, identical in all homologous proteins of the set, to the most variable ones, which are different in the original protein and its closest relative. The depth of the node in the dendrogram where the divergence took place is a quantitative measure of amino acid residue conservation. Having removed the residues below a certain degree of conservation, one can isolate clusters of residues which, according to the structural data, are in contact with one another. A correlation exists between the conserved clusters and the functional sites of the protein. The method allows correct determination of 70%–90% of the functional sites.

#### IV. Catalytically important groups and structure-forming amino acids in the active sites of enzymes

The answer to the question: which amino acids constitute active sites in enzymes the most often, was obtained by a comparison of amino acid sequences of proteins united in one large family.<sup>11, 73, 74</sup> The results of the alignment of sequences of large families of enzymes deposited with the database HSSP (<http://www.sander.embl-heidelberg.de/hssp/>) have been analysed.

The alignment is usually presented in the form of tables obtained by superposition of a protein sequence and a basic sequence. Visual detection of the conserved elements of a sequence is possible. Apparently, this method provides insufficient information where more than three to five proteins are to be compared. This can be automated to quantitate the conservation of amino acid positions in a sequence. The statistic criterion in the form of the Shannon entropy can serve as a quantitative measure of the conservation of each amino acid in the amino acid sequence of the protein.<sup>75–77</sup> It is noteworthy that the Shannon entropy is one of the most important functions in the theory of information. This was introduced as a measure of the degree of uncertainty which describes events characterised by a definite probability. In this case, the information can be defined as a measure of the level of uncertainty, which is corrected after the acquisition of information. Formally, the amount of information is presented as a difference between the information entropies before the experiment and upon its completion, *i.e.*, receipt of a message. The information entropy (the Shannon entropy) is the most convenient function for a comparison of related proteins differing in amino acid sequences. The alignment of sequences relative to a reference protein implies arrangement of their amino acid sequences one above the other with fixation of homologous sites, detection and elimination of the inserts. A comparison of a large panel of proteins allows calculation, with a sufficiently high degree of accuracy, of the probability of localisation of amino acids in each position of the protein sequence. This probability is defined as a relative frequency of the appearance of an amino acid of the type *i* in position *j*. The entropy function can be calculated for each position of all the 20 amino acids of the protein sequence.<sup>75</sup>

$$H_j = - \sum_i p_i^j \log_2 p_i^j$$

An important feature of this function is that it is close to zero for both the events occurring with high ( $p_i^j \rightarrow 1$ ) and low ( $p_i^j \rightarrow 0$ ) probabilities. Calculation of the Shannon entropy for a protein sequence may result in the detection of common (*i.e.*, absolutely conserved) sites for the whole large family of proteins. This is a position where the probability of appearance of the given amino acid is close to unity, whereas that in the remaining positions is close to zero. High values of the Shannon entropy are characteristic of amino acids with variable positions in the amino acid sequences, being low for amino acids with conserved positions in the amino acid sequence. At the limit, for  $p_i^j \rightarrow 1$  (absolute conservation),  $H_j \rightarrow 0$  (Fig. 1).

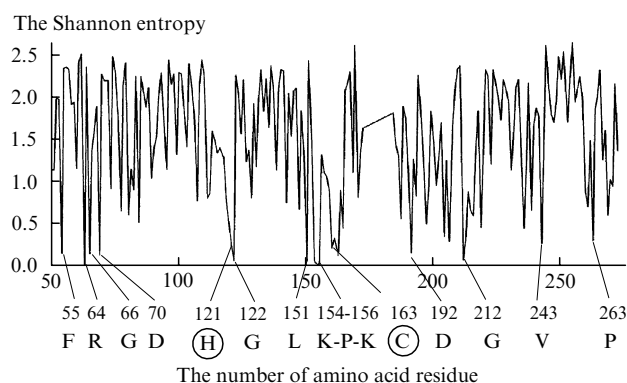


**Figure 1.** A presentation of alignment of the caspase family (PDB code 1cp3) in the form of the Shannon entropies. The amino acid residues of the active site are encircled.

The Shannon entropy criterion was used in the analysis of protein superfamilies with such basic proteins as trypsin/chymotrypsin, subtilisin, lipase, cytochrome C oxidase, pepsin/pepsinogen, enolase, lactate dehydrogenase, DNase, aminoacyl-tRNA synthase and lysozyme.<sup>73, 74</sup> This sample of enzyme families comprises 2281 proteins with the overall length of 249 252 amino acid residues.

This analysis revealed the following regularities.

1. Upon alignment of amino acid sequences in enzymes, the amino acids that form the catalytic site are always detected as conserved elements.

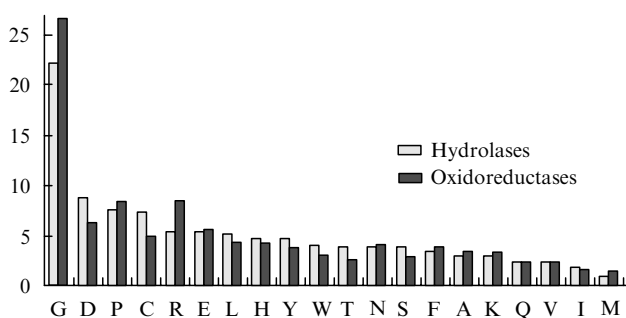
2. A comparison of amino acid sequences shows that glycine and aspartic acid are most commonly detected as absolutely conserved elements.

From our point of view, consideration of the results of the analysis of the most conserved amino acids with  $H_j = 0$  (or close to zero) is of interest. A somewhat unexpected finding was that glycine appeared to be the most common conserved amino acid. The second position was occupied by aspartic acid; in total, glycine and aspartic acid constitute approximately one third of the conserved amino acids altogether.

The rating of amino acids according to their conservation in the protein families studied has been carried out. To this end, the frequency of occurrence of each amino acid as a conserved element ( $H_j \approx 0$ ) was determined relative to the total number of conserved positions for all amino acids in the families. The conservation ratings of amino acids for two enzyme classes, *viz.*, hydrolases and oxidoreductases, are presented in Fig. 2. Despite the differences in the reactions catalysed by these enzymes, the mode of distribution of conserved amino acids virtually coincide.

It can be seen that glycine, aspartic acid, cysteine, proline, arginine and histidine in the amino acid sequences of enzymes usually manifest themselves as conserved amino acids and con-

Distribution of conserved amino acids (%)

**Figure 2.** The rating of conservation of amino acids.

stitute ~ 60% of all conserved positions. Methionine and isoleucine are never conserved.

It seems logical to divide all conserved amino acids into two groups, different in principle, namely, amino acids involved in the elementary acts of activation of substrates as acids and bases (aspartic acid, histidine, arginine) and amino acids responsible for the architectonics of the active site (glycine, cysteine, proline).

A physicochemical interpretation of the role of acids, bases and structure-forming amino acids (glycine, proline, cysteine) in enzymatic catalysis will be given below in the example of hydrolases.

## V. Classification of hydrolases according to the types of catalytic sites and catalytic mechanisms

In discussing the structures of active sites of enzymes, it is necessary to discriminate between two structural components of the active site, *viz.*, a sorption subsite responsible for the binding, fixation and orientation of substrates (its properties determine the specificity of the enzyme),<sup>1–3</sup> and a catalytic subsite responsible for general acid-base catalysed chemical transformations of substrates.<sup>4–6</sup>

The structures and functions of hydrolases are extremely diverse. In addition to traditional involvement in the cleavage of biopolymers (proteins, nucleic acids, polysaccharides) into constituent monomers, hydrolases play a central role in some vital processes, such as regulation of fibrinolysis and thrombolysis,<sup>78–80</sup> apoptosis,<sup>81–83</sup> signal transmission in protein phosphorylation–dephosphorylation systems,<sup>84–88</sup> restriction and modification of DNA,<sup>89,90</sup> resistance against antibiotics,<sup>91,92</sup> regulation of the level of proteins,<sup>93–95</sup> nerve pulse transmission,<sup>96</sup> carcinogenesis,<sup>97</sup> *etc.* Within the framework of a traditional enzyme classification approved by the International Union of Biochemistry and Molecular Biology, hydrolases are classified according to the type of the reaction catalysed by them (hydrolysis) and enzyme specificity (the substrate structure). At present, the imperfection of this nomenclature is becoming more and more evident. On the one hand, the majority of enzymes do not possess absolute specificity and, which is even more important, manifest different types of activity. On the other hand, many enzymes with the same specificity and utilising the same substrate differ essentially in their primary structures, compositions of the active sites and fold of the polypeptide chain.

The analysis of the published data devoted to the mechanisms of action of different hydrolases suggests that despite the great diversity of enzymes, the number of catalytic sites that are different in principle is rather small.<sup>73, 74, 98</sup>

Hydrolases differ in the nature of the catalytic groups activating the water molecule in the course of the catalytic cycle. In principle, this information is imprinted in the spatial structure of a protein. The difficulty consists of an unambiguous identification of the catalytic group and the water molecule underwent activa-

tion. An active site may contain several water molecules among which only one is activated in the catalysis.

A comparative analysis of the compositions of active sites of hydrolases and mechanisms of activation of water revealed four main types of catalytic sites that are directly involved in the activation of water, *viz.*:

(1) hydrolases containing aspartic or glutamic acid in their active sites (pepsin and retroviral pepsins, glycosidases, dehalogenases and epoxide hydrolases);

(2) hydrolases containing histidine in their active sites (ribonucleases including pancreatic ribonuclease and barnase, acid phosphatases, hydrolases containing the Ser-His-Asp triad and its isomorphic substitutions, thiol hydrolases);

(3) zinc-dependent hydrolases containing one (carboxypeptidase A) or two (alkaline phosphatase, organophosphate hydrolase) zinc ion(s) used for the activation of water and the substrate;

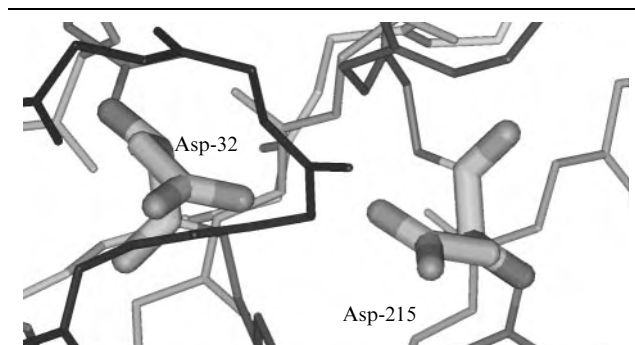
(4) magnesium-dependent hydrolases (enzymes of the inorganic pyrophosphatase type, aryl sulfatase).

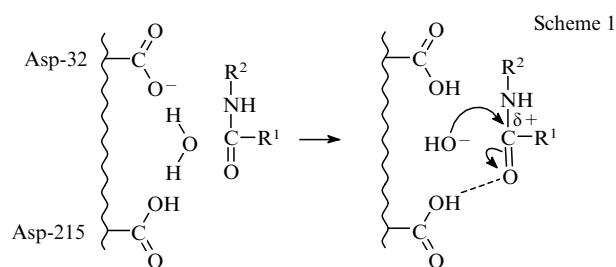
Taking into account the great abundance and significance of hydrolases containing serine, cysteine or threonine residues and a proton-transfer chain responsible for the activation of a hydroxy or a thiol group, it seemed expedient to group them in an individual subtype [the nucleophile–imidazole–aspartic (glutamic) acid subtype]. These enzymes form stable intermediates identified as acyl-enzymes in the course of catalysis.

The analysis of mechanisms of catalytic reactions shows that aspartic acid and histidine, in principle, play a crucial role in the majority of catalytic sites. The mechanisms of hydrolase catalysis can be illustrated by schemes that, though being rather approximate and not reflecting all the details of the reaction mechanisms, include their main stages, *viz.*, activation of water and substrate hydrolysis.

### 1. Hydrolases containing aspartic or glutamic acid in their active sites

Hydrolases containing aspartic or glutamic acid in their active sites cleave ester, amide and glycosidic bonds. The catalytic sites of these enzymes contain two or more carboxy groups.<sup>4,6</sup> The non-dissociated carboxy group acts as an electrophile and takes part in the activation of the substrate as a generalised acid, while the deprotonated group acts as a nucleophile in the activation of the water molecule.<sup>4,5</sup> Enzymes of this group usually manifest maximum activity at relatively low values of pH. Pepsin (protease) and lysozyme (glycosidase) are typical representatives of this group.<sup>99,100</sup> The essential role of the carboxy groups of Asp-32 and Asp-215 in pepsin consists of formation of a hydrogen bond with each other and with the water molecule attacking the substrate (the spatial arrangement of the Asp-32 and Asp-215 residues is shown in Fig. 3). At optimum pH values, the carboxy group of Asp-32 becomes ionised, whereas the carboxy group of Asp-215 exists in the non-dissociated form. The processes occurring in the active site are shown in Scheme 1.<sup>99–103</sup>

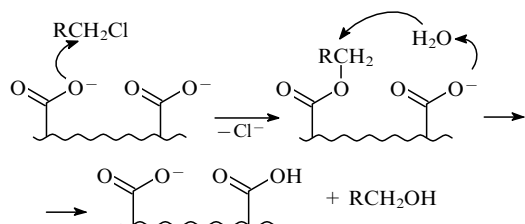
**Figure 3.** The active site of pepsin (PDB code 1flh). The residues of the active site are highlighted.



Human immunodeficiency virus protease (retroviral pepsin) has the same mechanism of action, but its two aspartic acid residues (Asp-25) are localised in two identical subunits. It is assumed that animal pepsin was formed from a protein precursor similar to retroviral pepsin by duplication and concatenation of the corresponding genes. In the course of evolution, the local environments of two aspartic acid residues of pepsin changed, which resulted in the enhancement of its catalytic properties.<sup>104</sup>

The active sites of glycosidases also contain two aspartic (or glutamic) acid residues localised on opposite sides of the bond to be hydrolysed. One of these carboxy groups, *viz.*, the non-ionised group, activates the substrate by a proton-transfer mechanism thus decreasing the electron density on the carbon atom of the bond to be hydrolysed. The second carboxy group activates the water molecule (the mechanism with inversion of configuration of the carbon atom) or attacks the substrate directly resulting in the formation of an intermediate which is further decomposed by the water molecule (the mechanism with retention of configuration).<sup>105, 106</sup> This mechanism operates in the case of lysozyme<sup>107–109</sup> and chitinases.<sup>110, 111</sup>

The three-dimensional structures of dehalogenases were established relatively recently.<sup>112, 113</sup> The interest in this group of enzymes is explained by the possibility of using them for the decomposition of halogen-containing organic environmental pollutants. The active sites of dehalogenases also contain two carboxy groups. One of them (a nucleophile) attacks the substrate with the elimination of the halide ion to give a covalent intermediate. The second carboxy group activates the water molecule involved in the dealkylation of the enzyme.



## 2. Hydrolases containing histidine residues in their active sites

Histidine residues of hydrolases are either involved in the activation of water or react with substrates directly.

According to classical concepts, the mechanism of catalytic cleavage of phosphodiester bonds in ribonucleic acids by pancreatic ribonuclease A (see Ref. 114) is provided by a concerted action of the imidazole groups of two histidine residues (Fig. 4). The imidazole group of His-12 activates the 2-hydroxy group of ribose by a proton transfer in the step involving the formation of a 2,3-cyclophosphate intermediate, whereas the imidazole group of His-119 activates the water molecule that hydrolyses the cyclophosphate.

The active site of barnase contains a glutamic acid residue (Glu-73) instead of His-12. A detailed mechanism of catalysis of barnase has been described.<sup>115, 116</sup>

In acid phosphatases,<sup>117</sup> histidine plays the role of a nucleophile that attacks the phosphorylated substrate. This results in the

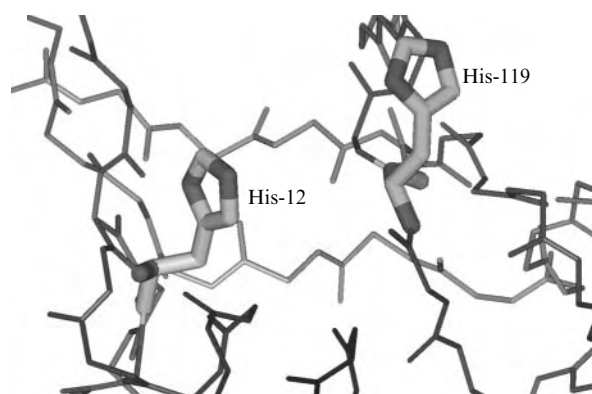


Figure 4. The active site of pancreatic ribonuclease (PDB code 1a5q).

formation of phosphohistidine and the liberation of the non-substituted substrate (in the next step, the phosphoenzyme is hydrolysed with water).

It is of note that there is no hydrolase known at present for which the catalytic mechanism includes the formation of substituted histidine with the nitrogen of histidine and the carbon atom of the substrate. Apparently, this can be attributed to the fact that such a bond is relatively stable, so its cleavage would be a limiting step in the catalytic cycle.

## 3. Hydrolases containing a nucleophilic serine, cysteine or threonine residue

Serine proteases (chymotrypsin and trypsin) and cysteine protease (papain) are typical representatives of this group of enzymes. Their catalytic mechanisms include acylation of the hydroxy or thiol group of the enzyme with the formation of an intermediate (acylenzyme) and its subsequent hydrolysis.<sup>4, 118, 119</sup> As the hydroxy group is a weak nucleophile, all the enzymes of this type contain amino acid residues essential for its activation and deprotonation (the proton-transfer chain). The same residues activate the water molecule in the enzyme deacylation step.

Hydrolases containing the catalytic triad Ser-His-Asp seem to be especially well studied. They include proteases (trypsin, chymotrypsin, elastase, subtilisin, carboxypeptidase Y and many others),<sup>4, 120–123</sup> lipase,<sup>124</sup> and acetylcholinesterase<sup>125</sup> (the latter contains a glutamic acid residue instead of aspartic acid). The active site of chymotrypsin contains Ser-195, His-57 and Asp-102 residues (Fig. 5). The catalytic mechanism of chymotrypsin is presented in Scheme 2.

Numerous isomorphous substitutions of the amino acids of the triad are known; this problem has been discussed in detail.<sup>126</sup> Thus thiol hydrolases contain a cysteine residue instead of serine. Since the thiol group is a stronger nucleophile than the hydroxy group, a shorter (in comparison with serine hydrolases) proton-transfer chain can be used. For example, many thiol proteases homologous

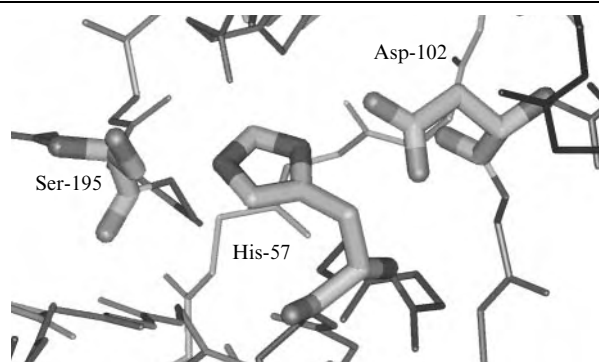


Figure 5. The active site of trypsin (PDB code 1fmg).

Scheme 2

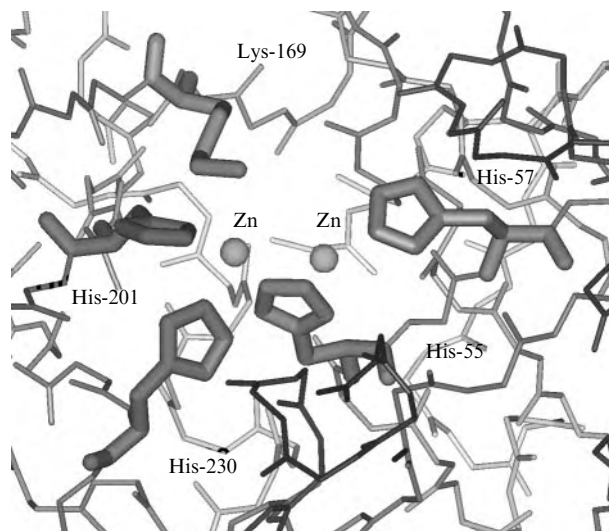
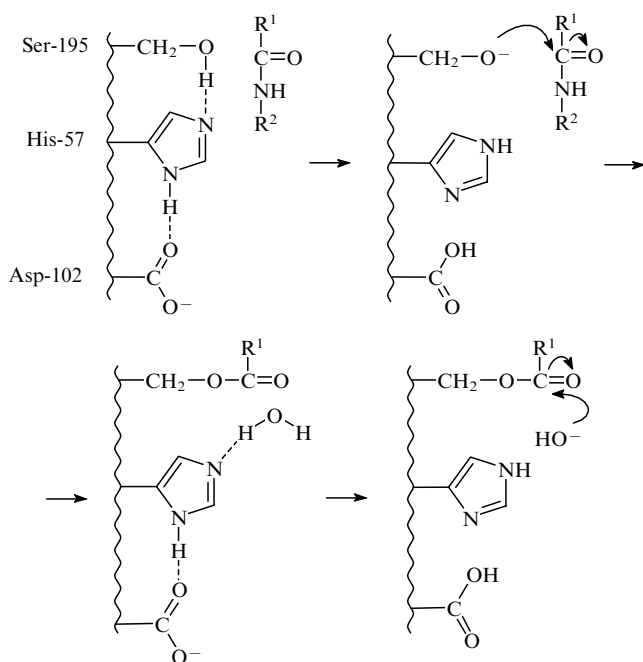


**Figure 6.** The active site of organophosphate hydrolase (PDB code 1dpm).

to trypsin proteases contain asparagine able to form a hydrogen bond with histidine instead of aspartic acid, which polarises the imidazole ring of histidine. Some enzymes which do not involve histidine for the activation of the thiol group are known.<sup>127</sup>

Enzymes in which the amino group acts as a proton acceptor<sup>128</sup> in the activation of the hydroxy group constitute a separate group of enzymes. An example is a non-charged amino group in the side chain of lysine ( $\beta$ -lactamase<sup>129</sup> and asparaginase<sup>130</sup>). Serine, threonine or cysteine are N-terminal amino acids in N-terminal hydrolases, which include proteasome<sup>131</sup> and penicillinase components;<sup>132</sup> the free amino group in the main protein chain activates the hydroxy or the thiol group of the same amino acid.

#### 4. Zinc(nickel, cobalt)-dependent hydrolases

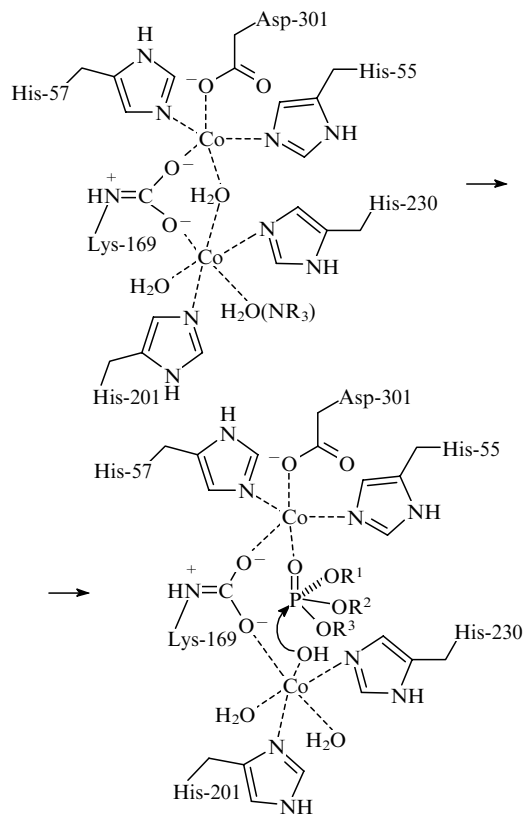
This type of hydrolase contains one or several zinc ions (which can be replaced by cobalt or nickel without any loss of activity). Metal ions localised in the active sites of enzymes fulfil two main functions,<sup>4, 133, 134</sup> viz., that of an electrophilic agent activating the reaction centre of the substrate that is being attacked, and that of an electrophilic activator of water as a source of hydroxyl ions.

Enzymes of the carboxypeptidase A type, thermolysin or botulinic toxin,<sup>135</sup> each contains one zinc ion in their active sites; the role of ligands is played by aspartic or glutamic acid, histidine or cysteine residues. The metal ion complexes in the active sites of these enzymes act as electrophilic reagents which activate the reaction centres of the substrates. The activation of the attacking water molecule is induced by the deprotonated carboxy group of glutamic acid that is not involved in the coordination sphere of the zinc ion.

Enzymes of the type of alkaline phosphatase,<sup>136–138</sup> urease,<sup>139</sup> metal-dependent  $\beta$ -lactamase<sup>92</sup> or organophosphate hydrolase<sup>140, 141</sup> contain two zinc ions in their active sites; these ions form structurally similar complexes with the protein (Fig. 6). Aspartic and glutamic acid residues as well as histidine (or cysteine) and N-carboxyllysine residues act as metal-ion ligands. As a rule, one of the zinc ions activates the substrate by reducing electron density on the atoms being attacked, whereas the second zinc ion activates the water molecule or, in the case of alkaline phosphatase, the hydroxy group of serine. For organophosphate hydrolase,<sup>140–144</sup> the enzyme catalysing hydrolysis of organo-

phosphorous pesticides and war gases such as Sarin, Soman or Vx, the catalytic mechanism<sup>145</sup> can be described by Scheme 3.

Scheme 3



#### 5. Magnesium(manganese)-dependent hydrolases

This type of hydrolase contains magnesium or doubly charged manganese ions in the catalytic site.<sup>146, 147</sup> As in the case of zinc-dependent enzymes, the metal complexes in the active sites of hydrolases behave as strong electrophilic reagents which activate the substrates (or the water molecule) by reducing electron density on the reaction centre. Such behaviour of metal ions became especially apparent in the analysis of the structure and catalytic mechanism of inorganic pyrophosphatase.<sup>148–153</sup> The substrate is fixed in the active site of the enzyme due to ionic interactions with

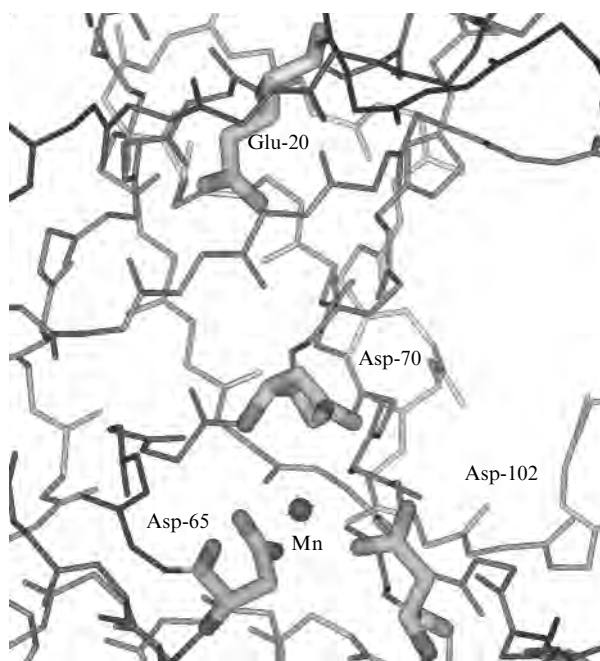
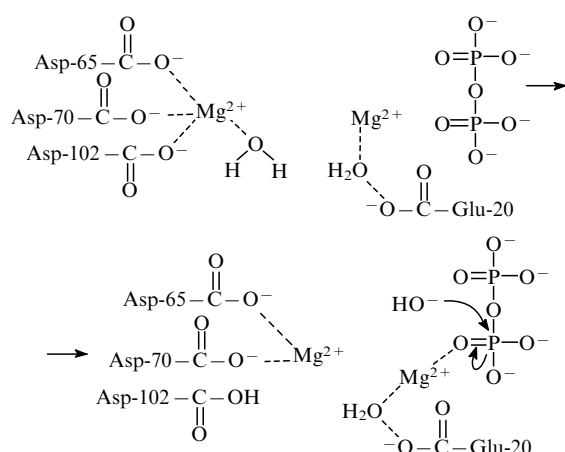


**Figure 7.** The active site of inorganic pyrophosphatase (PDB code 1ipw).

positively charged groups of the protein, Lys-103, Arg-78 or Lys-56. The main catalytic events involve two metal ions ( $Mg^{2+}$  or  $Mn^{2+}$ ).<sup>154</sup> The carboxy groups of the residues Asp-65, Asp-70 and Asp-102 and three water molecules play the role of ligands for the ions in the high-affinity site where the formation of the  $Mg^{2+}$  (or  $Mn^{2+}$ ) complex takes place. The low-affinity site is formed by the metal ion, water molecules and the carboxy group of the Glu-20 residue (Fig. 7). It can be assumed that the high-affinity site functions as the electrophilic activator of water (a generator of hydroxyl ions), while the low-affinity site plays the role of an electrophilic activator of the substrate.



These examples illustrate the role of aspartic acid and histidine in the mechanism of action of enzymes. Obviously, concerted action of nucleophilic and electrophilic components of the active site is the major principle in the functioning of active sites of enzymes.

It seems interesting to follow the transition from enzymes that catalyse hydrolysis of particular bonds to enzymes that catalyse the formation of these bonds. It is known that the active sites of exonucleases, which catalyse hydrolysis of DNA,<sup>155–159</sup> represent complexes of magnesium ions with the carboxy groups of aspartic and glutamic acids and resemble the active site of pyrophosphatase. The active site of DNA polymerase, which catalyses synthesis of DNA, is largely homologous to the active site of this nucle-

ase.<sup>155–159</sup> The same functional groups of DNA polymerase activate the reaction centre and the nucleophile; however, the hydroxy group of the sugar (but not water) becomes activated owing to the abstraction of a proton. The nucleophilic attack on the reaction centre of the phosphate group ensures the growth of the DNA chain.

It should be noted that the structural elements constituting the active sites of hydrolases were also detected in the active sites of other classes of enzymes. Thus the proton-transfer chain, which includes the pair 'imidazole–carboxy group of aspartic acid' is often identified in the active sites of oxidoreductases. In peroxidases and in the protein environment of heme, the pair 'imidazole–carboxy group' plays the role of a generalised nucleophilic reagent which activates the iron ion of heme.<sup>160–162</sup> The same structural element of the proton-transfer system, *viz.*, the imidazole complex with the carboxy group, is identified in the active sites of dehydrogenases.<sup>163–165</sup>

## VI. Glycosyl hydrolases, cellulases

The diversity of structures and fold of the polypeptide chain with simultaneous preservation of the main mechanism of water activation and the structure of the catalytic site can be illustrated in the examples of 1,4- $\beta$ -glycosyl hydrolases and cellulases. Two carboxy groups of these enzymes, which induce concerted cleavage of 1,4- $\beta$ -glycosidic bonds, are involved in the catalytic process.<sup>106, 166</sup> Xylanases, chitinases and lysozyme act in a similar way.<sup>107–111</sup> Cellulases are multidomain proteins, which contain one catalytic and one cellulose-binding domain. These enzymes are represented by a vast array of structures.<sup>167</sup> According to the fold of their polypeptide chains, they are classified into 15 clans, each containing > 90 structural families.<sup>167–173</sup> It is interesting to note that in contrast to 1,4- $\beta$ -glycosidases,  $\alpha$ -glycosidases are represented by only three families.<sup>167, 174</sup> The immense diversity of structural elements of catalytic domains of glycosyl hydrolases, of cellulases, in particular, is determined by the peculiarities of their primary sequences and the folding of their polypeptide chains. The database CAZY offers the most complete structural classification of glycosyl hydrolases. However, the structures of the catalytic sites of the whole array of proteins differing in their primary sequences and secondary structures are rather monotonous. The activation of the water molecule and the hydrolytic catalytic cycle are supported by the concerted action of two carboxy groups.

Enzymes containing two carboxy groups in their active sites, which represent concertedly acting electrophilic and nucleophilic agents, are especially widely occurring in nature. The results of alignment and calculation of the Shannon entropy for pepsin are shown in Fig. 8. As can be seen, Asp-32 and Asp-215 represent

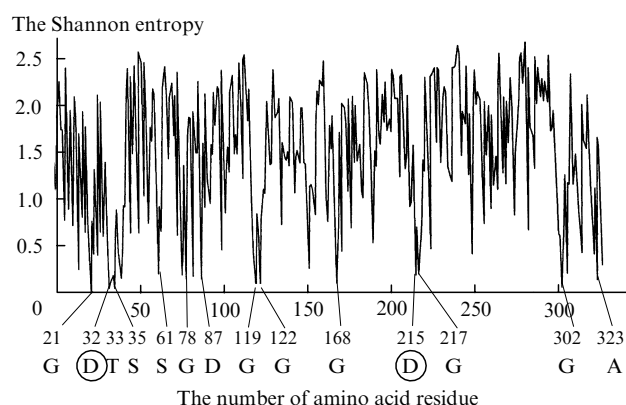


**Figure 8.** A presentation of alignment of the pepsin family (HSSP code 1ps0) in the form of the Shannon entropy. The amino acid residues in the active site are encircled.

conserved amino acids. The activities of other proteases as well as peptidases, lysozymes, chitinases and many other hydrolases (the set of structures is virtually unlimited) are also mediated by the two carboxy groups. All these proteins are built in such a way as to favour the spatial approach and concerted action of two carboxy groups of the catalytic site. These data clearly demonstrate the structural paradox of enzymatic catalysis, namely: the immense diversity of protein structures provides the formation and assembly of a limited number of unique catalytic sites.<sup>91, 175, 176</sup>

## VII. Serine hydrolases. Automatic search for a catalytic triad

We have carried out an automatic search for definite structures in the catalytic site of hydrolases based on an analysis of primary sequences within the framework of 'alignment' studies and calculations of the Shannon entropies using a template of three-dimensional structures of catalytically important residues. In the four classical types of active site structures of hydrolases, identification of catalytic groups of Zn(Co)- and Mg(Mn)-dependent enzymes is the least difficult. The localisation of the metal ion and its environment allows identification, with a high degree of reliability, of the components of the catalytic process. The identification of catalytic sites of hydrolases containing carboxy groups in the active sites was especially difficult because of the limited number of enzymes containing such catalytic sites and the lack of additional criteria characteristic of active sites and differentiating it from other potential structures, the use of an automatic procedure has led to the detection of a large number of false examples. Probably, this task would be solved more successfully in future upon introduction of additional structural limitations. The most adequate results were obtained in the analysis of protein structures containing the catalytic triad serine–histidine–carboxy group.

Serine hydrolases containing the catalytic triad Ser-His-Asp constitute the most well-studied representative group of hydrolases. This type of a catalytic site was first discovered in bovine pancreatic  $\alpha$ -chymotrypsin (for a review see Ref. 177). Later, an identical catalytic site was found in bacterial subtilisin which is not homologous to chymotrypsin. The same triad was also found in lipases, while a similar triad (Ser-His-Glu) was detected in acetylcholinesterases. In more recent studies, new families of hydrolases (brain cortex esterases, virus envelope proteins, *etc.*) non-homologous to the known enzymes and containing the same residues in the catalytic site with the same spatial arrangement were established.<sup>126</sup> Various physiologically active substances, *e.g.*, cocaine<sup>178</sup> or the platelet activation factor,<sup>179</sup> can serve as the substrates.

Serine hydrolases form covalent intermediates with these substrates; in their active sites, the hydroxy group of the serine residue is acylated by the acidic fragment of the substrate (the acyl-enzyme-type intermediate). In the active sites of all enzymes of this type, the spatial localisation of the triad Ser-His-Asp is similar despite the difference in the fold of the polypeptide chain.

The catalytically important groups were identified using the method previously developed for estimating the conservation of residues deposited with the database HSSP, which is based on pairwise alignment and the Shannon entropies and employs the data on the coordinates of individual atoms used for data retrieval in the structural bases of these proteins.

The data on the arrangement of residues in chymotrypsin and subtilisin (for typical arrangement of the residues see Fig. 9) were used for designing a template for the catalytic triad (the constraints on type of the appropriate amino acid residues are listed in Table 1); this was followed by a search on the set of non-homologous hydrolases from the data bank PDB. Over 100 structures with a required arrangement of catalytically important functional groups containing unique primary sequences were found.

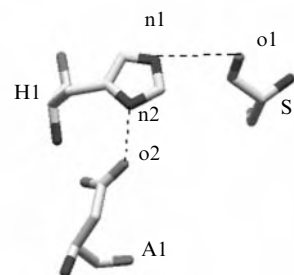


**Figure 9.** A typical distribution of catalytic triad residues. The names of amino acid residues are capitalised; the names of individual atoms are given in lower case letters. The dotted lines indicate the distances between the atoms on which certain restrictions were imposed in the search (for explanations see text).

**Table 1.** The criteria of a search for the triads Ser-His-Asp through the protein structures.

| Type of limitation                                  | Parameter <sup>a</sup>                                               | Allowable values, amino acids, atoms                                                                                                                                     |
|-----------------------------------------------------|----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Conservation of the amino acid residue              | value of the Shannon entropy                                         | < 0.9                                                                                                                                                                    |
| Limitation for the type of the amino acid residue   | residue S1<br>residue H1<br>residue A1                               | Ser<br>His<br>Asp or Glu                                                                                                                                                 |
| Limitation for the type of the atom                 | atom o1<br>atom n1<br>atom n2<br>atom o2                             | atom OG <sup>b</sup> of residue S1<br>atom NE2 <sup>b</sup> of residue H1<br>atom ND1 <sup>b</sup> of residue H1<br>atom OD1, OD2, OE1 or OE2 <sup>b</sup> of residue A1 |
| Limitation for the distance between atoms           | distance between atoms o1 and n1<br>distance between atoms n2 and o2 | $\leq 4 \text{ \AA}$<br>$\leq 3.4 \text{ \AA}$                                                                                                                           |
| Limitation for allowable angles between three atoms | angle between atoms o1, n1, n2<br>angle between atoms n1, n2, o2     | $100^\circ - 180^\circ$<br>$125^\circ - 180^\circ$                                                                                                                       |

<sup>a</sup> The designations of the atoms and amino acid residues coincide with those used in Fig. 9. <sup>b</sup> The names of the atoms correspond to the nomenclature of the Protein Data Bank.

The next step included the use of the database SCOP, where the proteins are systematised according to the fold of the polypeptide chain (see above). The data on the folding of the catalytic domain for each protein were retrieved from the database SCOP. The two upper levels of the hierarchy obtained are shown in Fig. 10. The most characteristic enzymes of each group are listed in Table 2. It was found that all serine hydrolases containing the triad Ser-His-Asp(Glu) are made up exclusively of  $\beta$ -sheets (*e.g.*, chymotrypsin), or irregularly alternating  $\alpha$ -helices and  $\beta$ -sheets (*e.g.*, subtilisin). None of the hydrolases of this type, known so far, are built up exclusively of  $\alpha$ -helices. Considering that primary sequences differ in the types of spatial folding of the peptide chain, all hydrolases can be divided into families according to this particular criterion. By choosing different levels of folding, hydrolases can be divided into families with different levels of similarity. From Fig. 10 it follows that all Ser-His-Asp-containing hydrolases form two clans; it is noteworthy that the clan of proteins built up of  $\beta$ -sheets comprises only one family, while the clan of  $\alpha$ ,  $\beta$ -proteins includes five different families. These families differ not only in the type of chain folding, but also in the order of

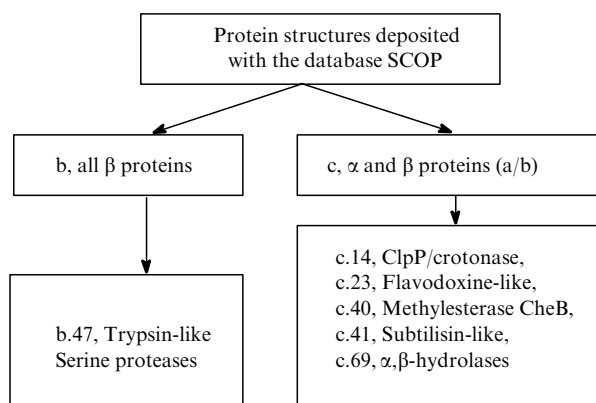


**Figure 10.** The classification of protein structures deposited with the database SCOP.

**Table 2.** The order of arrangement of amino acid residues in a catalytic centre and typical representatives of the serine hydrolase family containing the catalytic triad Ser-His-Asp, and classified according to the fold of the peptide chain.

| Type of folding of the polypeptide chain | Triads <sup>a</sup> | Typical representatives of the given class                                                                                                                                                 |
|------------------------------------------|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| b.47, Trypsin-like                       | His-Asp-Ser         | α-tryptase, viral proteases, collagenase, a complement component plasminogen, mast cell protease, prothrombins, strepto-grisin, trypsin, blood coagulation factors, chymotrypsin, elastase |
| c.14, ClpP/crotonase                     | Ser-His-Asp         | ATP-dependent Clp-protease                                                                                                                                                                 |
| c.23, Flavodoxin-like                    | Ser-Asp-His         | acyl-CoA-thioesterase, platelet activation factor methyl glutamate hydrolase                                                                                                               |
| c.40 Methylesterase CheB                 | Ser-His-Asp         |                                                                                                                                                                                            |
| c.41, Subtilisin-like                    | Asp-His-Ser         | kexin, subtilisin, furin                                                                                                                                                                   |
| c.69, α,β-Hydrolases                     | Ser-Asp(Glu)-His    | acetylcholinesterase, lipase, cocaine esterase                                                                                                                                             |

<sup>a</sup> The order of the distribution of the catalytic site residues in the primary protein sequence.

distribution of active site residues in the primary sequence (see Table 2).

It is of note that these results were obtained as a result of an automatic search for proteins in the structural database PDB and were confirmed by independent literature data. Thus, the approach based on the use of automatic bioinformatics methods and databases in the information selection step permits the processing of the tremendous bulk of accessible information.

### VIII. Mechanism of activation of substrates by active sites of hydrolases

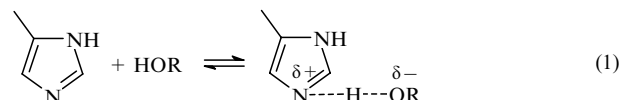
Acids and bases of the active sites play a crucial role in enzymatic catalysis by activating the substrates. Aspartic acid and histidine are most often involved in the activation of molecules in the enzymatic catalytic cycles in comparison with other amino acids. Presumably, the catalytic function of aspartic acid and histidine in

the active sites of enzymes is determined by their properties as an acid and a base.<sup>4, 5, 11</sup>

In the non-dissociated form, the carboxy group of aspartic acid represents a proton donor, which manifests pronounced electrophilic properties, whereas in the deprotonated form it plays the role of a proton acceptor (a nucleophilic agent), *viz.*, an electron density donor for the corresponding reaction centre. The imidazole group of histidine is a pronounced nucleophilic reagent able to donate unshared electron pairs of nitrogen atoms.

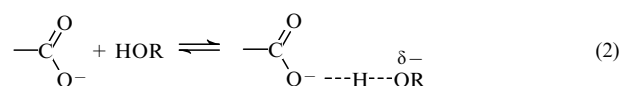
Several schemes of substrate activation by histidine and aspartic acid residues represent the main reactions occurring in the catalytic site.

1. Nucleophilic activation of the substrate by the imidazole group.

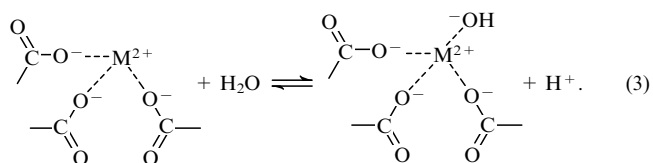


In this case, a negative charge is generated in the reaction centre.

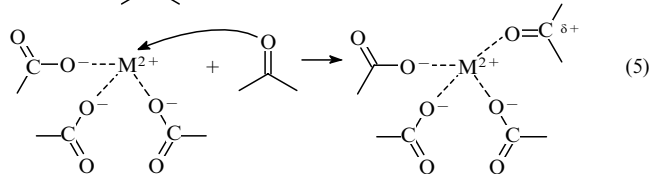
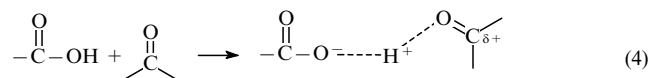
2. Nucleophilic activation of the substrate by the carboxy group of aspartic acid.



3. Electrophilic activation of water. Metal ions ( $\text{Zn}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Mn}^{2+}$ ) present in the active sites of enzymes as complexes with the carboxy groups of aspartic or glutamic acid can take part in the catalytic cycle as both acids and bases. Metal ions can replace the proton in the molecule of water thus inducing a highly reactive and mobile hydroxyl ion.

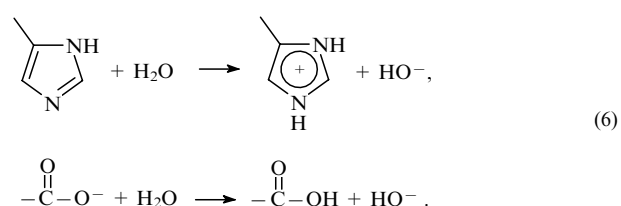


4. Electrophilic activation of the reaction centre. The electrophilic activation of the reaction centre of the substrate (*e.g.*, the carbonyl group) can be induced by both the carboxy group and the metal ion.



These reactions reduce the electron density on the reaction centre.

For hydrolytic reactions, the water activation steps in the nucleophilic catalysis can be presented as follows:





The reactivity of the water molecule increases  $10^7$ -fold upon its conversion into hydroxyl ions.<sup>5</sup> Assuming that the electrophilic activation of the reaction centre, which proceeds according to the mechanisms (4) and (5), increases its reactivity  $10^6$ – $10^7$ -fold, the high efficiency of the enzymatic catalysis and its ability to increase the reaction rate  $10^{13}$ – $10^{14}$ -fold can be explained in the first approximation. The hypothesis that acids and bases act concertedly in the catalysis was put forward on the basis of an analysis of some independent studies.<sup>5, 180, 181</sup>

The degree of charge transfer in various activation processes occurring in accordance with Schemes (1)–(6) in the transition states of enzymatic reactions is still questionable.<sup>182</sup> It is obvious, however, that the activation of well-oriented fixed (relative to one another) molecules takes place in the reaction centres. Of crucial importance is the fact that acids and bases within the catalytic site form a system of hydrogen bonds with one another, which opens up unique opportunities for the proton transfer. In systems containing hydrogen bonds, acids and bases react much faster than in solution. The interactions of hydroxyl ions with protons in a system of water molecules structured by hydrogen bonds in ice crystals (studied by Eigen<sup>183</sup>) provides an illustrative example. It was found that the reaction rates of the hydroxyl ion with hydrogen ion exceed those of diffusion-controlled processes by 3–4 orders of magnitude. As a matter of fact, the proton transfer and charge neutralisation are complete within a single vibration with a frequency of  $10^{14} \text{ s}^{-1}$ . The precise orientation of reactants and catalytic site components is a salient feature of enzymatic catalysis.<sup>184</sup>

Identification of acids and bases (electrophilic and nucleophilic reagents) within the catalytic site is the primary goal in the elucidation the mechanisms involved in the functioning of catalytic sites of enzymes. The activation mechanisms presented in Schemes (1)–(6) provide an explanation for the high efficiencies of the majority of presently known enzymatic reactions. We described an algorithm for identification of the active groups of the catalytic site. The knowledge of amino acid sequences of the protein allows determination of a group of proteins (enzymes) homologous to the given protein using bioinformatics methods. The alignment procedure and calculation of the Shannon entropies permits one to determine the positions of conserved amino acids. The latter represent, with a high degree of probability, catalytically important residues, which ensure substrate activation and, correspondingly, determine the mechanism of catalytic action.

## IX. Glycine, cysteine and proline as structure-forming amino acids

A comparison of amino acid sequences in homologous families showed that conserved glycine, cysteine and proline residues are essential elements in the active sites of enzymes. The role of glycine in the formation and functioning of active sites is not so apparent as the role of aspartic acid. Evidently, conserved glycine residues do not play any pronounced role in the activation reactions in the catalytic cycle. Nevertheless, this amino acid is a very important structural element of the protein<sup>73, 74, 185–190</sup> as can be evidenced from the results of its site-specific substitution for any other amino acid. As a rule, such a substitution results in a complete loss or a significant decrease of the enzyme activity.<sup>188</sup>

Studies of the substrate specificity of the functional domain of halogenocarboxylic acid dehydrogenases<sup>191</sup> revealed that mutations in the conserved Gly residue localised between the amino acid residues of the catalytic site to Pro, Val or Ala reduce dramatically the catalytic activity. Structural studies of mutants have demonstrated substantial conformational changes in the side chains of the residues forming the catalytic site. It was concluded that the presence of Gly is critical for conferring flexibility on the polypeptide chain in its folding in the vicinity of the active site. The

role of conserved Gly residues in the functioning of gramicidin S synthase has been studied.<sup>192</sup> It was shown that single mutations in three conserved Gly residues to Glu or Asp result in the loss of the valine-adenylate activity of this enzyme.

Apparently, conserved glycine residues are important in principle for the following reasons. First, glycine, being a unique amino acid with the smallest energy of rotation around the C–N and C–C bonds of the polypeptide chain plays the role of a node which determines the direction of the folding of the polypeptide chain in the assembly of the protein globule. Thus, the presence of conserved glycine residues accounts for the structural paradox of enzymatic catalysis, *viz.*, the ‘assembly’ of identical active sites from absolutely different polypeptide chains. The presence of conserved glycine residues and stabilisation factors in the ‘assembled’ structures, *e.g.*, disulfide bonds, are a common feature of these chains.

The substantial effect of conserved glycine residues on structure formation of the active sites of enzymes was established in computer studies.<sup>74</sup> Computer simulation was used to study the changes in the conformations of amino acid residues in the active sites of different types of hydrolases. Two series of calculations were carried out for each representative of the hydrolase family. In the first series, all conserved Gly were replaced by Ala and the corresponding conformational changes in the polypeptide chain in the vicinity of the active site were determined. Similar calculations were performed in the second series except that the non-conserved Gly residues were replaced by Ala. The root-mean-square deviation of the coordinates of the atoms in active site residues (calculated per one substituted amino acid residue) in the structure calculated after the substitutions from the coordinates in the active site of the native enzyme following superposition of these structures was used as a measure of distortion of the geometry of the active sites of these enzymes. It was found that the substitution of Ala for conserved Gly for all types of hydrolase under study caused more significant distortions in the geometry of the active sites of enzymes than the substitution for a greater number of non-conserved Gly. This suggests enhanced ‘sensitivity’ of the geometry of the active sites of enzymes to the presence of Gly residues in conserved positions.

Second, conserved glycine residues can play the role of conformational ‘hinges’ which impart conformational mobility to the catalytic groups. Supporting evidence can be derived from the fact that very often the conserved glycine residues are found in the vicinity of catalytically active groups. For example, the conserved motifs for hydrolases belonging to different families are as follows: Asp-215-X-Gly-217 (pepsin); Asp-170-X-X-Gly-173 (thermolysin); Asp-32-X-Gly-34, His-63-Gly-64, Gly-219-X-Ser-221 (subtilisin); Gly-173-X-Ser-177 (trypsin); His-76-Gly-77, Ser-153-X-Gly-155, Gly-175-X-Asp-177, Gly-X-Ser-X-Gly (lipases).<sup>193</sup> The residues Asp, Ser and His of these enzymes constitute the active sites.

Enzyme-catalysed transformation of the starting substrate into final products is accompanied by the formation of many intermediates with structures different from that of the starting substrate. Glycine residues of the active site can play the role of ‘relaxing’ elements by tuning the conformation of the active site for the subsequent elementary act.

A prominent role in the formation of the active site architecture is played by cysteine and proline residues (the fourth and third positions in the rating list of conserved amino acids). Proline is known to be a unique amino acid responsible for the unfolding of the polypeptide chain.

In all probability, the role of cysteine residues consists in the ‘fixing’ of the required configuration of the active site built up of different, often remote fragments of the polypeptide chain, by forming a chemical bond in the form of a disulfide bridge. For many enzymes, this process completes the formation of the active site architecture.

## X. The rates of conformational changes and proton transfer as the limiting steps

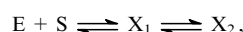
The numeric values of the rate constants ( $k_{\text{cat}}$ ) of the limiting and known elementary steps of catalytic processes involving enzymes are worth analysing and comparing. To date, much is known on  $V_{\text{max}}$ ,  $K_{\text{m}}$  (the Michaelis constant) and  $k_{\text{cat}}$  values.

Figure 11 shows the distribution density curves of different enzymes according to their  $k_{\text{cat}}$ ,  $K_{\text{m}}$  and  $k_{\text{cat}}/K_{\text{m}}$  values and the rate constants for the elementary steps ( $k_1$ ,  $k_{-1}$  and  $k_{\text{conf}}$ ) (see Ref. 11). The shapes of these curves are characteristic of normal logarithmic distribution.

The  $k_{\text{cat}}$  values lie in the range of  $10^1$ – $10^4$  s<sup>−1</sup>. Enzymatic reactions in which the limiting step is of the order of  $10^2$  s<sup>−1</sup> are especially abundant in nature. The distribution patterns of enzymes according to their  $K_{\text{m}}$  values are similar. This parameter changes in the range from  $10^{-2}$  to  $10^{-7}$  mol litre<sup>−1</sup>. The distribution density has a maximum at  $K_{\text{m}} \approx 10^{-4}$  mol litre<sup>−1</sup>. The  $k_{\text{cat}}/K_{\text{m}}$  values for different enzymes lie in the range of  $10^1$ – $10^{10}$  litre mol<sup>−1</sup> s<sup>−1</sup>; enzymes with  $k_{\text{cat}}/K_{\text{m}} = 10^6$  litre mol<sup>−1</sup> s<sup>−1</sup> are especially numerous.

These values define the limiting step of the substrate conversion in the active site of the enzyme. The energy barrier (10–17 kcal mol<sup>−1</sup>) seems to be determined by physicochemical factors. Other reaction steps proceed at faster rates.

Structural isomerisations are substantial steps of the catalytic cycle. If conformational changes affect the active site of the enzyme, this is reflected in the kinetics of the enzymatic reaction. In many cases, binding of the enzyme to the substrate (or the inhibitor) occurs by a two-step mechanism:



where E is the enzyme, S is the substrate,  $\text{X}_1$  is the primary complex and  $\text{X}_2$  is the enzyme–substrate (or enzyme–inhibitor) complex.

As the formation of enzyme–substrate (or enzyme–inhibitor) complexes is not accompanied by the formation of covalent bonds, the second step of the reaction represents a conformational transformation of the primary complex  $\text{X}_1$ . Presumably, this fact provides the strongest evidence in favour of conformational changes in the active site of the enzyme during enzymatic catalysis.<sup>11</sup>

Very often, the conformational changes  $\text{X}_1 \rightleftharpoons \text{X}_2$  occur at faster rates ( $10^3$ – $10^4$  s<sup>−1</sup>) than the limiting step of the catalytic process.

The rate constants of many conformational changes in proteins involved in catalytic transformations have now been established. These data can be used for conducting statistical analyses and revealing ‘typical’ characteristics of the catalytic reaction. Figure 11a shows the curve of the distribution density of rate constants of conformational changes ( $k_{\text{conf}}$ ). The maximum of the distribution density lies around  $10^3$  s<sup>−1</sup>. It can be seen that the distribution density curve  $k_{\text{conf}}$  is very similar to that for the

limiting steps. It may thus be assumed that sometimes the rates of conformational changes determine the rates of enzymatic reactions.

However, in the majority of cases conformational changes occur faster and precede the rate-limiting step. The role of conformational changes in enzymatic catalysis is evident. The mechanisms of enzymatic reactions are rather complex involving rearrangement of numerous bonds. Such processes cannot occur in one elementary step. The mechanisms of action of enzymes include the formation and conversion of a great number of intermediates. The enzyme ensures the reaction pathway with the least energy and entropy expenditures. The mechanism of action of an enzyme can be compared to that of a programmed control machine which operates at the molecular level and its functioning is provided by conformational changes.

In terms of chemical kinetics, this means that the structure similar to the transition state is formed as a result of conformational changes in the ground state. Conformational changes ‘push’ the reactants along the reaction pathway. The formation of a conformer structurally similar to the transition state or the reaction product significantly lowers the potential reaction barrier. The lowering of the reaction barrier the greater the more similar the structure of the conformer to that of the transition state or the reaction product.

Proton transfer is yet another process which limits the rate of an enzymatic reaction. It follows from the above-said that the acid-base nature of enzymatic reactions is their main characteristic feature.

Owing to the classical works by Eigen,<sup>194, 195</sup> the mechanisms of reactions of the proton with bases and of the hydroxyl ion with acids are now well understood. The main conclusion is that these reactions do not depend on the basicity or acidity of the reactants, but represent diffusion-controlled processes ( $k \approx 10^{10}$  litre mol<sup>−1</sup> s<sup>−1</sup>). Correspondingly, the rate constants of reverse reactions are determined by the values of equilibrium constants. In some cases, the proton transfer steps can be limiting for the enzymatic process.

Since in the course of an enzymatic reaction the catalytically active group undergoes both protonation and deprotonation, the proton transfer poses certain restrictions on the efficiency of acid-base catalysis. The reactions occurring in this process can be described as:



Since the reverse steps of these reactions are controlled by the diffusion of the reactants, the rate constants of the direct reactions can be presented as  $10^{10}K_{\text{a}}$  s<sup>−1</sup> and  $10^{10}(K_{\text{W}}/K_{\text{a}})$  litre mol<sup>−1</sup> s<sup>−1</sup> ( $K_{\text{a}}$  is the acid dissociation constant of  $\text{BH}^+$  and  $K_{\text{W}}$  is the ionisation constant of water). The maximum value of the rate constant of the overall reaction is approximately equal to  $10^3$  s<sup>−1</sup> at  $K_{\text{a}} \approx 10^{-1}$  mol litre<sup>−1</sup>. Indeed, for  $K_{\text{a}} < 10^{-7}$  mol litre<sup>−1</sup>, the dissociation rate constant of the acid  $\text{BH}^+$  [reaction (7a)] is

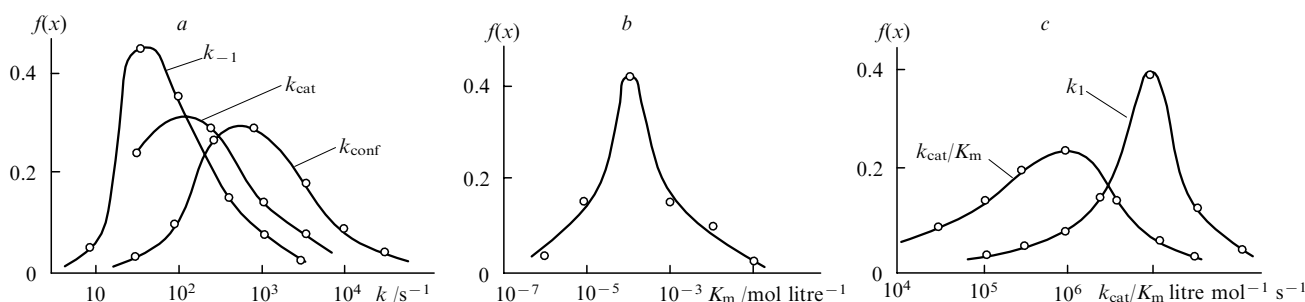
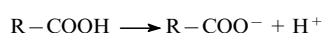


**Figure 11.** The distribution of enzymes according to their  $k_{\text{cat}}$  (a),  $K_{\text{m}}$  (b) and  $k_{\text{cat}}/K_{\text{m}}$  (c) values. (a) First-order rate constant, (b) the Michaelis constant, (c) second-order rate constant.

smaller than  $10^3 \text{ s}^{-1}$ , while at  $K_a > 10^{-7} \text{ mol litre}^{-1}$ , the hydrolysis rate constant of the base [reaction (7b)] is smaller than  $10^3 \text{ s}^{-1}$ . Therefore, the maximum value of the rate constant for an acid-base catalysis involving water is equal to  $10^3 \text{ s}^{-1}$ . This conclusion can be used for interpreting the maximum rates of enzymatic catalysis. The value  $10^3 \text{ s}^{-1}$  is characteristic of the turnover number of many enzymes (see Fig. 11a). Besides, the optimum value of  $\text{p}K_a \approx 7$ , which is necessary for effective catalysis, corresponds to  $\text{p}K_a$  of the imidazole group of the histidine residue.

Analysis of the structures of active sites of enzymes shows that in many cases the imidazole group of histidine participates in the catalytic act as a complex with a stronger nucleophile (proton conjugation), viz., a deprotonated carboxy group of aspartic or glutamic acid. The kinetic significance of such conjugation is obvious. The proton transfer from the protonated imidazole to the carboxy group in the last step of the catalytic cycle enables regeneration of properties of the catalytic site within microseconds. Indeed, the rate constant for the reaction



is equal to  $10^6 \text{ s}^{-1}$ .

Thus, the enzymatic catalysis illustrates the maximum catalytic accelerations which can be realised for the reactions occurring in solutions.

In all probability, the evolution of biocatalysis has long been searching for effective structures by the trial-and-error method. Having fixed these structures at the genetic level, the biosystems have learnt to use them for the formation of various active sites, and not only of the hydrolase type.

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# Covalent binding of modified nucleic acids to proteins as a method for investigation of specific protein – nucleic acid interactions

T S Zatsepin, N G Dolinnaya, E A Kubareva, M G Ivanovskaya, V G Metelev, T S Oretskaya

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**Abstract.** Methods for specific covalent binding of modified nucleic acids to proteins and enzymes with conservation of their native structures are discussed. Possible applications of synthetic nucleic acids containing reactive (nucleophilic and electrophilic) groups and groups that can be photoactivated for testing protein – nucleic acid contacts and studying protein functioning are considered. The structures of protein – nucleic acid conjugates formed in the enzymatic reactions are described. Methods for the isolation and analysis of covalently bound protein – nucleic acid complexes are generalised. The main attention is given to methods for determination of protein sites attached to nucleic acids. The bibliography includes 226 references.

## I. Introduction

Protein – nucleic acid interactions determine numerous processes occurring in cells, *viz.*, replication, transcription and translation of DNA as well as RNA processing. Amino acid residues involved in the formation of protein – nucleic acid complexes are identified by various methods. These can be divided into two groups, *viz.*, instrumental methods (*e.g.*, X-ray diffraction analysis, NMR spectroscopy, *etc.*) and molecular-biological methods (site-directed mutagenesis of proteins, cross-linking, *etc.*).

Undoubtedly, the most reliable information about the structures of NA – protein conjugates can be obtained from X-ray diffraction data, however, isolation and crystallisation of the corresponding complexes are not always possible.<sup>†</sup> In addition, X-ray diffraction analysis often fails to establish the conformational reconstructions of the proteins in their interactions with NA and to determine the effects of the nucleotide sequences of NA flanking the protein-binding sites.<sup>2</sup> The dynamics of protein – nu-

cleic acid complexes in solution is usually studied by NMR spectroscopy, but the latter is often inapplicable to the study of multisubunit complexes and processes associated with significant changes in the structures of biopolymers. Other spectroscopic methods, *e.g.*, fluorescence spectroscopy including stop-flow technique, Raman and small-angle X-ray scattering and electron microscopy, provide little information about the structures of NA – protein complexes.

Among other molecular-biological methods used in the analysis of NA – protein interactions, site-directed mutagenesis and addressed chemical modification of proteins are most popular, but they are rather laborious and sometimes provide incorrect information due to changes in the biopolymer structure caused by the substitution of the functional amino acid residues. Moreover, this demands localisation of the protein domain involved in binding. This group of methods also includes covalent binding of proteins to NA, which is optimum for solution of many problems. In the first place, it allows identification of the protein domain and even particular amino acids interacting with a specific NA fragment within the NA – protein complex.<sup>3–7</sup> It is also used in the study of multiprotein complexes formed upon replication, translation, *etc.* In particular, this can also be employed for identification of a protein component interacting with a specific site in NA.<sup>8</sup> This approach can be used in the study of cell extracts (particularly, for detecting proteins selectively interacting with specific nucleotide sequences) and in the SELEX technology<sup>‡</sup> for selection of oligonucleotides with specific primary structures (*e.g.*, NA aptamers) that bind to proteins irreversibly.<sup>9, 10</sup>

Covalent binding of proteins to NA has been used for the study of NA – protein interactions virtually from the moment of the origin of molecular biology, *i.e.*, since the mid-1960 s.<sup>11</sup> At present, photoaffinity modification of proteins is the most popular; this is based on covalent binding of non-modified nucleic acids to proteins upon UV irradiation.<sup>12</sup> However, it can hardly be regarded as a versatile procedure because of low yields of conjugates, radiation-induced damage of biopolymers and the necessity to identify the nucleotide unit to which the protein is attached. The use of NA analogues that can be photoactivated to generate radicals and biradicals under the influence of UV light seems to be a more promising approach. It excludes the necessity

T S Zatsepin, N G Dolinnaya, V G Metelev, T S Oretskaya Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax (7-095) 939 31 81, tel. (7-095) 939 31 49, e-mail: tsz@yandex.ru (T S Zatsepin), tel. (7-095) 939 54 07, e-mail: dolinnaya@hotmail.com (N G Dolinnaya), metelev@belozersky.msu.ru (V G Metelev), tel. (7-095) 939 54 11, e-mail: oretskaya@belozersky.msu.ru (T S Oretskaya)  
E A Kubareva, M G Ivanovskaya A N Belozersky Institute of Physico-Chemical Biology, Leninskie Gory, 119992 Moscow, Russian Federation. Fax (7-095) 939 31 81, tel. (7-095) 939 31 48, e-mail: kubareva@belozersky.msu.ru (E A Kubareva), tel. (7-095) 939 31 52, e-mail: img@genebee.msu.ru (M G Ivanovskaya)

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<sup>†</sup> Considerable progress in crystallisation of covalently bound NA – protein complexes and study of their structures by X-ray diffraction analysis achieved in the past decade is considered in detail in the review by Verdine and Norman.<sup>1</sup>

<sup>‡</sup> SELEX is an abbreviation from 'Systematic Evolution of Ligands by EXponential enrichment'.

to identify the nucleotide unit involved in binding and diminishes the risk of destruction of biopolymers, since in this case irradiation is performed under less destructive conditions (*i.e.*, with longer wavelengths). Several reviews devoted to the synthesis,<sup>13</sup> properties<sup>14</sup> and applications<sup>15–17</sup> of NA analogues that can be photoactivated are available.

Chemical methods for the attachment of proteins to NA are based on either the use of non-specific binding reagents (*e.g.*, formaldehyde<sup>18–20</sup>), or selective introduction of reactive groups into the protein or NA. A novel procedure for the covalent binding of proteins to NA in the presence of metal complexes has been developed recently.<sup>21</sup> It was found that UV irradiation of DNA in the presence of complexes with platinum-group metals results in specific oxidation of guanosine residues within the oligonucleotide.<sup>22–24</sup> When such nucleotides come closer to the protein, cross-linking occurs. However, despite the obvious originality of this technique, it has not found wide application because of low yields of protein–NA conjugates and commercial inaccessibility of the most efficient metal complexes.

The present review is devoted to the use of modified NA for the study of specific protein–nucleic acid interactions (here, we do not consider the methods based on the use of chemically modified proteins).<sup>25–27</sup> The review by Sheflyan *et al.*<sup>3</sup> published in 1996 was devoted to methods for covalent attachment of nucleic acids and their derivatives to proteins; however, many new NA derivatives have been synthesised in the past 7 years and, most importantly, the methodology of determination of amino acid residues covalently bound to NA has been finally stated and brought to practice.

## II. Covalent binding of modified nucleic acids to proteins

### 1. Methods for functionalisation of nucleic acids

Modified NA can be synthesised using chemical or enzymatic methods. The former approach includes preparation of modified nucleosides (as a rule, in the form of 3'-phosphoroamidite derivatives) which are further used in automated oligonucleotide synthesis. These nucleosides have to be stable under conditions of the synthesis and post-synthetic workup, which is not always possible. In addition, this method makes it possible to prepare oligomers having no more than 80–100 nucleotide units.

The enzymatic approach entails incorporation of modified 5'-nucleoside triphosphates into NA using various polymerases. As a rule, C(5)-substituted pyrimidine and C(8)-substituted purine nucleosides are used, the use of cytidine derivatives modified at N(4) has also been described. In this case, the length of the NA synthesised can reach thousands of nucleotides. However, the limitations of the enzymatic chain elongation method consist of impossibility of incorporation of certain modified nucleotides into the chain. The enzymatic method enables statistical functionalisation of NA and if 5'-nucleoside triphosphate terminates the growth of the oligonucleotide, it is the 3'-terminus of NA that is modified.

Substituents can be introduced into NA in the course of post-synthetic workup. Various reactive groups, *e.g.*, aliphatic amino groups, thiol groups, phosphorothionate internucleotide groups, *etc.*, can be used as substituents. An original procedure for the introduction of reactive internucleotide groups by chemical ligation of modified oligonucleotides has been developed in the laboratory headed by Z A Shabarova at MSU (see a review<sup>28</sup> and Section II.3).

### 2. Photoactivatable derivatives of nucleic acids

As mentioned above, the use of photoactivatable derivatives of NA in the study of specific protein–nucleic acid interactions is a promising approach. A comprehensive review by Meisenheimer and Koch<sup>14</sup> published in 1997 dealt with a detailed consideration of the mechanism and selectivity of covalent binding of side groups of amino acid residues of a polypeptide chain to the

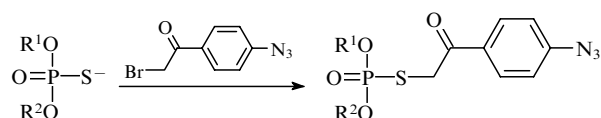
modified nucleotide units of nucleic acids containing photoactivatable groups.

Arylazide derivatives have become especially popular among other photoactivatable NA analogues due to their high reactivities.<sup>8</sup> Nucleosides containing arylazido groups can be introduced into NA by both enzymatic and chemical methods.

The main disadvantages of arylazide derivatives of NA include the lack of selectivity in the binding to proteins and large size of the arylazido group, which can lead to disturbances in the local structure of an NA–protein complex and to cross-linking with remote protein fragments. Nevertheless, this type of modified NA is widely used in the study of structures of protein–nucleic acid complexes.

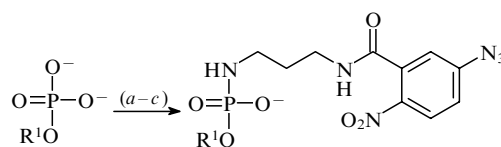
Arylazides can be introduced into NA

— at the internucleotide phosphorothioate bond of modified oligonucleotides:<sup>29–31</sup>



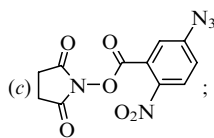
R<sup>1</sup>, R<sup>2</sup> are fragments of the oligonucleotide chain;

— at the 5'-phosphate group of oligonucleotides:

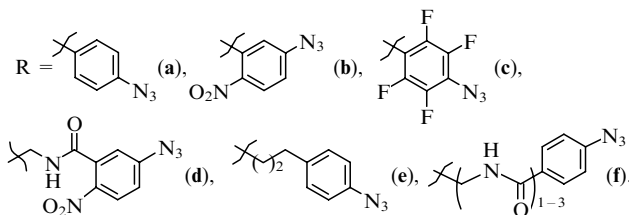
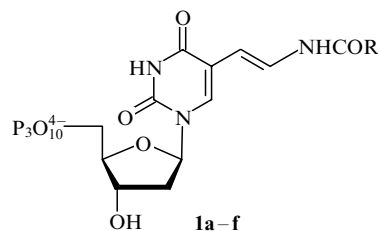


R<sup>1</sup> is a fragment of the oligonucleotide chain;

(a) Ph<sub>3</sub>P, ; (b) NH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>NH<sub>2</sub>;

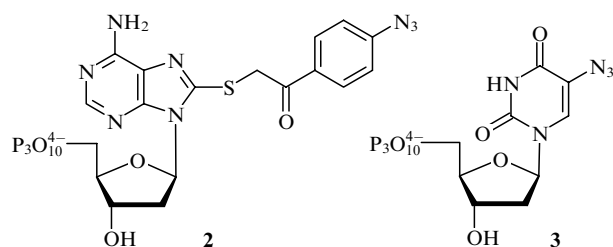


— in the course of a polymerase reaction using 5'-nucleoside triphosphates **1–3** modified at the heterocyclic base as one of the reactants (see Refs 32–43).

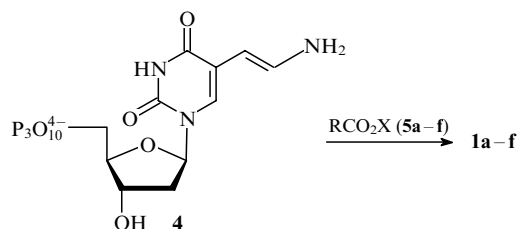


§ Highly reactive short-living arylnitrene biradicals, which react with the majority of amino acids, are formed upon irradiation of arylazido groups.





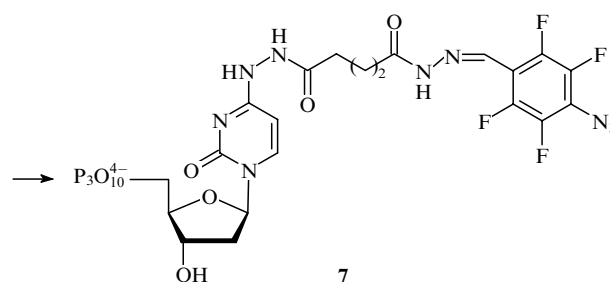
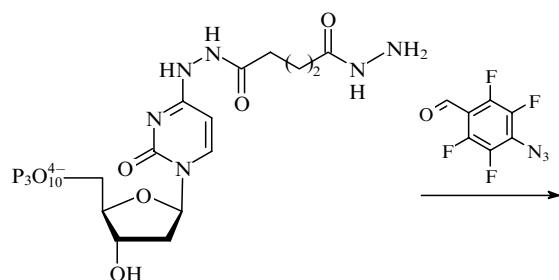
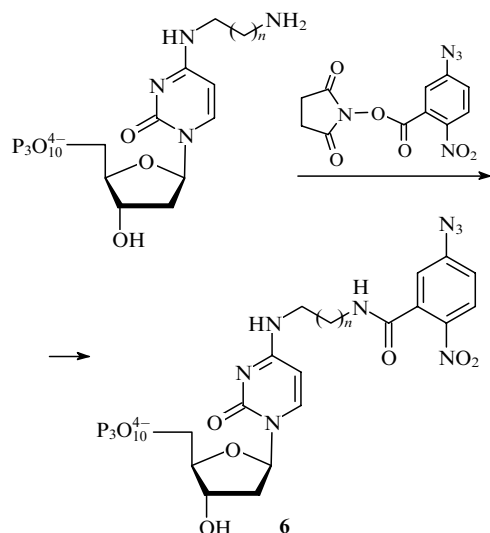
The photoactivatable triphosphates **1a–f** were prepared by the acylation of 5-(2-aminovinyl)-2'-deoxyuridine-5'-triphosphate (**4**) with an activated ester of the corresponding azidobenzoic acid (**5a–f**).



X = C<sub>6</sub>F<sub>5</sub>, succinimido.

The electron-withdrawing groups in the benzene ring of the arylazide stabilise the nitrene formed upon irradiation of the azide, as a result of which the yield of the protein–nucleic acid conjugate increases.<sup>44</sup>

The introduction of amino and hydrazide groups at C(4) of pyrimidine and their subsequent acylation or alkylidenylation is yet another approach to the synthesis of triphosphates containing an arylazide group. The synthesis of the corresponding compounds **6** and **7** has been described.<sup>45–49</sup>



The photoreagents **1–3**, **6** and **7** were used for the study of the human replication protein A,<sup>32, 50–53</sup> HIV-1 reverse transcriptase,<sup>54</sup> DNA polymerases,<sup>55, 56</sup> helicase Rep from *E. coli*<sup>35</sup> and excision repair proteins (BER, Base Excision Repair).<sup>57, 58</sup> The previously obtained data on the structures of DNA polymerases have been reviewed.<sup>59</sup> The use of arylazide derivatives of NA for structure–function studies has also been described.<sup>15–18</sup>

Lavrik *et al.*<sup>60</sup> have developed an original procedure for sensitised photomodification of DNA polymerase  $\beta$  which involves the use of an arylazido group. First, a nucleotide containing an arylazido group at the 3'-end was synthesised from a primer using DNA polymerase  $\beta$ . Then, pyrene-containing uridine-5'-triphosphate that binds to polymerase is added to the reaction mixture, and the resulting complex is irradiated with light with the wavelength of 365–450 nm. Irradiation induces the excitation of the pyrenyl residue and the fluorescence-resonance-energy transfer (FRET) to the arylazido group (Fig. 1). The activation of the latter brings about covalent binding of the 3'-end of the primer to the polymerase. Such a binary system allows the use of significantly longer irradiation wavelengths required for the formation of NA–protein conjugates in comparison with those commonly used for the photoactivation of arylazide derivatives (325–350 nm). The use of this approach has made it possible to reduce the photodamage of DNA and proteins and to increase (by an order of magnitude) the initial rate of photomodification. Later, this approach was repeatedly used for the study of functioning of DNA polymerases in both model systems and cellular extracts.<sup>54, 61–65</sup>

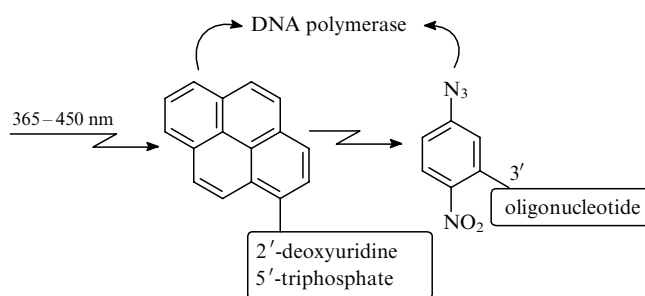
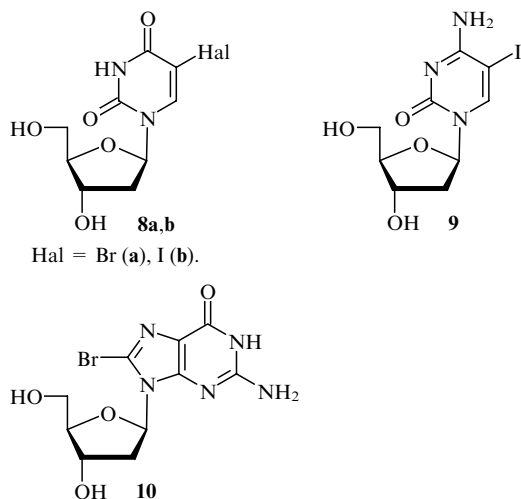


Figure 1. Sensitised modification of DNA polymerase.

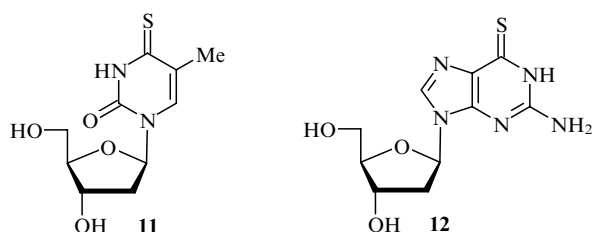
Among other commonly used photoactivatable NA derivatives, mention can be made of 5-halogenopyrimidine and 8-halogenopurine nucleosides, *e.g.*, 5-bromo- (**8a**)<sup>33, 66–72</sup> and 5-iodo-2'-deoxyuridine (**8b**),<sup>31, 40, 67, 73–95</sup> 5-iodo-2'-deoxycytidine (**9**)<sup>77, 96</sup> and 8-bromo-2'-deoxyguanosine (**10**).<sup>97</sup>



Photolysis of these photoactivatable NA produces stable radicals which react with electron-donor amino acid residues of proteins, particularly, with aromatic and sulfur-containing side groups. In the case of bromo derivatives, the optimum wavelength of the UV light necessary for the abstraction of the halogen atom is 308 nm, while that for iodo derivatives is 325 nm. The increase in the wavelength reduces photoinduced damage of proteins and NA, but decreases the yields of the photoaddition products. By virtue of their small size (the van der Waals radii of iodine and bromine atoms correspond approximately to that of the methyl group), halogen atoms do not induce any significant changes in the structure of NA and do not prevent protein–nucleic acid recognition. This makes halogen derivatives of NA highly attractive tools for probing protein–nucleic acid contacts in the binding sites of biopolymers.

Halogen derivatives of NA were used in the studies of a broad array of NA-recognising proteins, such as the transcription factor NF- $\kappa$ B;<sup>33</sup> the transcription factor binding the CCAAT motif of DNA (CBF);<sup>69</sup> the restriction–modification enzymes EcoP15I,<sup>66</sup> EcoRI,<sup>78,87</sup> EcoRII,<sup>93,94,96</sup> EcoRV,<sup>84,95</sup> SsoII,<sup>88</sup> CviBIII and TaqI,<sup>81</sup> homing endonuclease PI-SceI;<sup>79,80</sup> the eukaryotic ribosome L5 protein;<sup>89</sup> the herpes simplex virus helicase—primase subcomplex;<sup>83,90</sup> the replication terminator Tus;<sup>67</sup> HIV-1 integrase;<sup>74,77</sup> the repair protein MutS;<sup>77</sup> the protein HMG1;<sup>91</sup> the replication protein A;<sup>82</sup> the recombination proteins RAG1 and RAG2;<sup>85</sup> telomerase of *Euplotes aediculatus*;<sup>75</sup> the protein SSB;<sup>92</sup> the fibroblast growth factor (bFGF<sub>155</sub>);<sup>70</sup> vimentine;<sup>71</sup> the phage capsid protein MS2<sup>73</sup> as well as the multiprotein centromeric complex (CBF3).<sup>68</sup>

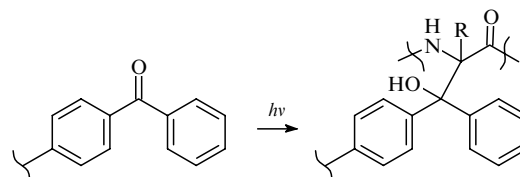
Nucleoside derivatives in which the oxo group in the heterocyclic base is substituted for the thioxo group, e.g., 4-thiothymidine (**11**)<sup>34,98–100</sup> and 6-thio-2'-deoxyguanosine (**12**),<sup>101–103</sup> belong to yet another class of photoactivatable NA derivatives.



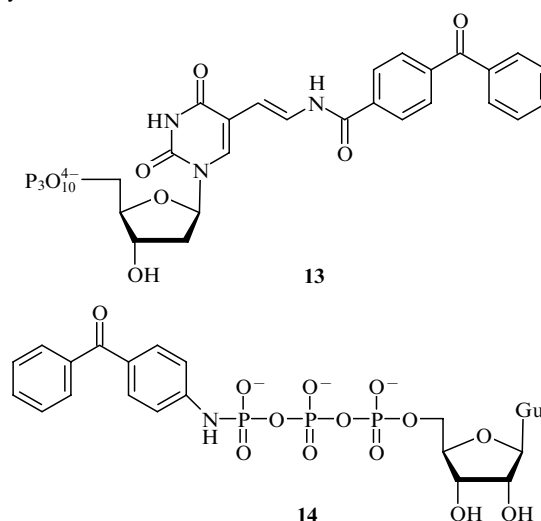
Replacement of the oxygen atom by sulfur induces minimum structural changes in the biopolymer, which, together with the high reactivity of thiones, makes them rather promising compounds. Upon irradiation with light with the wavelengths > 300 nm, these derivatives react with proteins by a free-radical mechanism. They were successfully used in the studies of the binding site of TAR RNA to the Tat-protein of HIV-1<sup>98,103</sup> (testing of NA–protein contacts in the large groove of the double

helix of RNA) as well as of DNA methyl transferase EcoR124I,<sup>102</sup> the transcription factor SRF,<sup>101</sup> integrase of the bacteriophage lambda<sup>100</sup> and the protein Rev of HIV-1.<sup>99</sup>

It is known that the benzophenone residue incorporated into NA<sup>40,104</sup> reacts with the  $\alpha$ -carbon atom of the polypeptide chain upon UV irradiation.<sup>105</sup>

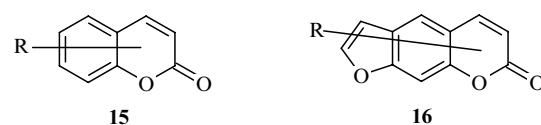


It seemed therefore interesting to consider possible applications of such NA for the study of NA–protein interactions. Thus triphosphates **13** and **14** containing a benzophenone residue were tested as photoreagents for the study of the transcription complex of yeast RNA polymerase III<sup>40</sup> at the RNA-binding site of RNA polymerase T7.<sup>104</sup>



With rare exception, the yields of cross-linked products of such NA derivatives to proteins are extremely low; therefore, they have not found wide application.

Coumarins (**15**) and furocoumarins (**16**, psoralenes)<sup>¶</sup>



are widely used for the introduction of various non-radioactive labels<sup>107,108</sup> and the synthesis of covalently bound NA<sup>109</sup> as well as in the photochemistry<sup>110</sup> and diagnostics of genetic diseases.<sup>111</sup>

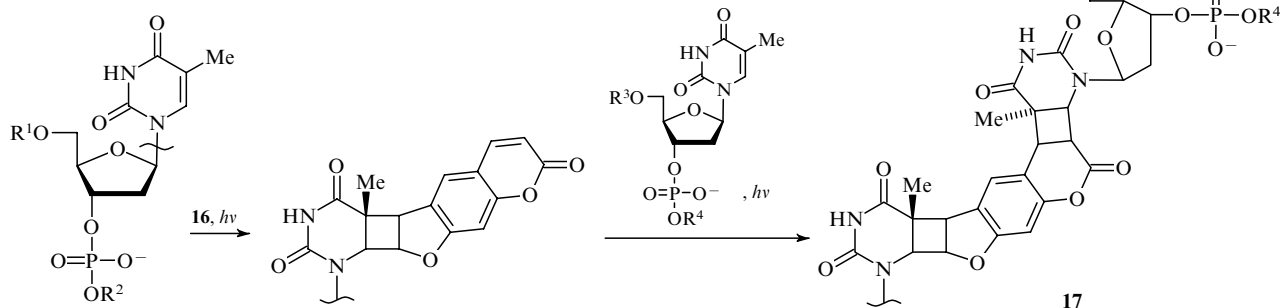
Psoralenes contain two photoactivatable double bonds by virtue of which they add to the double bond C(5)=C(6) of thymine to give compound **17** (Scheme 1). This reaction occurs upon UV irradiation ( $\lambda = 300–340$  nm). It was suggested<sup>112–115</sup> to use DNA fragments containing the thymidine residue **18** modified by 4'-hydroxymethyl 4,5',8-trimethylpsoralene for photoaffinity modification of proteins.

Coumarin can be introduced into NA by direct incorporation, into the oligonucleotide chain, of compound **19** with a carbohydrate-mimicking fragment.<sup>111,116</sup>

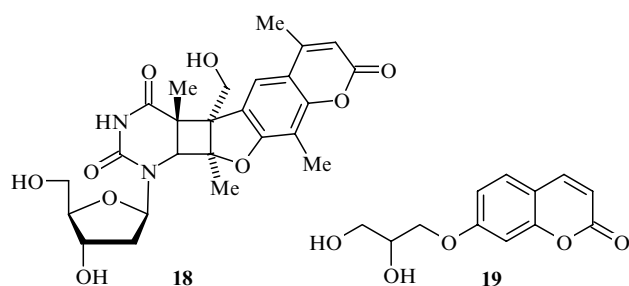
Psoralene- (or coumarin-) modified NA were used for the study of T7 RNA polymerase,<sup>106,112–114</sup> proteins RecA and Max,<sup>114</sup> as well as complex TFIIH proteins.<sup>115</sup>

¶ Psoralenes are also used for the modification of protein chains *in vivo*.<sup>106</sup>

Scheme 1

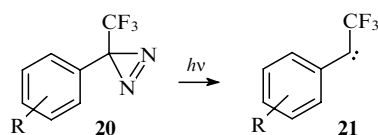


$R^1$ – $R^4$  are fragments of the oligonucleotide chain.

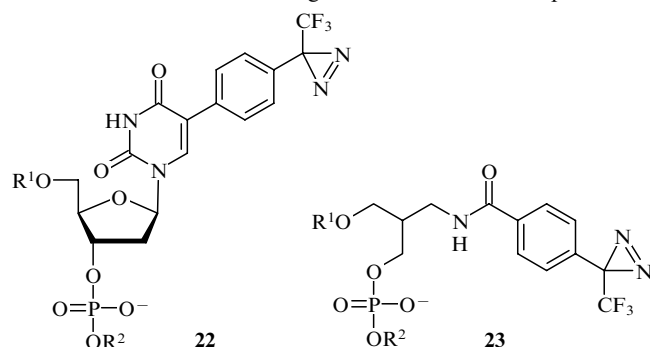


The optimum wavelength of UV light triggering the formation of protein–nucleic acid cross-links is 300 nm. The mechanism and selectivity of photoaddition of amino acid residues of proteins to psoralene-containing NA have not been established.

Aryl(trifluoromethyl)diazirine is yet another photosensitive reagent for the modification of NA. Upon UV irradiation, diazirines **20** are converted into reactive carbenes **21**, which react with virtually any molecule.



The review<sup>117</sup> published in 2000 is devoted to the use of aryl(trifluoromethyl)diazirines for the study of NA–protein interactions. Later, three other papers<sup>94, 118, 119</sup> devoted to the use of NA **22** and **23** containing diazirine residues were published.



$R^1$ ,  $R^2$  are fragments of the oligonucleotide chain.

DNA methyl transferase EcoRII<sup>94</sup> and HIV-1B integrase<sup>118</sup> were used as subjects of studies.

Unfortunately, the yields of cross-linked binding products of diazirine derivatives of NA to proteins are low because of side reactions of carbenes with water.

### 3. Chemical modification of nucleic acids

The non-specificity of the above-described photoactivatable NA reagents is their main disadvantage. Besides, their activation requires UV irradiation which can damage biopolymers. In contrast, NA reagents containing reactive groups react selectively with spatially close amino acid residues of the protein without any external factors. The introduction of a reactive group into a preset position of the oligonucleotide chain allows the probing of point contacts between different regions of biomolecules, whereas variations of the chemical nature of the reactive group enable selective binding of a definite type of amino acid residues within the NA–protein complex.

Reactive groups can be introduced into any position of NA, *i.e.*, the heterocyclic base, the sugar–phosphate backbone or the ends of the oligonucleotide chain. The introduction of these groups into the sugar–phosphate backbone of NA is the most promising approach, while modification of heterocyclic bases can disturb complementary interactions of NA and specific interactions within the protein–nucleic acid complex.

The following properties should be characteristic of the NA reagents used for the cross-linking with proteins:

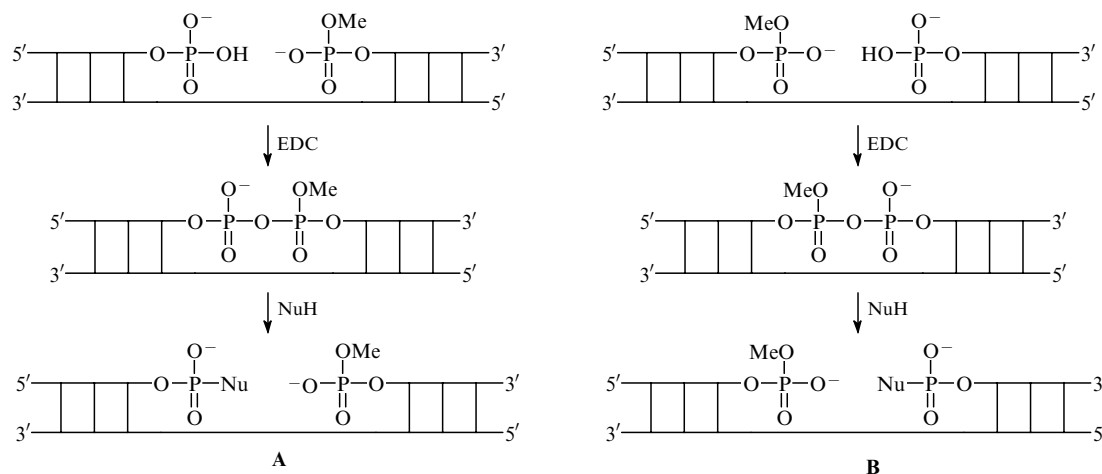
- (1) the possibility to react specifically with spatially close functional amino acid groups of the protein;
- (2) formation of stable conjugates with the protein without any additional activation at physiological values of pH (6.0–8.0);
- (3) retention of stability in neutral aqueous solutions over a long period of time without any loss of reactivity.

#### a. Modification of nucleic acids at the internucleotide phosphodiester bond

It is known that nonspecific interactions make a significant contribution to the structural organisation and stability of virtually all macromolecular complexes including NA–protein complexes. In this connection, modification of the phosphate groups of NA, which are involved in the majority of cases in these interactions, seems to be important for the study of NA–protein contacts. In the early 1990s, Shabarova *et al.*<sup>120–123</sup> proposed to substitute trisubstituted (TSP) groups for the natural 3',5'-phosphodiester bonds in NA.

The trisubstituted pyrophosphate group possesses all the properties necessary for the interaction with proteins, *viz.*, it is stable in aqueous media and is readily cleaved by amines. It was found that oligonucleotides containing TSP groups react exclusively with lysine and histidine residues as well as with the terminal  $\alpha$ -amino group of the protein;<sup>124</sup> the nucleophilic substitution occurs only with the disubstituted phosphate to yield a covalently linked protein–oligonucleotide complex. If the phosphoramidate bond is formed with involvement of the  $\epsilon$ -amino group of Lys or the terminal  $\alpha$ -amino group of the protein, this bond is stable at pH > 4; if the amino group of His is involved, the bond is cleaved in weakly acidic media or under the action of *N*-methylimidazole, which allows discrimination of lysine and histidine residues.<sup>125</sup>

Scheme 2



NuH are Lys and His residues of the protein.

Template-directed condensation of oligonucleotides carrying mono- and disubstituted terminal phosphate groups using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (Scheme 2, chemical ligation) is employed for the introduction of the TSP group into the predetermined position of the oligonucleotide. The use of chemical ligation for the preparation of various single- and double-stranded TSP-modified oligonucleotides has been described in detail in the reviews.<sup>3, 18, 126</sup>

The formation of two isomeric TSP-containing oligonucleotides **A** and **B** (see Scheme 2) is possible depending on which of the terminal phosphate residues (3'- or 5'-) in the starting oligonucleotide is esterified. It was found that the synthesis of the isomer **B** is far more effective than that of the isomer **A** due to the difference in the reactivities and availabilities of the reacting mono- and disubstituted phosphate residues. At the same time, the isomer **B**, which is formed more easily, reacts more slowly with the amino group of lysine than the isomer **A**.

The human transcription factor NF- $\kappa$ B was used as a target protein.<sup>127, 128</sup> This belongs to the class of multifunctional eukaryotic proteins (the family Rel), which control gene expression and play an important role in such vital processes as immune response,<sup>129</sup> apoptosis,<sup>130</sup> cell growth<sup>131</sup> and proliferation.<sup>130</sup> It has been shown that synthetic DNA duplexes containing TSP groups in different positions of the recognition site of the transcription factor NF- $\kappa$ B differ substantially in the efficiency of their covalent binding to the protein. Thus in the case of isomers **A** the yield of the protein–nucleic acid conjugate was 35%, while for isomers **B** it did not exceed 7%. The observed regularity was taken into consideration in subsequent studies aimed at the design of DNA reagents containing the TSP groups.

A series of DNA duplexes containing *O*-methyl pyrophosphate in different positions of the binding site of the transcription factor HNF-1 was used for the probing of DNA contacts with this protein in nuclear extracts of rat liver<sup>132</sup> and the study of DNA formamido–DNA glycosylase contacts.<sup>133</sup>

The synthesis of TSP-containing oligoribonucleotides has been described by Shabarova *et al.*<sup>134</sup> These were used to confirm the existence of contacts between individual phosphate groups of RNA within the TAR RNA complex with the Tat-peptide<sup>135</sup> predicted on the basis of NMR spectroscopic data. The aim of this study was to specify the architecture of the natural TAR RNA–Tat-protein complex. The amino acids interacting with the RNA duplex were determined using chemical and enzymatic cleavage of the protein fragment in the covalently bound complex with subsequent analysis of the conjugate by mass spectrometry.<sup>135</sup> The natural TAR RNA–Tat-protein complex plays a key role in the activation of transcription of the human immunodeficiency virus. It was found that the Tat-protein after formation of the complex with TAR RNA initiates indirect activation of RNA

polymerase II.<sup>136</sup> This reaction is the determining step in the initiation of transcription of HIV-1, since no elongation of transcription takes place in the absence of the Tat-protein.

The structural polymorphism of proteins including that induced by irradiation and crystallisation has been studied especially intensely in recent years. It remains to be hoped that the use of nucleic acids containing TSP groups will enable a more accurate determination of individual contacts between the biopolymers within the protein–nucleic acid complexes which exist in the native state in aqueous media and a comparison of the results obtained from X-ray diffraction analysis. The main advantages of this approach include selectivity of interaction (Lys or His) and the absence of extended spacers between the phosphate group responsible for the binding and the nucleophilic groups of proteins. Thus some of the contacts of the Lys and His residues in RNA polymerase of bacteriophage T7 with the phosphate groups of the promoter were established<sup>137</sup> with the use of synthetic fragments of the promoter (10–20 b.p.) containing a TSP group in positions that, according to data from X-ray diffraction analysis, are close to particular amino acids. The functional significance of such contacts has been established previously in biochemical studies.

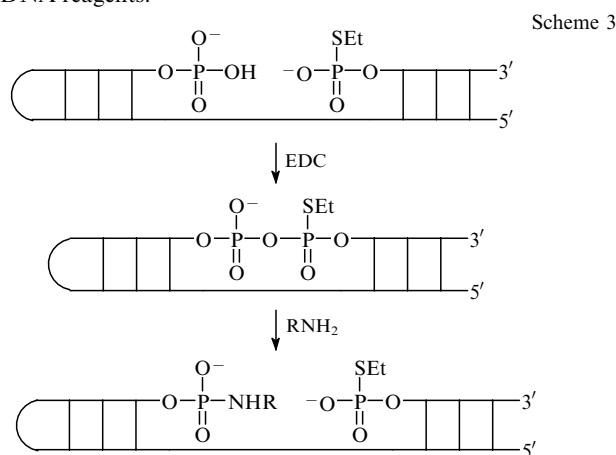
This approach was used in the study of the complex of the transcription factor NF- $\kappa$ B with DNA duplexes with different primary structures.<sup>128</sup> Covalent binding made it possible to establish an important fact that in principle the structure of the NF- $\kappa$ B complex with DNA is determined not only by the nucleotide sequence in the protein-binding site, but also by flanking regions. Later, this fact was confirmed by X-ray diffraction analysis.<sup>138–141</sup>

Studies by Shabarova *et al.*<sup>142</sup> have shown that DNA duplexes containing TSP groups are promising reagents for the probing of conformational changes in the enzyme during functioning of the enzyme–substrate complex. Restriction endonuclease MvaI (R.MvaI) was used as a subject of investigation, while a 14-membered DNA duplex containing a recognition site for the enzyme with a TSP group instead of a hydrolysable phosphodiester bond was used as a substrate.<sup>142</sup> This system was used for the study of conformational changes in the restriction endonuclease MvaI in the enzyme–substrate complex induced by different concentrations of magnesium ions (the latter is a cofactor of the cleavage of DNA). It was found that magnesium ions favour conformational rearrangements in the protein as a result of which one of the nucleophilic groups in the catalytic site of R.MvaI (presumably, histidine) comes closer to the modified bond in the DNA substrate.

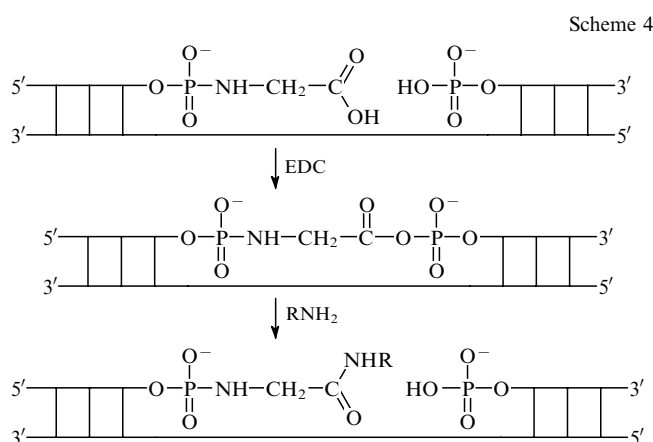
In order to enhance the reactivities of internucleotide bonds, it was proposed to replace the TSP groups in DNA duplexes by their sulfur-containing analogues.<sup>143</sup> Oligonucleotides containing thio

analogues of the TSP groups appeared to be more reactive with respect to aliphatic amines, since dialkyl thiophosphoric acid is a stronger acid (in comparison with dialkyl phosphoric acid) and, as a consequence, the better leaving group.

Hairpin DNA duplexes containing a recognition site of the human transcription factor NF- $\kappa$ B, the position of the modified fragment (*i.e.*, the sulfur-containing TSP group) in which corresponded to the position of the group the most close to the lysine residue, were bound covalently to the protein (Scheme 3). In contrast to oxygen-containing TSP, both isomers differing in the position of the trisubstituted phosphorothioate residue reacted with the same efficiency. However, the lability of sulfur-containing TSP groups and the relative difficulty of their incorporation into oligonucleotides prevent large-scale application of this type of DNA reagents.



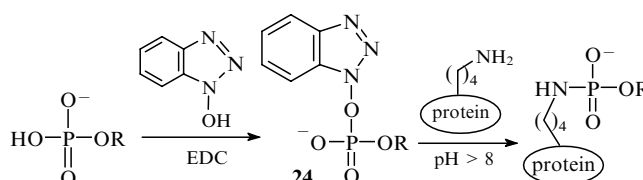
It was proposed<sup>124,144</sup> to use oligonucleotides containing a reactive acylphosphate group instead of one phosphodiester bond for the study of NA–protein interactions. This group was introduced into the preset position of the sugar–phosphate backbone by template-directed chemical ligation of two oligonucleotides one of which served as a phosphate donor, while the other one was used as a carboxyl donor (Scheme 4).<sup>124</sup> The mixed anhydride formed undergoes cleavage in aqueous solution ( $\text{pH} \geq 8$ ) under the action of amines to give a carboxamide (rather than phosphoramidate) (see Scheme 4).<sup>124</sup> In reactions with amines, such acyl phosphate-containing oligonucleotides play the role of mild acylating reagents. A comparison of the properties of DNA duplexes containing an acyl phosphate or a TSP group in the same position of the recognition site of the transcription factor NF- $\kappa$ B revealed that the yields of the protein–nucleic acid conjugates in the case of acyl phosphate-containing DNA were three times lower than those from TSP-containing DNA.<sup>124</sup> The lower reactivities and the formation of side products in the



synthesis of acyl-phosphate oligonucleotide derivatives are the reasons for their low utility for the covalent binding to proteins.<sup>†</sup>

#### b. Modifications of the terminal phosphate groups of nucleic acids

Oligonucleotide derivatives with activated terminal phosphoester groups are more accessible than other reactive phosphorylating agents. *N*-Hydroxybenzotriazole esters (HOBt-derivatives) of oligonucleotides **24** are the most popular reagents of this type. They are prepared in one step from oligonucleotide-3'- or 5'-phosphates and *N*-hydroxybenzotriazole under the action of water-soluble carbodiimide in water-organic media.<sup>147,148</sup>



R is the oligonucleotide residue.

HOBt-Derivatives of the oligonucleotides **24** manifest phosphorylating properties in reactions with amino acids, peptides and proteins. In this case, the reaction with the protein occurs at the N-terminal  $\alpha$ -amino group, at the  $\epsilon$ -amino group of Lys or at the imidazole residue of histidine.<sup>149</sup>

Reactive *N*-hydroxybenzotriazole esters of oligonucleotides were successfully used in the study of DNA-<sup>125</sup> and RNA-binding<sup>149</sup> proteins. The structure of the complex of RNA polymerase of *E. coli* with a DNA promoter has been studied<sup>125</sup> with the help of a large series of hydroxybenzotriazole derivatives of single- and double-stranded oligonucleotides corresponding to various fragments of the promoter responsible for different transcription initiation steps (–35 and –10 relative to the transcription initiation point). The RNA polymerase subunit of the holoenzyme built up of five subunits and the amino acid residues involved in the binding to each oligonucleotide were determined based on the results of covalent binding.<sup>125</sup> The results obtained with the use of hydroxybenzotriazole derivatives were confirmed by Naryshkin *et al.*<sup>150</sup> who have used photoactivatable arylazide analogues of DNA for the solution of the same task.

The use of hydroxybenzotriazole derivatives of RNA has also been described in the study<sup>149</sup> on the binding of Tat-proteins to the fragment of TAR RNA. The high efficiency of the covalent binding of RNA to the peptide suggests that this type of derivatives can be used for the construction of 'decoys' that slow down the transcription of the immunodeficiency virus in infected cells.

It should be noted that HOBt and TSP derivatives of nucleic acids containing modified phosphate groups both inside the NA chain and at its termini are the only currently available reagents for testing the contacts of Lys and His residues of proteins. The high efficiency of formation of protein–nucleic acid conjugates (yields up to 50%), the high selectivity of binding to proteins and the availability of chemical means of analysis of covalent binding products open up broad opportunities for further applications of these reagents for determination of the structures and analysis of conformational rearrangements in NA–protein complexes during their functioning or upon changes in their environments.

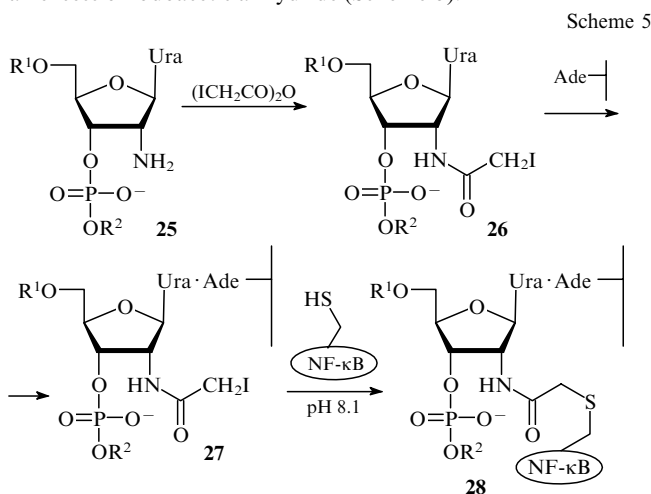
#### c. Modification of sugar moieties of nucleic acids

Only a small number of NA reagents containing reactive groups in the sugar moiety have been obtained so far. At the same time, it is known that NA-recognising proteins react with NA exclusively by generating hydrophobic and van der Waals contacts with the

<sup>†</sup> The methods for the introduction of carboxy groups into DNA and the chemical properties of such derivatives have been studied fairly extensively.<sup>145,146</sup>

ribose residue.<sup>151</sup> Of special interest are NA reagents modified in the 2'-position of ribose which plays a crucial role in the discrimination of DNA and RNA molecules by proteins.

It was suggested<sup>152</sup> that the 2'-iodoacetamide group within DNA duplexes can be used for selective covalent binding of proteins containing a cysteine residue in the active centre. The iodoacetamido group was chosen due to its higher (in comparison with the bromoacetamido group) activity in the alkylation of the thiol group of cysteine.<sup>153</sup> Synthetic oligonucleotides containing 2'-amino-2'-deoxyuridine **25** in the preset position instead of thymidine were used as starting compounds for the directed introduction of the iodoacetamido group (this approach enables easy changes in the position of the reaction centre in the target oligonucleotide sequence). The 2'-deoxy-2'-iodoacetamidouridine derivatives **26** were prepared by acylation of the amino group with an excess of iodoacetic anhydride (Scheme 5).



$\text{R}^1, \text{R}^2$  are fragments of the oligonucleotide chain.

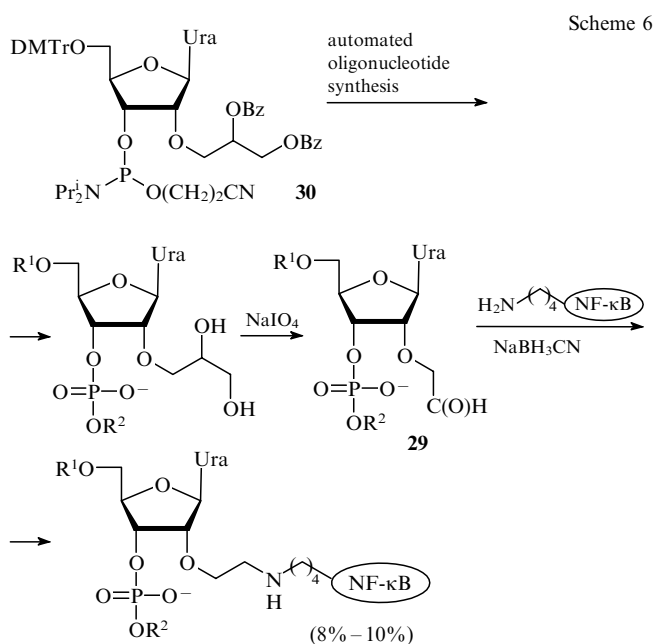
Studies of reactions of DNA reagents containing an iodoacetamide group in position 2' of the uridine residue with various low-molecular-mass nucleophiles (including amino acids and peptides) revealed that they react only with thiol-containing compounds, particularly, with cysteine-containing proteins. It is of note that the iodoacetamide groups at the 2'-position of the sugar-phosphate backbone of DNA react with the cysteine residues of the protein only within specific protein-nucleic acid complexes (*e.g.*, within the duplex **27**, see Scheme 5).

Such DNA duplexes were used for the affinity modification of a series of DNA-recognising cysteine-containing proteins, *e.g.*, the transcription factor NF- $\kappa$ B, the restriction-modification enzyme SsoII and uracil DNA glycosylase.<sup>152</sup> Thus the reaction of the modified DNA duplexes **27** with the transcription factor NF- $\kappa$ B is complete within 15 min at pH 8.1 and yields the covalently bound adducts **28**. These data altogether suggest that this reaction occurs with good efficiency (the yield of the conjugates reaches 25%) and high specificity.

The amino groups of lysine residues of DNA-recognising proteins can also be involved in the interaction with the sugar-phosphate backbone of DNA. To this end, aldehyde groups are to be introduced into the sugar-phosphate backbone. The synthesis and properties of oligonucleotides containing dialdehyde groups are considered in the reviews.<sup>154-156</sup>

Synthesis of oligodeoxyribonucleotides **29** containing a 2-oxoethyl group at the O(2') atom has been described.<sup>157,158</sup> The protected phosphoramidite 2'-O-(2,3-dihydroxypropyl)uridine derivative **30** was used as a starting compound in the oligonucleotide synthesis of such DNA (Scheme 6).

Oxidation of the diol group into the aldehyde group was carried out under mild conditions by treatment with a twofold



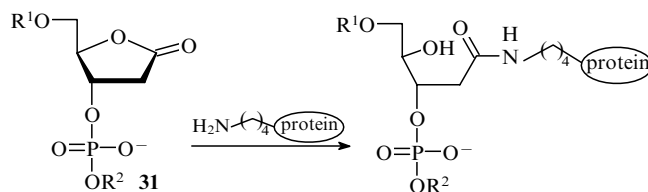
DMTr is dimethoxytrityl;

$\text{R}^1, \text{R}^2$  are fragments of the oligonucleotide chain.

excess of sodium periodate. The oligonucleotides **29** obtained react efficiently with different amino compounds.<sup>159</sup> The possibility of covalent binding of DNA containing a 2'-O-(2-oxoethyl)-uridine fragment to the transcription factor NF- $\kappa$ B (see Scheme 6) has been demonstrated.<sup>160</sup> The oligonucleotide **29** appeared to be more efficient in the reaction with NF- $\kappa$ B than the dialdehyde derivatives, since in this case  $\beta$ -elimination is excluded and the small size of the 2'-O-(2-oxoethyl) residue allows the  $\epsilon$ -amino groups of lysine to approach the most close to DNA. The advantage of this methodology is the possibility to vary the position of the modified unit and the number of modifications in the oligonucleotide. The yields of the addition products of the transcription factor NF- $\kappa$ B to DNA ligands were 8% - 10%.

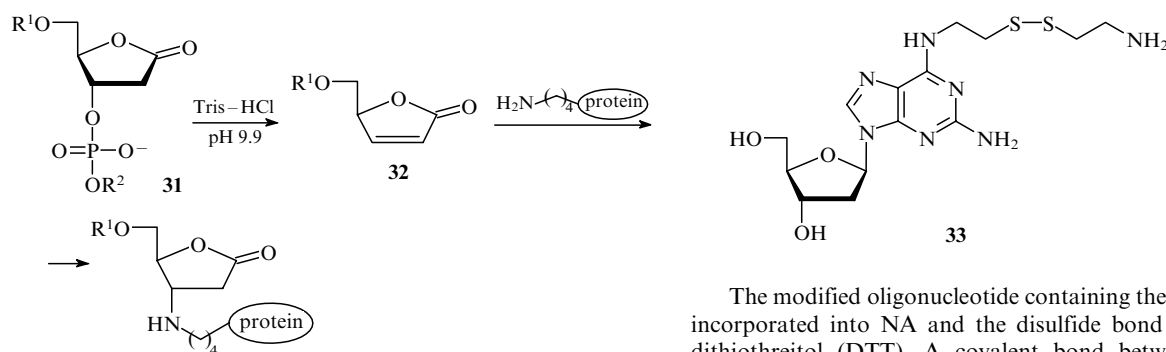
It was proposed<sup>161</sup> that the DNA ligands **29** were used for the study of the mechanism of functioning of DNA methyltransferase SsoII. With a set of duplexes containing one or two modifications in the recognition site, two types of DNA-protein conjugates have been obtained in 70% yields. From determination of molecular masses of such conjugates it was suggested that DNA methyltransferase SsoII interacts with DNA as a dimer.

Oligonucleotides **31** containing a 2-deoxyribonolactone fragment were used for the covalent binding of some repair enzymes.<sup>162,163</sup>



$\text{R}^1, \text{R}^2$  are fragments of the oligonucleotide chain, the protein is endonuclease III or human DNA polymerase.

Such oligonucleotides appeared to be versatile for the covalent addition of various excision repair proteins. It was suggested<sup>164</sup> that the oligonucleotides **31** were used for the synthesis of oligonucleotides **32** containing furan-2(5H)-one at the 3'-end of the chain.



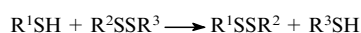
$R^1, R^2$  are fragments of the oligonucleotide chain.

The latter represent substrates for only those BER enzymes that catalyse  $\beta, \delta$ -elimination of the apurine site, which allows selective binding of these proteins, particularly, in cellular extracts.

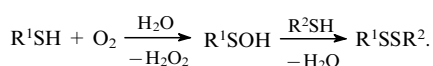
#### d. Modification of nucleic acids at the heterocyclic bases

It has been noted above that the introduction of reactive groups into heterocyclic bases is seldom used for modification of NA. Nevertheless, such examples are known. In particular, substituents containing  $-\text{SH}$  or  $-\text{SS}$  groups were introduced into the heterocyclic base in order to achieve covalent binding of cysteine-containing proteins to DNA through formation of disulfide bridges. Introduction of these groups into the oligonucleotide allows its covalent binding to the protein either by thiol–disulfide exchange or as a result of oxidation of the thiol groups under the action of atmospheric oxygen.

The thiol–disulfide exchange



proceeds efficiently at room temperature in water at physiological values of pH despite the fact that this reaction includes the cleavage and formation of a stable covalent  $\text{S}—\text{S}$  bond with the energy of  $60 \text{ kcal mol}^{-1}$  (see Ref. 165). The formation of the disulfide bond through the oxidation of thiols by oxygen occurs in two steps.<sup>166</sup>

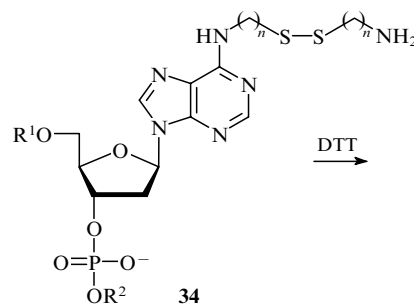


For the first time, the formation of a disulfide bond in the DNA–protein complex has been used in order to confirm the specificity of binding of a modified oligonucleotide ligand to the active site of (methylguanine)–DNA methyltransferase (MGMTase) of *E. coli* containing a cysteine residue.<sup>167</sup> The action of this key repair enzyme is directed at the removal of the methyl and other alkyl groups from position O(6) of guanine or from position O(4) of thymine by their transfer to the cysteine residue in the active site of the protein. In the ‘dormant’ state, the cysteine residue is localised inside the protein globule.<sup>168</sup> It was assumed that the binding of MGMTase to the substrate or its repair are accompanied by conformational rearrangements; however, the information on the nature of these changes was absent. In order to corroborate this hypothesis, 2-amino-6-cystamino-2'-deoxy- $\beta$ -D-ribofuranosyl purine (**33**) was introduced into the 21-membered oligodeoxyribonucleotide instead of deoxyguanosine by automated synthesis.

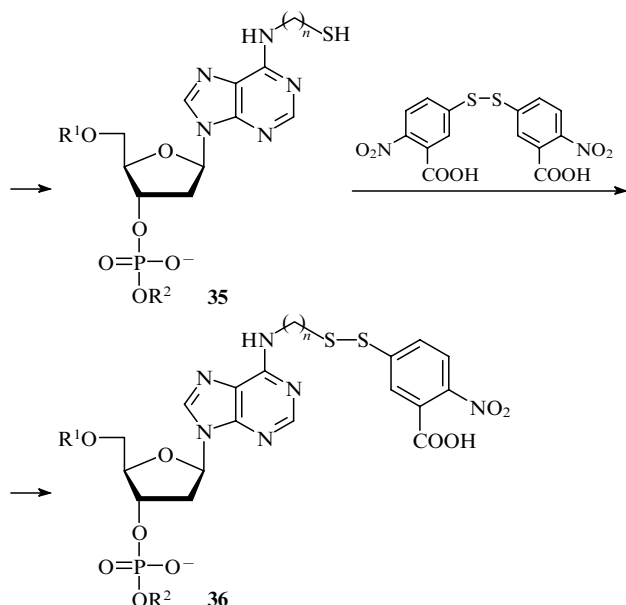
The modified oligonucleotide containing the fragment **33** was incorporated into NA and the disulfide bond was reduced by dithiothreitol (DTT). A covalent bond between the double-stranded oligonucleotide and MGMTase was formed under the action of atmospheric oxygen (the yield of the NA–protein conjugate was low). The formation of the disulfide bond between DNA and the protein was confirmed by its cleavage with DTT. Analysis of the primary structure of the polypeptide fragment covalently bound to the oligonucleotide confirmed the fact that it was cysteine that was involved in the formation of the disulfide bridge. Supporting evidence for the involvement of this amino acid residue in the formation of the covalent complex MGMTase–DNA was obtained in the following experiment. The cysteine residue in the active site of the enzyme was methylated by its incubation with an oligomer containing an O(6)-methylguanosine residue. The protein obtained did not form conjugates with reduced DNA substrates containing the nucleoside analogue **33** with a free thiol group. These studies have shown that MGMTase undergoes conformational rearrangements during its functioning which favour the convergence of the cysteine residue to the alkylated guanosine derivative.<sup>167</sup>

A similar approach based on the site-specific attachment of proteins to reactive analogues of DNA aimed at the formation of disulfide bonds was used<sup>169</sup> in order to establish the contacts in the active complex of HIV integrase with viral cDNA. At the beginning, additional cysteine residues were introduced into the predetermined positions of integrase by site-directed mutagenesis and modified fragments of 2'-deoxyadenosine containing a disulfide group at the N(6) atom were introduced into the predetermined positions of DNA by automated synthesis. It was expected that the cysteine residue in the DNA–protein complex would be localised in the vicinity of the modification site of DNA, since thiol–disulfide exchange demands a more ‘close’ arrangement of two interacting groups than photo-induced covalent addition.

The reactivity of DNA **34** containing a disulfide group could be enhanced by converting it into the thiol form by treatment with DTT; the reaction of DNA **35** with the cysteine residue of a protein occurs upon oxidation with atmospheric oxygen. Treatment of DNA **35** with 5,5'-dithiobis(2-nitrobenzoic acid) yields an even more reactive DNA derivative **36**.







R<sup>1</sup>, R<sup>2</sup> are fragments of the oligonucleotide chain; *n* = 2, 3.

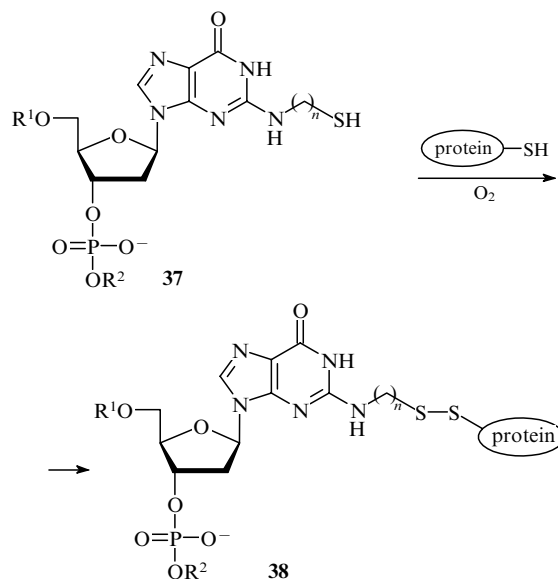
It is of note that the introduction of reactive groups at N(6) of adenine does not influence its ability to form Watson–Crick hydrogen bonds.

It was found that the yields of covalent binding products of the highly reactive substrates **36** to all mutant forms of integrase containing single additional cysteine residues are nearly identical. The use of less reactive substrates **35** or **34** is recommended to increase the specificity of the covalent binding. In fact, the required specificity of the covalent binding was achieved with the least reactive oligonucleotides **34**: a noticeable yield of the conjugate was observed only for one mutant form of integrase. It was shown also that the use of a propylene linker instead of an ethylene linker increases significantly the yields of the protein–nucleic acid conjugates. The effect of 2-mercaptoethanol as an additive on the yields of the protein–nucleic acid conjugates has also been examined.<sup>167</sup> It was shown that high concentrations of 2-mercaptoethanol (> 5 mmol litre<sup>-1</sup>) block completely the formation of the reaction product; however, lower concentrations (2 mmol litre<sup>-1</sup>) enhance the specificity of the covalent binding of HS- and SS-containing DNA. Under these conditions, the formation of the protein–nucleic acid complex is reversible and spatially close arrangement of the reactive groups is the only prerequisite for cross-linking.

These studies have demonstrated the *trans*-interaction between viral cDNA and integrase, *i.e.*, the enzyme–substrate complex represents a DNA bound to the C-terminal domain of one integrase monomer and the catalytic domain of the other integrase monomer. Moreover, site-specific covalent binding revealed conformational changes in the integrase–DNA complex concomitant with the terminal processing reaction.

Oxidation of thiol groups by atmospheric oxygen was successfully used in the synthesis of a covalently bound complex of reverse transcriptase of HIV-1 with a DNA duplex consisting of a matrix and a primer. This reaction was carried out in the presence of deoxynucleoside triphosphates, which provided the formation of a functionally active supramolecular associate.<sup>170, 171</sup> The reactive mercaptoalkyl group was introduced at the amino group in position 2 of guanine (compound **37**). This group was localised in the small groove of DNA and was spatially close to the cysteine residue<sup>‡</sup> of the H helix of reverse transcriptase. One of the conjugates (complex **38**) was crystallised and examined by X-ray

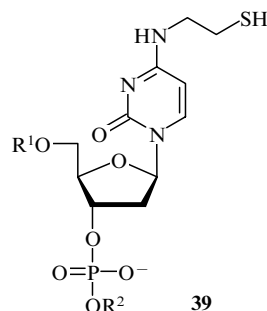
diffraction, which made it possible to determine the structure of the reverse transcriptase complex with the primer, the DNA template and 2'-deoxynucleoside triphosphate.



R<sup>1</sup>, R<sup>2</sup> are fragments of the oligonucleotide chain; *n* = 2, 3; the protein is HIV-1 reverse transcriptase.

A similar strategy was used for the study of conformational changes in reverse transcriptase during its binding to 2'-deoxynucleoside triphosphate.<sup>172, 173</sup>

He and Verdine<sup>174</sup> used the oligonucleotide **39** containing a cytidine residue modified at the amino group for the study of the N-terminal domain of the mutant Ada-protein from *E. coli*. Studies of specific covalent addition of modified DNA **39** to mutant proteins has made it possible to establish some DNA–protein contacts.

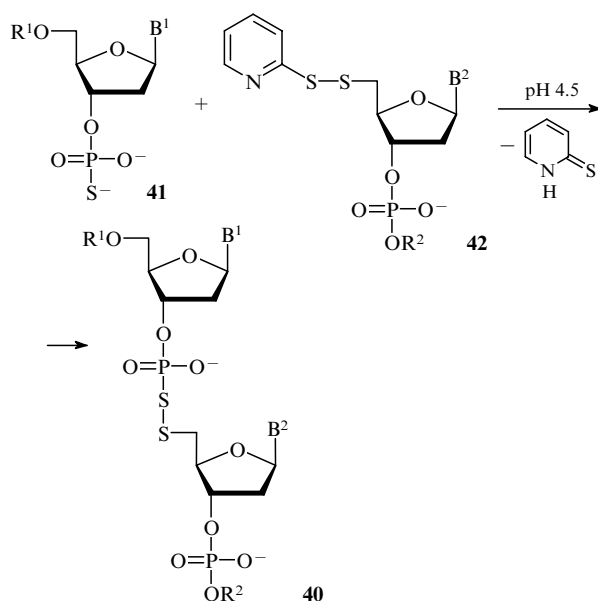


R<sup>1</sup>, R<sup>2</sup> are fragments of the oligonucleotide chain.

#### e. Miscellaneous examples of modification of nucleic acids

It was suggested<sup>175–178</sup> that oligodeoxyribonucleotides containing phosphoryl disulfide and diphosphoryl disulfide groups in the sugar–phosphate backbone were used for selective binding of cysteine in proteins and peptides. Interaction of DNA methyltransferase SsoII with DNA containing a methylated site was studied using a series of DNA duplexes where one of the phosphodiester internucleotide bonds was replaced by the phosphoryl disulfide (PDS) group (one of the duplex strands represented a modified oligonucleotide **40**).<sup>179, 180</sup> The modified bond was introduced into the positions directly flanking the methylated cytidine residue using thiol–disulfide exchange between the 3'-thiophosphorylated oligonucleotide **41** and the 2-pyridyldithio-substituted oligonucleotide **42**.

<sup>‡</sup> The cysteine residue was introduced instead of glutamine into the native enzyme using site-directed mutagenesis.

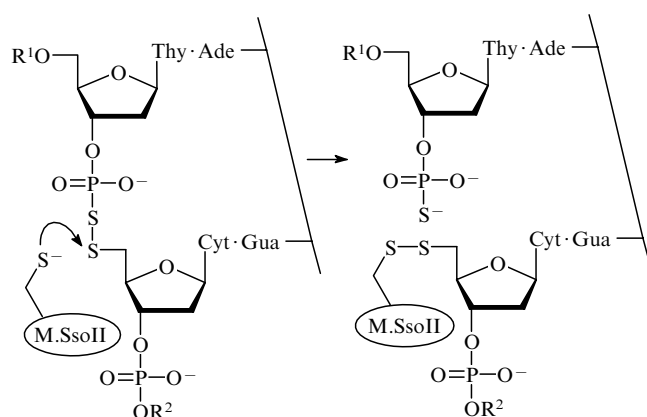


R<sup>1</sup>, R<sup>2</sup> are fragments of the oligonucleotide chain; B<sup>1</sup>, B<sup>2</sup> are heterocyclic bases.

This reaction proceeded with equal efficiency both in the presence and in the absence of the template oligonucleotide.<sup>177, 178, 180</sup> It was shown that PDS-containing DNA duplexes form conjugates with M.SsoII with different degrees of efficiency, which depended on the position of modification.<sup>179</sup>

It is known that the cleavage of the mixed disulfide R<sup>1</sup>SSR<sup>2</sup> by a nucleophilic thiolate ion R<sup>3</sup>S<sup>-</sup> results in the formation of a more stable anion R<sup>1</sup>S<sup>-</sup> and a new mixed disulfide R<sup>3</sup>SSR<sup>2</sup> (see Refs 165 and 181). With regard to PDS-containing DNA duplexes, this suggests that the thiolate ion attacks the sulfur bound to the carbon atom (but not the sulfur bound to phosphorus), since thiophosphoric acid is a much stronger acid than thiol. This was confirmed experimentally by an analysis (PAAG electrophoresis and mass spectrometry) of conjugates of PDS-containing DNA duplexes with M.SsoII (Scheme 7) and glutathione, a simple tripeptide model of cysteine-containing proteins.<sup>179</sup>

Scheme 7



R<sup>1</sup>, R<sup>2</sup> are fragments of the oligonucleotide chain.

The internucleotide PDS bond within DNA is selective with respect to the cysteine residues and does not react with the ε-amino group of lysine.<sup>179</sup>

It is of note that the formation of a new disulfide bond between the cysteine residue and the PDS group is only possible where these are spatially close in the supramolecular DNA–protein complex. It has been shown<sup>182</sup> that the formation of the conjugate of the restriction endonuclease SsoII (R.SsoII) and the DNA

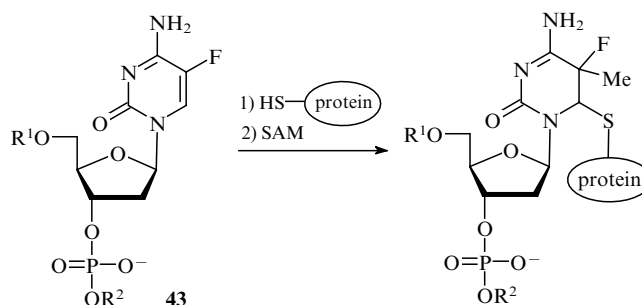
duplex containing a PDS group in the recognition site proceeds with an extremely low efficiency. This phenomenon was attributed to the remoteness of the Cys residue from the binding and catalytic sites of R.SsoII. Evidence for this hypothesis can be derived from the fact that the R.SsoII variants in which the Arg-(116, 117, 119) or Lys-122 residues interacting with the sugar–phosphate backbone of DNA were replaced by the Cys residue form conjugates with PDS-containing DNA substrates in high yields.<sup>182</sup>

### III. Natural protein–nucleic acid conjugates formed in the enzymatic reactions

Reactions of certain enzymes with NA yield unstable intermediates which represent covalently bound biopolymer complexes. In some cases, dissociation of these intermediates can be prevented by modification of NA and they can be investigated.

The transfer of the methyl group onto 5-fluoro-2'-deoxyuridine monophosphate by thymidylate synthase is a classical example of an enzymatic reaction which results in the formation of a stable covalently bound protein–nucleic acid complex.<sup>183</sup> Substitution of the fluorine atom for the hydrogen atom in 2'-deoxyuridine monophosphate prevents the cleavage of the nucleotide–enzyme bond.<sup>184</sup> Cytosine-5-DNA methyltransferases and methyltransferases that react with RNA also belong to enzymes that form conjugates with oligonucleotides. Oligonucleotides containing a 5-fluorocytidine or 5-fluoro-2'-deoxycytidine residues (compound 43) are widely used for the stabilisation of such conjugates.

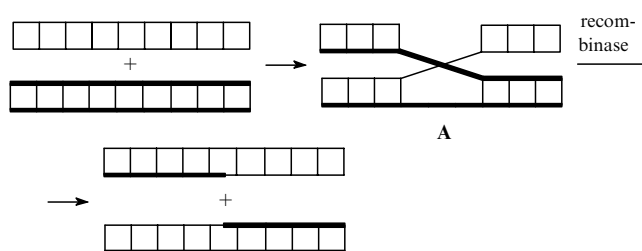
A more detailed description of these processes is given in the reviews;<sup>10, 185</sup> see also Ref. 186.



R<sup>1</sup>, R<sup>2</sup> are fragments of the oligonucleotide chain, protein is cytosine-5-DNA methyltransferase, SAM is S-adenosyl-L-methionine.

Landy *et al.*<sup>187–189</sup> studied the covalent binding of DNA to recombinases catalysing the homologous recombination of DNA in the cross-like structures A (the Holiday structures) (Scheme 8) resulting in transfer of fragments of one region of a genome into the other region.

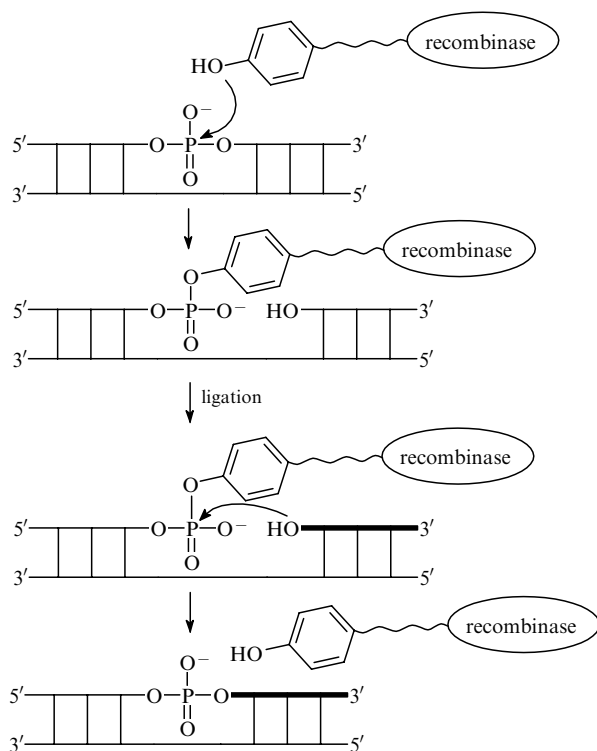
Scheme 8



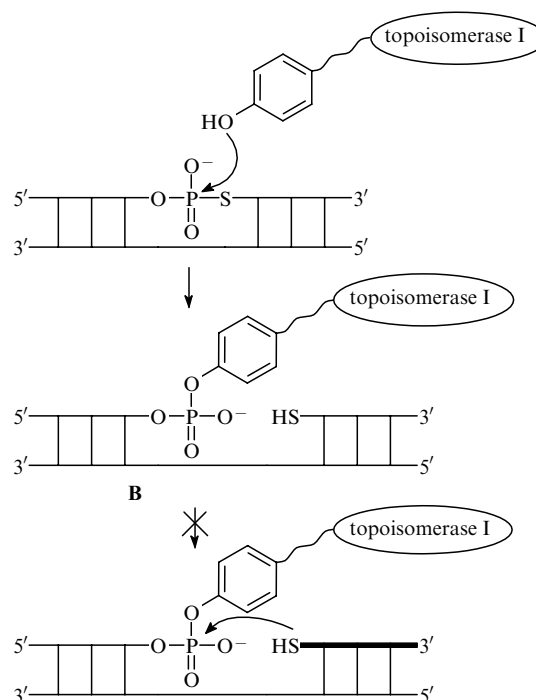
Hereinafter, are the strands of recombining fragments of DNA.

The mechanism of action of recombinases includes an attack of the hydroxy group of tyrosine on the internucleotide phosphate of DNA (Scheme 9) resulting in the cleavage of the phosphodiester bond and the formation of a conjugate between the 5'-terminal site of DNA and recombinase with subsequent ligation

Scheme 9



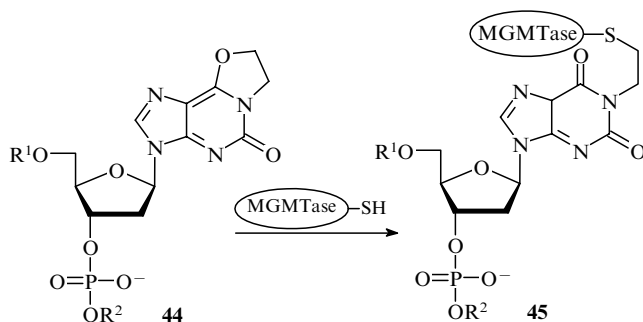
Scheme 10



of recombining DNA fragments and release of recombinaise. It was suggested that shortened oligonucleotides were used so that cleavage in a single strand resulted in dissociation of the short 3'-terminal fragment of DNA. This prevented recombination in the ligation step and, as a consequence, stabilised the recombinaise–DNA conjugate.

It was suggested<sup>190, 191</sup> that modified DNA containing phosphorothioate internucleotide bonds (Scheme 10) were used for the study of covalent binding of topoisomerases.<sup>8</sup> No ligation took place after the formation of the protein–nucleic acid conjugate **B**, since the replacement of the P–O bond by the P–S bond is energetically unfavourable. This enabled selective inhibition of topoisomerase I and isolation of a conjugate in high yield.

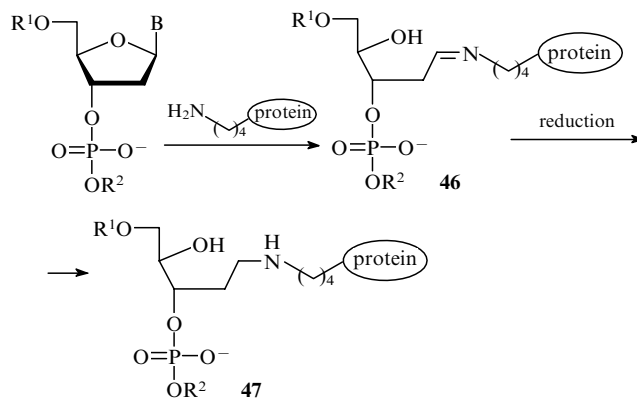
The modified oligonucleotide **44** was used<sup>192</sup> for the study of the mechanism of action of MGMTase. The reaction of the oligonucleotide **44** with MGMTase containing a cysteine residue in the active site gave the conjugate **45**. Even in the presence of a 10-fold excess of the protein this reaction was rather slow (48 h).



R<sup>1</sup>, R<sup>2</sup> are fragments of the oligonucleotide chain.

In a review<sup>193</sup> on bifunctional DNA glycosylases, which possess N-glycosylase and β-lyase activities, the formation of the

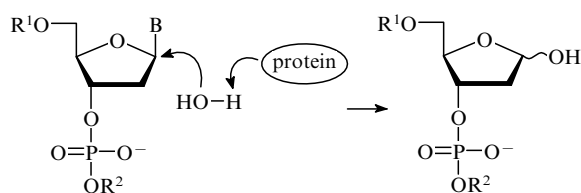
Shiff base **46** upon reaction of the lysine side amino group of DNA glycosylase with an apurine site of the oligonucleotide was considered as a key reaction; subsequent reduction was aimed at the access to the stable conjugate **47**.



R<sup>1</sup>, R<sup>2</sup> are fragments of the oligonucleotide chain; the protein is DNA glycosylase.

Strengthening of the bond between the enzyme and the substrate by the reduction of the Schiff base has also been used elsewhere.<sup>194–197</sup> Detailed studies of the mechanism of this reaction were carried out using model peptides.<sup>198</sup> Virtually all studies on glycosylases<sup>193</sup> made use of MutY from *E. coli*<sup>194–196</sup> and human endonuclease III.<sup>197</sup> Study of 8-oxoguanine-DNA glycosylase made it possible, for the first time, to establish the involvement of one of the reaction products, viz., 8-oxoguanine, in the cascade of reactions triggered by the β-lyase activity of this enzyme.<sup>199</sup>

It is of note that this approach cannot be applied to monofunctional DNA glycosylases, since they function according to a different mechanism which includes cleavage of the N-glycosidic bond with the participation of the water molecule.



R<sup>1</sup>, R<sup>2</sup> are fragments of the oligonucleotide chain; the protein is DNA glycosylase

#### IV. Identification of protein sites covalently bound to nucleic acids

Amino acid residues in the proteins involved in the complex formation with NA can be identified by direct and indirect methods. The former entail isolation of the NA–protein conjugate, partial cleavage of the protein, isolation of an oligonucleotide–peptide fragment and elucidation of the primary structure of the peptide and identification of the amino acid involved in the formation of the covalent bond. The latter make use of mutant proteins and X-ray diffraction analysis. The amino acid residue of the protein, which is thought to react with DNA, is replaced by a non-reactive residue with subsequent analysis of whether the covalent bond is formed between the protein and the oligonucleotide.<sup>162, 163</sup> Obviously, this method is inapplicable to photoactivatable NA, which react with any amino acids. Data from X-ray diffraction on the arrangement of side groups of amino acid residues are used as evidence of proximity of definite amino acids of the protein to the specific fragment of NA.

Let us consider the direct method used for the analysis of protein–nucleic acid conjugates in more detail. The conjugates are usually isolated by polyacrylamide gel (PAAG) electrophoresis under denaturing conditions (Table 1).

The analysis of the data presented in Table 1 suggests that the conditions of isolation of protein–nucleic acid conjugates are analogous or are much the same as those used for the separation of

proteins by PAAG electrophoresis according to Laemmli (12.5% PAAG, 250 mM Tris–HCl, 0.1% sodium dodecyl sulfate, pH 8.8).<sup>202</sup> The conjugate is eluted from the gel using a buffer in which subsequent partial cleavage of the protein is carried out. In some cases, the isolated product is desalted, dialysis being the most efficient and versatile procedure.

Medium-pressure ion-exchange chromatography (FPLC MonoQ HR5/5)<sup>203</sup> and anion-exchange HPLC (Porous HQ, PerSeptive Biosystems),<sup>204</sup> which permit separation of the DNA–protein conjugate from the nonbound protein, are also used for the isolation of conjugates.

The protein and the covalently bound biopolymer complex were precipitated with 10% trichloroacetic acid or antibodies, which made it possible to separate the bulk of the nonbound NA.<sup>69, 74, 205</sup> Dialysis of the reaction mixture can also be used for this purpose.<sup>100</sup> Nucleic acid–protein conjugates could be separated from excess protein if oligonucleotides carrying biotin at the 3'-end were used with subsequent immobilisation of the oligonucleotide (both free and within the conjugate) on avidin-coated magnetic particles.<sup>74</sup> Isolation of NA and the NA–protein conjugate by affinity chromatography was described.<sup>76</sup> To this end, an oligoadenylate sequence (oligo-dA) was attached to the 3'-end of a modified oligonucleotide followed by chromatography on a microcolumn with oligothymidylate-cellulose (oligo-dT). In this case, the separation of the complex from NA was achieved due to the formation of the oligo-dA · oligo-dT duplex.

It should be noted that the purification of the covalently bound protein–NA complex is not compulsory and in some cases<sup>12, 79, 88, 206</sup> the covalent binding is immediately followed by the next stage, *viz.*, partial chemical or enzymatic cleavage of the protein.

The methods for the cleavage of the protein within the protein–nucleic acid complex are summarised in Table 2.

The data listed in Table 2 suggest that such proteases as trypsin and chymotrypsin are most commonly used for partial cleavage of the protein component of the conjugate. Enzymatic treatment is carried out in weakly alkaline solutions under

**Table 1.** Isolation of a NA-protein conjugate by gel electrophoresis.

| Protein                                       | Composition of gel <sup>a</sup>                                                              | Conditions of isolation from gel                                                                                             | Desalting conditions                                                               | Ref.    |
|-----------------------------------------------|----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|---------|
| Protein Tax of leukemia virus                 | 10% PAAG, 250 mM Tris–HCl, 0.1% SDS, pH 8.8                                                  | 10 mM Tris–HCl, 1 mM EDTA, 0.1% SDS, pH 7.0, 4 °C, 18 h                                                                      | no desalting                                                                       | 37      |
| Replication terminator Tus                    | 10% PAAG, 250 mM Tris–HCl, 0.1% SDS, pH 8.8                                                  | H <sub>2</sub> O, 37 °C, 24 h (3-fold)                                                                                       | sedimentation with 0.3 M AcONa, EtOH                                               | 67      |
| DNA methyltransferase EcoRI                   | 12% PAAG, 250 mM Tris–HCl, 0.1% SDS, pH 8.8                                                  | —                                                                                                                            | dialysis against buffer 50 mM NH <sub>4</sub> HCO <sub>3</sub> , pH 7.8, 4 °C, 8 h | 87      |
| DNA methyltransferase EcoRII                  | 12% PAAG, 90 mM Tris–HCl, 90 mM H <sub>3</sub> BO <sub>3</sub> , 2 mM EDTA, 7 M urea, pH 8.0 | see <sup>b</sup>                                                                                                             | no desalting                                                                       | 96      |
|                                               | 12% PAAG, 100 mM Tris–HCl, 0.1% SDS, pH 8.8                                                  | 1% SDS, 37 °C, 5–7 h                                                                                                         | the same                                                                           | 94, 200 |
| HIV-1 integrase                               | NuPage 4%–12% MES gel (Novex, Inc.), pH 6.4                                                  | 20 mM Tris–HCl, 0.5% SDS, pH 8.5, 37 °C, 18 h                                                                                | precipitation with 10% CCl <sub>3</sub> CO <sub>2</sub> H, acetone                 | 77      |
| HIV-1 Tat-protein                             | 20% PAAG, 100 mM Tris–HCl, 0.1% SDS, pH 8.3                                                  | 45 mM Tris–H <sub>3</sub> BO <sub>3</sub> , 1 mM EDTA, 3 M AcONa, pH 5.5                                                     | reversed-phase HPLC                                                                | 98      |
| Ttk-protein of <i>Drosophila melanogaster</i> | 16% PAAG, 250 mM Tris–HCl, 0.1% SDS, 7 M urea                                                | 10 mM Tris–HSCH <sub>2</sub> CO <sub>2</sub> H, 0.1 mM EDTA, 0.1% Triton X-100, 0.1 mM PMSF, <sup>c</sup> pH 8.0, 45 °C, 4 h | no desalting                                                                       | 201     |

<sup>a</sup> Abbreviations: PAAG is polyacrylamide gel; Tris is tris(hydroxymethyl)aminomethane; SDS is sodium dodecyl sulfate; MES is morpholinoethane-sulfonic acid. <sup>b</sup> The conjugate was not eluted from the gel. <sup>c</sup> PMSF is phenylmethylsulfonyl fluoride.

**Table 2.** Cleavage of the protein component within the NA–protein conjugate.

| Reagent or enzyme (A)            | Protein (B)                                       | $c_A$ or A : B (see <sup>a</sup> ) | Reaction conditions                                                                  | Ref.    |
|----------------------------------|---------------------------------------------------|------------------------------------|--------------------------------------------------------------------------------------|---------|
| Chymotrypsin                     | homing endonuclease PI-SceI                       | 40 $\mu\text{g ml}^{-1}$           | 50 mM Tris–HCl, 1 mM $\text{CaCl}_2$ , pH 8.0, 37 °C, 2 h                            | 79      |
|                                  | DNA methyltransferases CviBIII and TaqI           | 1 : 1                              | 10 mM Tris–HCl, 20 mM $\text{CaCl}_2$ , pH 8.0, 37 °C, 16 h                          | 81      |
|                                  | restriction endonuclease SsoII                    | 500 $\mu\text{g ml}^{-1}$          | 100 mM $\text{NH}_4\text{HCO}_3$ , 37 °C, 2 h                                        | 88      |
| Chymotrypsin (see <sup>b</sup> ) | protein U1 of the small nuclear ribonucleoprotein | 1 : 20                             | 50 mM Tris–HCl, 1 M urea, 1 mM DTT, 1 mM $\text{CaCl}_2$ , pH 7.5, 37 °C, 16 h       | 205     |
| BrCN                             | DNA methyltransferase EcoRII                      | 1 M                                | $\text{HCOOH}$ , 25 °C, 48 h                                                         | 94, 200 |
|                                  | HIV-1 integrase                                   | 100 mM                             | 70% $\text{CF}_3\text{CO}_2\text{H}$ , 70 °C, 45 min                                 | 77      |
| Protease Glu-C                   | the same                                          | 1 : 5                              | 50 mM Tris–HCl, 1 M NaCl, 5 mM EDTA, 5 mM DTT, 0.1% SDS, pH 8.5, 37 °C, 12 h         | 77      |
|                                  | "                                                 | 1 : 5                              | 50 mM Tris–HCl, 1 M NaCl, 5 mM EDTA, 5 mM DTT, 0.01% SDS, pH 8.0, 37 °C, 12 h        | 74      |
| BNPS-scatol (see <sup>c</sup> )  | DNA methyltransferase EcoRII                      | 70 mg $\text{ml}^{-1}$             | 1% SDS, 70% AcOH, 37 °C, 2 h                                                         | 94      |
| Trypsin (see <sup>d</sup> )      | the same                                          | 1 : 25                             | 400 mM $\text{NH}_4\text{HCO}_3$ , 2 M urea, 0.1 mM $\text{CaCl}_2$ , 37 °C, 24 h    | 12      |
| Trypsin (see <sup>e</sup> )      | "                                                 | 1 : 1 to 1 : 10                    | 50 mM Tris–HCl, 1 mM $\text{CaCl}_2$ , 10% MeCN, pH 8.5, 37 °C, 16 h                 | 96      |
| Trypsin                          | Ttk protein of <i>Drosophila melanogaster</i>     | 5 $\mu\text{g ml}^{-1}$            | 100 mM $\text{NH}_4\text{HCO}_3$ , 0.2% Triton X-100, 1 mM DTT, 37 °C, 6 h           | 201     |
|                                  | DNA methyltransferase EcoRI                       | 1 : 20                             | 50 mM $\text{NH}_4\text{HCO}_3$ , pH 7.8, 37 °C, 12 h                                | 87      |
|                                  | HIV-1 Tat-protein                                 | 0.05 $\mu\text{g ml}^{-1}$         | 100 mM Tris–HCl, 10 mM $\text{CaCl}_2$ , pH 7.8, 25 °C, 4 h                          | 98      |
|                                  | the same                                          |                                    | 100 mM Tris–HCl, pH 8.5, 37 °C, 24 h                                                 | 67      |
|                                  | "                                                 |                                    | 100 mM $\text{NH}_4\text{HCO}_3$ , 2 M urea, pH 7.8, 37 °C, 24 h                     | 100     |
|                                  | DNA polymerase $\beta$                            | 1 : 10                             | 50 mM $\text{NH}_4\text{HCO}_3$ , 10% MeCN, pH 8, 37 °C, 3 h                         | 203     |
|                                  | DNA endonuclease VIII                             | 1 : 6                              | 20 mM Tris–HCl, 3.4 M urea, pH 7.5, 37 °C, 18 h                                      | 204     |
| Trypsin (see <sup>b</sup> )      | HIV-1 Tat-protein                                 | 1 : 20                             | 50 mM Tris–HCl, 1 M urea, 1 mM DTT, 1 mM $\text{CaCl}_2$ , pH 7.5, 37 °C, 16 h       | 205     |
|                                  | the same                                          | 5 $\mu\text{g ml}^{-1}$            | 2.5 mM Tris–HCl, 5 mM $\text{CaCl}_2$ , 0.25 mM EDTA, 0.025% SDS, pH 8.0, 37 °C, 2 h | 37      |
|                                  | "                                                 | 160 $\mu\text{g ml}^{-1}$          | 50 mM Tris–HCl, 2 mM $\text{CaCl}_2$ , pH 8.0, 37 °C, 18 h                           | 76      |
| Clostripaine                     | repair protein MutS                               | 80 $\mu\text{g ml}^{-1}$           | 30 mM Tris–HCl, 2 mM $\text{CaCl}_2$ , 2 mM DTT, 0.5% SDS, pH 7.5, 37 °C, 18 h       | 76      |
| Proteinase K                     | gene conversion endonuclease PI-SceI              | 2 mg $\text{ml}^{-1}$              | 50 mM Tris–HCl, 1 mM $\text{CaCl}_2$ , pH 8.0, 37 °C, 16 h                           | 79      |

<sup>a</sup>The concentration of the reagent ( $c_A$ ) or the enzyme:substrate ratio (A : B). <sup>b</sup>Preliminary denaturation of the protein–nucleic acid conjugate.

<sup>c</sup>Functionalisation with 3-bromo-3-methyl-2-(2-nitrophenylsulfenyl)-3*H*-indole. <sup>d</sup>Preliminary denaturation of the protein–nucleic acid conjugate and treatment with iodoacetic acid. <sup>e</sup>Preliminary treatment of the protein–nucleic acid conjugate with iodoacetamide.

denaturing conditions. In some cases, preliminary denaturation of the protein, reduction of the disulfide bonds and alkylation of the thiol groups of cysteine with iodoacetic acid or iodoacetamide are performed in order to reduce the proteolysis time and to obtain more homogeneous protein–nucleic acid conjugates. Proteinase K is often used for the treatment of analytical amounts of protein–nucleic acid conjugates; however, this enzyme is not used in a large scale due to its low specificity, which results in the formation of a mixture of peptide–nucleic acid conjugates and, as a consequence, prevents the identification of the covalently bound site of the protein. Nevertheless, the use of proteinase K permits a comparison of stabilities of DNA–protein conjugates and of the original protein, which facilitates the selection of conditions for the trypsinolysis of a conjugate in subsequent studies.

Partial cleavage of the protein is followed by purification of the peptide–oligonucleotide conjugate. This is achieved by

reversed-phase HPLC, gel filtration, anion-exchange HPLC and PAAG electrophoresis (Table 3). Elucidation of the primary structure according to Edman or using mass spectrometry demands preliminary isolation and desalting of the conjugates. The most efficient chromatographic procedures make use of buffer solutions based on volatile salts, *e.g.*, ammonium formate or triethylammonium acetate. In this case, multiple evaporation with water or aqueous ethanol is sufficient to desalt the conjugate isolated by HPLC. However, in some cases protein admixtures cannot be removed by reversed-phase HPLC and gel filtration, and a two-step purification procedure of a conjugate seems to be more reliable, first, by anion-exchange HPLC or electrophoresis in PAAG with subsequent desalting by microcolumn gel filtration or reversed-phase chromatography or ultracentrifugation. The transfer of a conjugate to poly(difluorovinylidene) (PVDF) membrane (blotting) with subsequent determination of the primary

**Table 3.** Isolation of peptide–oligonucleotide conjugates.

| Isolation procedure                                                         | Separation conditions                                                                                                | Detection procedure <sup>a</sup> | Desalting procedure                                                                                                                                                       | Ref.   |
|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|
| <b>Anion-exchange HPLC</b>                                                  |                                                                                                                      |                                  |                                                                                                                                                                           |        |
| Vydac 301VHP552                                                             | 25 mM Et <sub>3</sub> NH <sup>+</sup> AcO <sup>−</sup> , pH 8.0; gradient (0.5 M NaCl): 0% to 60% (40 min)           | SP (215 + 260)                   | reversed-phase chromatography on a cartridge C <sub>18</sub> (Sep-Pak Plus, Waters), precipitation with ethanol                                                           | 87     |
| Mono Q (Amersham-Pharmacia-Biotech)                                         | 50 mM Tris–HCl, 1 mM EDTA, pH 7.5; gradient (1 M NaCl): 0% to 80% (40 min)                                           | RA                               | precipitation with ethanol or gel filtration on a cartridge NAP-10, 10 mM NH <sub>4</sub> HCO <sub>3</sub>                                                                | 79, 88 |
| Sychrom AX 300                                                              | 20 mM NaH <sub>2</sub> PO <sub>4</sub> , pH 6.8, 20% MeCN; gradient (NaCl): 0 (30 min) to 1 M (60 min), 1 M (20 min) | SP (254)                         | —                                                                                                                                                                         | 100    |
| Poros HQ10 (PerSeptive Biosystems)                                          | 10 mM Tris–HCl, pH 7.4; gradient (1 M KCl): 0% (5 min), 0% to 100% (15 min)                                          | SP (260)                         | ultrafiltration (Microsep 3K, Pall-Gelmann Sciences)                                                                                                                      | 81     |
| <b>Gel filtration</b>                                                       |                                                                                                                      |                                  |                                                                                                                                                                           |        |
| Superose 12 (Amersham-Pharmacia-Biotech)                                    | 0.1 M NH <sub>4</sub> HCO <sub>3</sub> , 2 M urea, 1 M NaCl, pH 8.0                                                  | —                                | gel filtration on Sephadex G25 column, 10 mM HEPES, <sup>b</sup> 10 mM NaCl                                                                                               | 12     |
|                                                                             | 20 mM Tris–HCl, 50 mM NaCl, 5 mM EDTA, 8 M urea, pH 7.8                                                              | SP (254)                         | precipitation with ethanol                                                                                                                                                | 205    |
| <b>Reversed-phase HPLC</b>                                                  |                                                                                                                      |                                  |                                                                                                                                                                           |        |
| C <sub>18</sub> , Vydac                                                     | 0.1% CF <sub>3</sub> COOH, 5% MeCN; gradient (MeCN): 5% (30 min), 5% to 45% (120 min), 45% to 90% (20 min)           | SP (220, 260)                    | no desalting                                                                                                                                                              | 205    |
|                                                                             | 10 mM Et <sub>3</sub> NH <sup>+</sup> AcO <sup>−</sup> ; gradient (MeCN): 0% to 30%                                  | SP (254)                         | the same                                                                                                                                                                  | 100    |
| C <sub>18</sub> , Phenomenex                                                | 0.1% HCOOH; gradient (MeCN): 0% to 40%, 20 min                                                                       | MS                               | —                                                                                                                                                                         | 70     |
| μK3C C <sub>2</sub> /C <sub>18</sub> SC 2.1/10 (Amersham-Pharmacia-Biotech) | 5 mM K <sub>2</sub> CO <sub>3</sub> , pH 7.0; gradient (MeCN): 0% to 70%, 50 min                                     | SP(214, 254, 280)                | —                                                                                                                                                                         | 206    |
| <b>Electrophoresis</b>                                                      |                                                                                                                      |                                  |                                                                                                                                                                           |        |
| 10% PAAG                                                                    | —                                                                                                                    | RA                               | no desalting                                                                                                                                                              | 76     |
| 12% PAAG                                                                    | 45 mM Tris–H <sub>3</sub> BO <sub>3</sub> , 1 mM EDTA, 6 M urea, 1 mM HSCH <sub>2</sub> CO <sub>2</sub> H, pH 7.0    | —                                | gel filtration on a column with Sephadex G25, 10 mM NH <sub>4</sub> HCO <sub>3</sub>                                                                                      | 79, 88 |
|                                                                             | 50 mM Tris–H <sub>3</sub> BO <sub>3</sub> , 1 mM EDTA, 8 M urea                                                      | RA                               | elution from the gel with a buffer 20 mM NH <sub>4</sub> HCO <sub>3</sub> , 10% MeCN, pH 8.5, evaporation                                                                 | 37     |
| 20% PAAG                                                                    | 50 mM Tris–H <sub>3</sub> BO <sub>3</sub> , 1 mM EDTA, 8 M urea                                                      | SP                               | elution from the gel with a buffer 10 mM Tris–HCl, 1 mM EDTA, pH 7.5                                                                                                      | 204    |
|                                                                             | 50 mM Tris–H <sub>3</sub> BO <sub>3</sub> , 1 mM EDTA, 8 M urea                                                      | RA                               | elution from the gel with a buffer 45 mM Tris–H <sub>3</sub> BO <sub>3</sub> , 1 mM EDTA, 3 M AcONa, pH 5.5; reversed-phase chromatography on a cartridge C <sub>18</sub> | 98     |
| NuPage 4%–12% MES gel (Novex, Inc.)                                         | —                                                                                                                    | RA                               | transfer to PVDF membrane (Trans-Blot, Bio-Rad Laboratories)                                                                                                              | 77     |
| 15% Tris-Tricin (Novex, Inc.)                                               | —                                                                                                                    | RA                               | transfer to PVDF membrane                                                                                                                                                 | 74     |

<sup>a</sup> Abbreviations: SP, spectrophotometric detection (the wavelengths, nm, are indicated in parenthesis); RA, autoradiographic detection; MS, mass-spectrometric detection. <sup>b</sup> HEPES is 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid.

structure of the peptide in the immobilised NA–peptide complex has been described. The transfer of conjugates onto anion-exchange filters is also used.<sup>207</sup>

The final step includes determination of the primary structure of the covalently bound peptide using chemical or enzymatic sequencing. In some studies,<sup>37, 67, 74, 76, 79, 81, 87, 88, 96, 100, 201, 205</sup> the primary structures of the proteins were determined by sequencing

which included chemical degradation according to Edman.<sup>208</sup> This procedure is usually performed on automatic sequencers, which demands significant amounts of the conjugate (50–150 pmol). The substituted amino acid is determined by the absence of a standard *N*-phenylthiocarbonyl derivative (the so-called ‘blank’ sequencing cycle). In the case of incomplete purification of the conjugate, *i.e.*, when a mixture of oligonucleotide–

peptide conjugates differing in one or two amino acids is present in the solution, the use of this approach is significantly complicated.

An interesting approach to determination of the primary structure of a cross-linked peptide was proposed by Mucke *et al.*<sup>96</sup> These authors carried out a comparative analysis of trypsinolysis products of free restriction endonuclease EcoRII and its conjugate with an oligonucleotide using reversed-phase HPLC. A short protein–nucleic acid conjugate was not absorbed on the column and the ‘extra’ fragment present in the tryptic hydrolysate of the free protein could unambiguously be determined. Sequencing of this peptide allowed identification of the amino acid that reacted with the 5-iodopyrimidine residue of NA. Unfortunately, this method is not versatile, since the presence of several reactive residues in the peptide under study casts doubts on the structure of the conjugate.

Sequencing of peptides can also be performed using mass spectrometry.<sup>209–215</sup> A comparison of several approaches to the determination of substituted amino acids using mass spectrometry has been carried out.<sup>92</sup> Currently, determination of molecular masses and sequencing of biopolymers are usually performed using matrix-assisted laser desorption/ionisation (MALDI)<sup>209</sup> and electrospray ionisation (ESI) mass spectrometry.<sup>210</sup> In MALDI MS, the biomolecule is separated from the neighbouring molecules using matrices, *i.e.*, various low-molecular-mass aromatic compounds excitable under the action of laser irradiation. Irradiation of samples is accompanied by ionisation of a biomolecule with the predominant formation of a single-charged ion. In ESI MS, the solution containing the biopolymer is fed into the ionisation chamber of the mass spectrometer through a capillary. Application of a strong electrostatic field results in the formation of ionised aerosol at the capillary tip. The ionisation of the biopolymer occurs after evaporation of the solvent.

In the analysis of proteins, it is positively charged ions that are registered, while negatively charged ions are recorded in the analysis of oligonucleotides, which is the main problem in the use of MS for the characterisation of protein–nucleic acid conjugates. Nevertheless, some authors believe<sup>216–218</sup> that MALDI MS and ESI MS can be used for detecting and sequencing of these conjugates. The choice of an effective matrix in the sequencing of protein–nucleic acid conjugates by MALDI MS is a central task, since no versatile matrices for the detection of both peptides and oligonucleotides exist. The mass-spectrometric analysis of protein–nucleic acid conjugates by ESI MS is facilitated by removal of the nucleic acid component using enzymatic degradation of NA.<sup>70, 83, 87, 219, 220</sup> The advantage of the ESI MS is the possibility of its application for the analysis of fractions after high-performance liquid chromatography or electrophoresis.

In the study,<sup>92</sup> the structure of a DNA–protein conjugate was determined by mass spectrometry. After partial trypsinolysis of the isolated conjugate, the reaction mixtures were analysed by MALDI TOF (time-of-flight) MS and the data obtained were compared with the analogous data for the free protein. This enabled determination of the peptide fragment covalently bound to DNA. The use of proteinase K instead of trypsin has made it possible to diminish the peptide fragment to four amino acid residues. However, the amino acid covalently bound to the oligonucleotide could only be determined after complete degradation of DNA by phosphodiesterase and alkaline phosphatase and subsequent sequencing of the resulting DNA–protein conjugate by tandem nanoESI MS.<sup>†</sup>

Tandem MS entails the presence of two consecutively arranged detectors with an ionisation chamber in-between. The first detector permits the passage of only ions with a definite mass/charge ratio into the ionisation cell. These undergo fragmentation in the ionisation chamber. The ionisation products (the so-called

daughter ions) pass into the second detector for determination of the primary structure of the peptide. As a rule, this method allows determination of amino acid sequences in proteins containing up to 30 amino acids.

Tandem ESI MS is the most efficient method for the determination of the structures of peptide–oligonucleotide conjugates and, hence, of the target amino acid. The use of tandem nanoESI MS<sup>92</sup> has made it possible to determine the structure of a protein at its content in the solution of about  $10^{-10}$  moles. However, low yields of the conjugates and inevitable losses in numerous intermediate steps require femtomolar amounts of the protein. The sensitivity of mass-spectrometric methods was found to exceed significantly those of traditional sequencing methods based on the Edman procedure, since they permit direct determination of the attached amino acid from its molecular mass (tandem MS) and direct sequencing of both the oligonucleotide and the peptide and do not require thorough purification of the samples.

The use of mass-spectrometric techniques for the determination of the structures of the attached peptides has also been considered elsewhere.<sup>206, 207, 219, 221, 222</sup> However, despite the obvious merits of mass spectrometry in the analysis and determination of structures of peptide–oligonucleotide conjugates, this method has not found wide application due to low accessibility of tandem mass spectrometers.<sup>†</sup>

Hybrid instruments, *e.g.*, quadrupole time-of-flight (Q-TOF) and Fourier-transform ion-cyclotron resonance mass spectrometers,<sup>92</sup> (FTICR) and quadrupole ion traps<sup>92</sup> (QIT), are used along with traditional time-of-flight mass spectrometers with a linear detector designed for the study of biomolecules. The use of FTICR MS ensures a much higher accuracy in the determination of molecular masses ( $> 10$  kDa) in comparison with TOF MS; however, its high cost and complexity of calibration for the analysis of peptide–oligonucleotide conjugates make them unclaimed, at least at present. Mass spectrometers supplied with quadrupole ion traps do not ensure the resolution comparable to that of TOF MS. A more detailed description of various mass-spectrometric techniques used in the study of structures of protein–nucleic acid complexes and conjugates can be found in the reviews.<sup>224–226</sup>

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<sup>†</sup> The prefix ‘nano’ designates that the solution in the capillary is fed at the rate of  $\text{nl s}^{-1}$  (this enables to reduce the amount of the protein and to increase the sensitivity of the detector).

<sup>†</sup> In the past decade, significant investments were made to investigations in the field of proteomics,<sup>223</sup> which made it possible to increase significantly the number of tandem mass spectrometers.



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# Design of supramolecular metal complex catalytic systems for organic and petrochemical synthesis

E A Karakhanov, A L Maksimov, E A Runova

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**Abstract.** The state-of-the-art in investigations into the supramolecular catalysis by metal complexes using macrocyclic receptor molecules is surveyed. The emphasis is placed on issues related to the design of novel metal complex catalysts capable of molecular recognition and to their applications in organic synthesis, in particular, in such reactions as hydrogenation, hydroformylation, carbonylation, hydroxylation, Wacker oxidation, biomimetic oxidation, and some others. The factors affecting the activity, stability and selectivity of such catalytic systems are discussed. The bibliography includes 159 references.

## I. Introduction

Nowadays, the vast majority of industrial processes are based on catalytic reactions. Catalysts are utilised in diverse fields ranging from large-scale processes, such as petroleum refining, hydro-treatment, production of ammonia, *etc.*, to the synthesis of drugs and chemical reagents and sewage and exhaust gas purification. In this respect, catalysis is a key element of technological progress, since development and implementation of new highly efficient and selective catalysts will stimulate production and contribute to the solution of global problems, such as rational exploitation of natural resources and environmental protection.

Although numerous homogeneous and heterogeneous catalysts for oxidation, hydrogenation, hydroformylation, carbonylation, *etc.* are known, these catalysts do not always possess high selectivity for reactions involving substrates with several active sites. Furthermore, if the substrates contain heteroatoms, systems of conjugated bonds and functional groups, the reactions should be carried out under conditions as mild as possible in order to avoid side reactions, *e.g.*, isomerisation or decomposition. Ordinary catalysts often exhibit low activities or selectivities under mild conditions. Metal complex catalysts represent an important alternative.

The application of principles of supramolecular chemistry, which deals with studies of ordered molecular ensembles secured

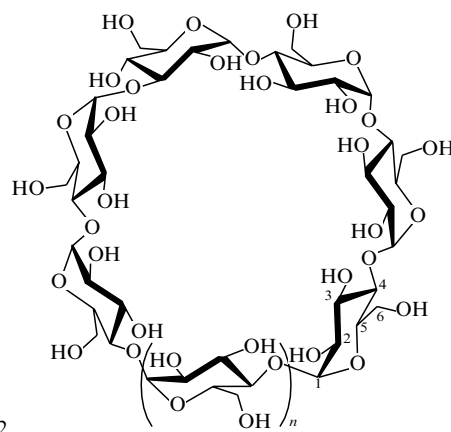
by intermolecular forces,<sup>1–5</sup> to catalysis has an enormous potential in the design of novel highly selective catalysts. The design of compounds capable of molecular recognition of cations, anions or neutral molecules is the main area of progress in the chemistry of molecular ensembles and intermolecular bonding. When such compounds are used as catalysts, the conversion of reactants into reaction products is preceded by formation of a ‘supramolecule’ due to selective binding of a substrate molecule by the respective receptor molecule.<sup>1,6,7</sup> This approach enables development of catalysts whose activity and selectivity is governed by the intermolecular interactions of a substrate with the catalyst.

Among molecules capable of molecular recognition, macrocyclic receptors (*e.g.*, cyclodextrins and calixarenes) are of primary interest. These can form host–guest complexes with substrates due to intermolecular interactions, such as van der Waals forces or H bonds.<sup>1–7</sup> These molecules possess hydrophobic cavities with diverse shapes enabling selective binding of the substrates that match the size and shape of the cavity, which implies molecular recognition.<sup>1,8,9</sup>

The present review is devoted to issues related to the design of novel metal complex catalytic systems containing macrocycles, primarily cyclodextrins and calixarenes.

It is of note that, despite intense development of investigations into supramolecular catalysis,<sup>8</sup> it is only recently that macrocyclic receptor molecules capable of molecular recognition have started to be exploited as components of metal complex catalytic systems, predominantly as models of enzymes.<sup>7,10–13</sup> The number of publications on this subject is relatively small as compared to, for instance, supramolecular catalysis with the use of dendrimers, which has been thoroughly surveyed.<sup>14–20</sup>

Cyclodextrins are cyclic oligomers built up of 1,4-linked D-glucopyranose residues.<sup>21–27</sup>



E A Karakhanov, A L Maksimov, E A Runova Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax (7-095) 932 88 46, tel. (7-095) 939 19 51, e-mail: kar@petrol.chem.msu.ru (E A Karakhanov), tel. (7-095) 939 55 69, e-mail: max@petrol.chem.msu.ru (A L Maksimov), tel. (7-095) 939 15 43, e-mail: runova@petrol.chem.msu.ru (E A Runova)

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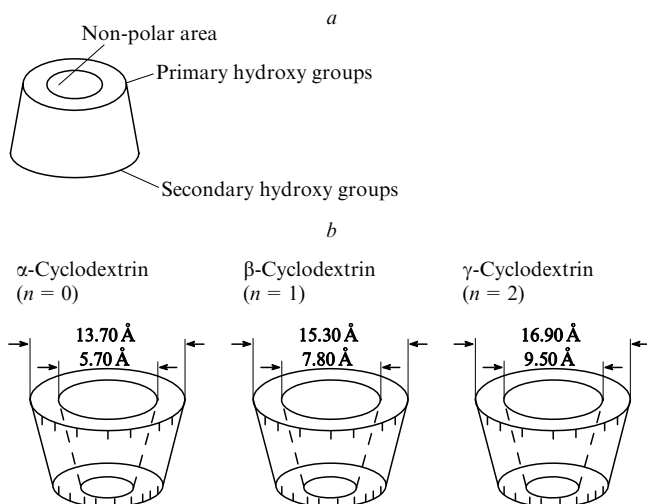


**Figure 1.** The arrangement of the hydroxy groups in cyclodextrins (a), the sizes of cyclodextrin molecules and of their internal cavities (b).

The most common representatives of this class are  $\alpha$ -,  $\beta$ - and  $\gamma$ -cyclodextrins containing, respectively, 6, 7 and 8 glucose residues. The size of the cavity inside the macrocycle increases from 5.7 Å to 9.5 Å on going from  $\alpha$ - to  $\gamma$ -cyclodextrin (Fig. 1). The hydrogen atoms H(3) and H(5) are always directed inward, toward the molecular cavity, whereas the hydroxy groups are directed outward. As a result, a hydrophobic cavity is formed, which is capable of accommodating fragments of molecules with suitable sizes and polarities to yield respective host–guest complexes. In the case of calixarenes, which represent cyclic oligomers of phenol and formaldehyde with different numbers of aromatic units, the non-polar cavity formed by several monomeric units has a bowl-like shape.<sup>28–32</sup> An increase in the number of these units from 4 in calix[4]arene to 8 in calix[8]arene substantially increases the sizes of the macrocycle and the cavity (Fig. 2a). Both cyclodextrins and calixarenes can readily be functionalised with various complex-forming groups, which allows synthesis on their base of metal complex catalysts capable of molecular recognition.

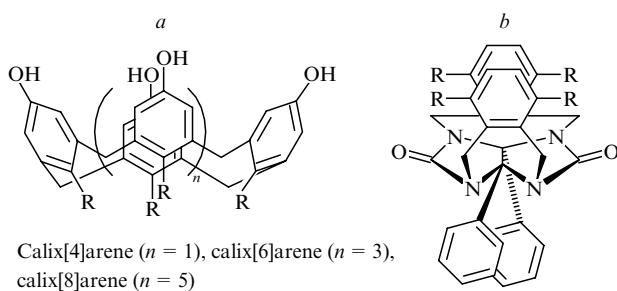


**Figure 2.** Calixarenes (a) and ‘molecular clips’ (b).

A few examples of metal complex catalysts based on other macrocycles, *e.g.*, modified ‘molecular clips’ [synthesised from diphenylglycoluril (Fig. 2b)] and cyclophanes will also be given.

The review is subdivided into two sections. The first considers catalytic systems involving non-coordinated macrocyclic receptors. The second section is devoted to metal complex catalysts where the corresponding receptor molecules act as ligands.

## II. Metal complex catalytic systems based on non-coordinated receptor molecules

Catalytic systems based on metal complexes can include compounds capable of forming host–guest complexes as their components. In the first step, the formation of an inclusion complex of the macrocyclic receptor with either the metal complex or the substrate occurs. Thus, the macrocyclic receptor can affect the mechanism of a catalytic process in two ways that are depicted in Figs 3 and 4.

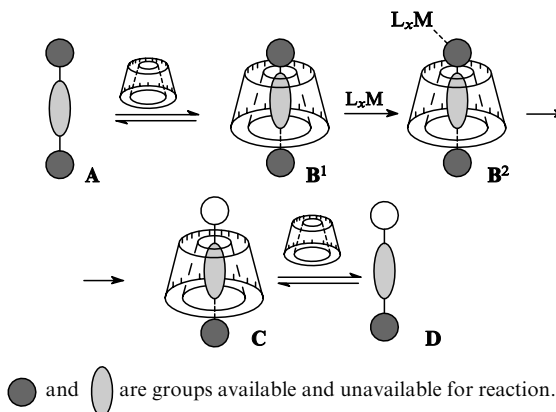


**Figure 3.** Formation of a host–guest complex with the substrate. A is a substrate; B<sup>1</sup> and B<sup>2</sup> are inclusion complexes with the substrate; L<sub>x</sub>M is a metal complex; C is an inclusion complex with the product; D is a reaction product.

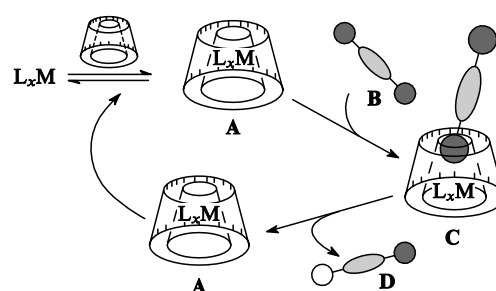


**Figure 4.** Formation of a host–guest complex with the metal complex L<sub>x</sub>M.

A is an inclusion complex, B is a substrate, C is the inclusion compound metal complex–substrate, D is a reaction product.

In the first case, which is postulated in the majority of studies, the substrate inclusion complex rather than the substrate itself is involved in the catalytic cycle. The selectivity of the reaction with respect to the substrate is determined by the stability of the respective host–guest inclusion complex, which in turn depends on the size and structure of the host molecule (see Fig. 3).

The host molecule acts as a ‘microreactor’ and can stabilise the transition state of the reaction thus increasing its rate.<sup>1,6,7</sup> Furthermore, the formation of the inclusion complex can significantly affect the regio- and stereoselectivity of the process by favouring a specific orientation of the substrate (complexes B<sup>1</sup> or B<sup>2</sup>). Some parts of the substrate molecule can be shielded and thus escape reaction. The reaction product can also form an inclusion complex with the receptor (C). This leads to a decrease in the concentration of the receptor molecules and to deceleration of the reaction [the so-called product inhibition effect (see Fig. 3)].

In the second of the two above cases, it is a ligand or the metal complex itself that acts as a guest in the formation of the inclusion complex (see Fig. 4). The role of the macroligand-host can consist of stabilisation of a catalytically active complex and the respective

activated complex or of the ligand environment of the metal atom. The regioselectivity and stereoselectivity of the reaction are governed by the orientation of the substrate in the metal complex.

The stability of the host–guest complex strongly depends on the nature of the solvent used for the reaction. In aqueous media, it is the hydrophobic interactions that make the dominant contribution to the energy of formation of the complex and thus substantially enhance its stability. In this respect, the use of calixarenes and cyclodextrins as components of biphasic catalytic systems based on water-soluble metal complexes is of particular interest.<sup>13, 33–35</sup> An advantage of this approach is that the water-soluble catalyst can easily be separated from insoluble products and recycled.

It should be stressed that the activities of traditional catalysts in the case of substrates poorly soluble in water are low. Owing to the formation of the host–guest inclusion complexes, the macrocyclic receptors can both affect the activity and the selectivity of the reaction and act as phase-transfer carriers of the substrate from an organic medium to the aqueous phase.

### 1. Oxidation

Catalytic systems involving cyclodextrins and calixarenes have been tested for Wacker oxidation, hydroxylation, oxidative coupling and oxidation of hydrocarbons (Table 1).

Biphasic Wacker oxidation of unsaturated compounds to ketones, catalysed by systems based on palladium and copper salts in combination with different cyclodextrins, has been studied.<sup>36–42</sup> In this case, a complex of cyclodextrin and alkene is formed and transferred to the aqueous phase, where the oxidation reaction occurs (Fig. 5).

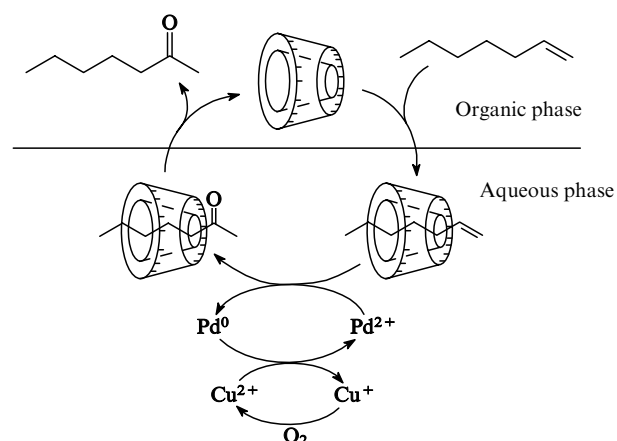


Figure 5. Cyclodextrin-assisted Wacker oxidation of alkenes.

The addition of  $\beta$ -cyclodextrin at the optimum concentration accelerates oxidation of dec-1-ene more than 20-fold.<sup>36, 37</sup> The activity of the catalytic system for the oxidation of linear alkenes and dienes depends on the nature of the cyclodextrin. Generally, systems containing  $\beta$ -cyclodextrin are somewhat more active than those containing  $\alpha$ -cyclodextrin and substantially (by several times) more active than  $\gamma$ -cyclodextrin systems. In particular, the initial rate of the oxidation of dec-1-ene in the case of  $\beta$ -cyclodextrin is virtually the same as in the case of  $\alpha$ -cyclodextrin and more than three times higher than in the case of  $\gamma$ -cyclodextrin.<sup>36</sup>

Table 1. Oxidation and hydroxylation reactions catalysed by systems containing receptor molecules.

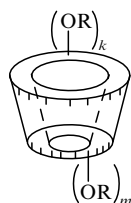
| Catalytic system                                                                                                                                                                          | Reaction                                                                                                                                                                                                                  | Ref.      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
|                                                                                                                                                                                           | Wacker process                                                                                                                                                                                                            |           |
| $\text{Pd}^{2+}/\text{Cu}^{2+}$ or $\text{Pd}^{2+}/\text{Cu}^{2+}/\text{H}_3+\text{n}[\text{PV}_n\text{Mo}_{12-n}\text{O}_{40}]$ ,<br>$n = 1-3$ , non-modified and modified cyclodextrins | $\text{R}-\text{CH}=\text{CH}_2 \xrightarrow{\text{H}_2\text{O}, \text{O}_2} \text{R}-\text{C}(=\text{O})\text{CH}_3$                                                                                                     | 36–44     |
| $\text{Pd}^{2+}/\text{Cu}^{2+}$ , water-soluble calixarenes                                                                                                                               | $\text{R}-\text{CH}=\text{CH}_2 \xrightarrow{\text{H}_2\text{O}, \text{O}_2} \text{R}-\text{C}(=\text{O})\text{CH}_3$                                                                                                     | 34, 45–47 |
|                                                                                                                                                                                           | Hydroxylation                                                                                                                                                                                                             |           |
| $\text{Fe}^{3+}$ , oxyethylated $\beta$ -cyclodextrin                                                                                                                                     | $\text{R}-\text{C}_6\text{H}_4 \xrightarrow{\text{H}_2\text{O}_2} \text{R}-\text{C}_6\text{H}_4\text{-OH}$<br>$\text{R} = \text{H}, \text{OH}$                                                                            | 34, 48–50 |
| Iron(III) tetrakis(n-hexadecyloxyphenyl)-<br>porphyrinate chloride, $\beta$ -cyclodextrin<br>and 2,6-dimethyl- $\beta$ -cyclodextrin                                                      | $\text{Cyclohexane} \xrightarrow{\text{PhIO}} \text{Cyclohexanol}$                                                                                                                                                        | 51        |
| Iron(III) tetrakis(n-hexadecyloxyphenyl)-<br>porphyrinate chloride, $\beta$ -cyclodextrin<br>and 2,6-dimethyl- $\beta$ -cyclodextrin                                                      | $\text{1-octanol} \xrightarrow{\text{PhIO}} \text{2-octanol} + \text{3-octanol} + \text{4-octanol}$                                                                                                                       | 51        |
|                                                                                                                                                                                           | Oxidation                                                                                                                                                                                                                 |           |
| $\text{Fe}^{3+}$ , $\beta$ -cyclodextrin                                                                                                                                                  | $\text{R}-\text{C}_6\text{H}_4 \xrightarrow{\text{H}_2\text{O}_2} \text{R}-\text{C}_6\text{H}_4\text{-C}(=\text{O})\text{H}$                                                                                              | 52        |
| $\text{Fe}^{3+}$ , $\beta$ -cyclodextrin                                                                                                                                                  | $\text{Cyclohexyl-O(CH}_2)_3\text{NMe}_2 \xrightarrow{\text{H}_2\text{O}_2} \text{Cyclohexyl-C(=O)-O(CH}_2)_3\text{NMe}_2 + \text{Cyclohexyl-C(=O)H-O(CH}_2)_3\text{NMe}_2$<br>$\text{Y} = \text{O}, \text{H}, \text{OH}$ | 52        |
|                                                                                                                                                                                           | Oxidative coupling                                                                                                                                                                                                        |           |
| $\text{Fe}^{3+}$ , $\alpha$ - or $\gamma$ -cyclodextrin                                                                                                                                   | $\text{R}-\text{C}_6\text{H}_4 \xrightarrow{\text{H}_2\text{O}_2} \text{R}-\text{C}_6\text{H}_4\text{-C(=O)-C(=O)-C}_6\text{H}_4\text{-R}$<br>$n = 1, 2$                                                                  | 53        |

Presumably, the difference in the activity is due to different stabilities of the respective host–guest inclusion complexes with the substrates. For  $\alpha$ -cyclodextrin, complex formation is hampered by the relatively small volume of its cavity; for  $\gamma$ -cyclodextrin, the entrance to the cavity is too wide such that the resultant complex becomes unstable.<sup>43</sup>

It should be emphasised that the oxidation in the cases where terminal alkenes and isomeric alkenes with internal double bonds were present in the reaction mixture proceeded regioselectively: methyl ketones were the single carbonyl products. The rate of oxidation of non-terminal alkenes is too low due to the structure of the respective inclusion complexes: for such substrates, the double bond occurs inside the cyclodextrin cavity and thus is unavailable for reaction.<sup>36, 38–40</sup> Isomeric ketones were detected as the oxidation products of dec-1-ene in the presence of  $\alpha$ - or  $\gamma$ -cyclodextrins only where the reaction was conducted in a homogeneous solution (water–propan-2-ol), *i.e.*, when no formation of the inclusion complexes occurred.<sup>36</sup>

The substrate selectivity has been revealed for the oxidation of a number of linear alkenes in the presence of the catalytic systems listed in Table 1.<sup>38, 39</sup> In the case of systems containing  $\alpha$ -cyclodextrin, the maximum reactivity at atmospheric pressure of oxygen was found for non-1-ene whereas the system based on  $\beta$ -cyclodextrin is most active towards dec-1-ene.<sup>40</sup> Apparently, these two substrates provide the optimum matches to the sizes of the respective cyclodextrin molecules. This suggestion is further supported by data on the stability of complexes of  $\beta$ -cyclodextrin with linear alcohols: the complex with decan-1-ol is the most stable.<sup>44</sup> At elevated oxygen pressures, hept-1-ene manifested the highest rate of oxidation among alkenes studied.<sup>42</sup> With an increase in the cyclodextrin concentration, the reaction rate first abruptly increases and then remains virtually constant, which could be due to diffusion-limited formation of the complex.<sup>35</sup>

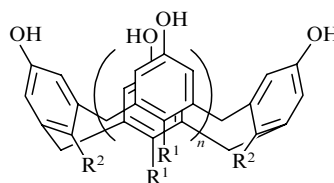
The rate of substrate interphase transfer can be substantially increased if modified  $\beta$ -cyclodextrins are used, in which methyl [2,6-dimethyl- $\beta$ -cyclodextrin (**1**)] or hydroxypropyl (the compounds **3**, **4**) groups substitute some of the hydrogen atoms of the hydroxy groups.<sup>35, 39</sup>



R = Me:  $k + m = 14$  (**1**),  $k + m = 21$  (**2**);  
 R =  $\text{CH}_2\text{CH}(\text{OH})\text{Me}$ :  $k + m = 4$  (**3**), **6** (**4**);  
 R =  $\text{SO}_3^- \text{Na}^+$ :  $k + m = 6$  (**5**);  
 R = Ac:  $k + m = 6$  (**6**), **14** (**7**), **21** (**8**);  
 R =  $(\text{CH}_2\text{CH}_2\text{O})_n\text{H}$ :  $k + m = 8$ ,  $n = 2-5$  (**9**);  
 R =  $\text{CH}_2\text{CH}_2\text{OH}$ :  $k + m = 5$  (**10**).

This gives rise to enhanced activity with retention of the substrate selectivity. The maximum activity with respect to oxidation of alkenes was observed for the system containing  $\beta$ -cyclodextrin **1**, which is well soluble in water and partly soluble in organic solvents thus providing fast phase transfer of the substrate. If respective sulfate (**5** (which is insoluble in the organic phase) is used instead of  $\beta$ -cyclodextrin, the activity drops. Similar results were obtained for permethylated  $\beta$ -cyclodextrin **2** and partially or fully acylated  $\beta$ -cyclodextrins **6–8** that are virtually insoluble in water. A decrease in the binding constant of a methyl ketone, *i.e.*, the reaction product, to the respective cyclodextrins is yet another factor that enhances the activity of catalytic systems containing substituted cyclodextrins. Indeed, no additional stabilisation of the complex of substituted cyclodextrins with the reaction product is possible, whereas for non-substituted cyclodextrins it is achieved through the H-bonding with the hydroxy groups.<sup>35, 41</sup>

The catalytic activity of water-soluble sulfonated and glycidylated calixarenes **11–15** in the Wacker oxidation of alk-1-enes has also been studied<sup>34, 45, 46</sup>



R<sup>1</sup> = R<sup>2</sup> =  $\text{SO}_3^- \text{Na}^+$ :  $n = 1$  (**11**), **3** (**12**), **5** (**13**);  
 R<sup>1</sup> = R<sup>2</sup> =  $(\text{CH}_2\text{CH}_2(\text{OH})\text{CH}_2\text{O})_m$ :  $n = 1$ ,  $m = 2-4$  (**14**),  
 $n = 3$ ,  $m = 2-4$  (**15**); R<sup>1</sup> = R<sup>2</sup> =  $\text{CH}_2\text{NMe}_2$ :  $n = 1$  (**16**);  
 R<sup>1</sup> =  $\text{CH}_2\text{NMe}_2$ , R<sup>2</sup> = Bu<sup>t</sup>:  $n = 3$  (**17**), **1** (**18**).

These systems are characterised both by high chemoselectivity (as regards formation of the respective methyl ketones) and substrate selectivity, which is governed by the correspondence between the sizes of the cavity within the host molecule and the substrate molecule, as for cyclodextrins considered above. In the oxidation of hex-1-ene, the reaction rate is a maximum in the case of water-soluble calix[4]arenes **11** and **14** and calix[8]arene **13**. Similarly, in the oxidation of oct-1-ene, calix[6]arenes **12** and **15** were the most active (Fig. 6).<sup>47</sup> The catalytic activity correlates with the stability constants of the respective host–guest complexes.<sup>44</sup>

| Calixarene                                             | Stability constant ( $k_s$ ) / litre mol <sup>-1</sup> |           |
|--------------------------------------------------------|--------------------------------------------------------|-----------|
|                                                        | hex-1-ene                                              | oct-1-ene |
| Tetrasodium calix[4]arene-tetrasulfonate ( <b>11</b> ) | 280                                                    | 50        |
| Hexasodium calix[6]arene-hexasulfonate ( <b>12</b> )   | 20                                                     | 85        |

In the oxidation of different styrenes, the maximum yield of products was observed where the size of the substrate matched the size of the calixarene cavity: *p*-methylstyrene is the optimum substrate for calix[6]arene **12** whereas styrene is the optimum for calix[4]arene **11**.<sup>47</sup>

Modified  $\beta$ -cyclodextrins have been used as components of catalytic systems for the oxidation of aromatic hydrocarbons. Hydroxylation of benzene with hydrogen peroxide, catalysed by iron ions in a phase-transfer system containing  $\beta$ -cyclodextrin, gave rise to phenol in 29% yield. The yield increased to 69% with

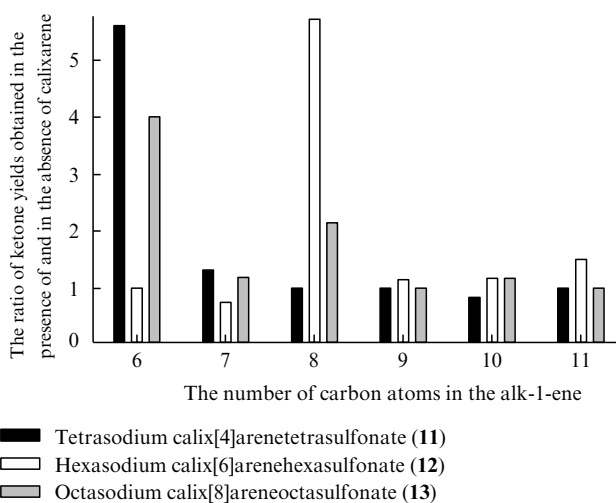


**Figure 6.** The substrate selectivity of the catalytic system  $\text{PdSO}_4\text{--CuCl}_2\text{--water-soluble calixarene}$  in the Wacker oxidation as a function of the nature of the calixarene and the number of carbon atoms in the alk-1-ene.<sup>44</sup>



oxyethylated  $\beta$ -cyclodextrin **9**, which is well soluble both in water and benzene.<sup>34, 48–50</sup>

Upon similar hydroxylation of phenol in the system dichloroethane–water, products with the hydroxy group in the *para*-position, *i.e.*, quinone and hydroquinone, are predominantly formed. The selectivity of hydroquinone formation was >95% with oxyethylated cyclodextrin. The reaction proceeds through the host–guest complexes,<sup>50, 54–57</sup> in which all the carbon atoms of the benzene ring except for that at the *para*-position are shielded, which results in the high selectivity (Fig. 7). Oxidation of alkyl-substituted aromatic hydrocarbons in the presence of oxyethylated cyclodextrins involves the alkyl groups yielding the corresponding ketones as the major products. In these cases, the whole aromatic moiety in the host–guest complexes is shielded against attack, and the reaction has been used in the synthesis of (hydroxyphenyl)acetic acids.<sup>58</sup>

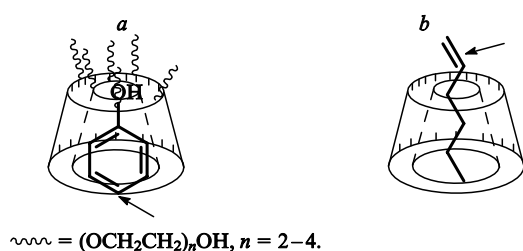


**Figure 7.** Orientation of the phenol molecule in the cavity of cyclodextrin **9** in the hydroxylation (a) and orientation of the hex-1-ene molecule in the cavity of  $\beta$ -cyclodextrin upon oxidation by PhIO (b). The arrows indicate positions available to attack by the active species.

It has been shown that the formation of host–guest complexes with cyclodextrin can also affect the direction of the oxidative oligomerisation of alkylphenol derivatives.<sup>51</sup> In particular, in the

oxidation of *p*-cresol by iron ions, the addition of  $\alpha$ -cyclodextrin substantially increases the yield of a trimer whereas the addition of  $\gamma$ -cyclodextrin favours formation of a dimer. In the latter case, the complex of the dimer and  $\gamma$ -cyclodextrin is insoluble in the reaction medium, which prevents further oligomerisation.

In the oxidation of cyclohexane by a PhIO–iron(III)tetrakis(n-hexadecyloxyphenyl)porphyrin chloride catalytic system, the yield of cyclohexanol (relative to the oxidant consumed) increased from 0.8% to 9% and 14% upon addition of  $\beta$ -cyclodextrin and methylated cyclodextrin **1**, respectively.

In the oxidation of n-hexane by the same catalytic system, an abrupt increase in the comparative reactivity of the methyl groups was observed. This was explained by partial shielding of the secondary C–H groups of the substrate in the host–guest complex that is formed in a biphasic system. The relative reactivity per terminal C–H bond in benzene as a solvent is 0.01 [the unity reactivity corresponds to that of the C(3)–H bond in hexane], whereas the use of catalytic systems containing  $\beta$ -cyclodextrin or 2,6-dimethyl- $\beta$ -cyclodextrin increases this reactivity up to 0.59 and 0.77, respectively.<sup>52</sup>

The oxidation of bicyclic [1-benzyl-1-(3-dimethylamino-propoxy)cycloheptane fumarate] represents yet another example of the influence of  $\beta$ -cyclodextrin on the reaction selectivity.<sup>53</sup> Only C–H bonds of the cycloheptane ring in the molecule undergo oxidation in the presence of  $\beta$ -cyclodextrin whereas the aromatic moiety, being incorporated in a host–guest complex, is shielded and thus does not react. In a biphasic water–substrate system, the ratio of *cis*- and *trans*-isomers of  $\gamma$ -hydroxybicyclic is 7 : 1, while without the receptor, the respective ratio is  $\sim 1 : 1$ . Presumably, this increase in the stereoselectivity is due to specific orientation of the substrate in the inclusion complex.

## 2. Reactions with hydrogen and carbon monoxide

Receptor molecules were also employed as components of metal complex catalytic systems for such reactions as hydrogenation, hydroformylation and hydrocarboxylation (Table 2).

**Table 2.** Catalytic systems containing receptor molecules for reactions with hydrogen and carbon monoxide.

| Catalytic system                                                                                                        | Starting compound | Reagent             | Reaction product                                                    | Ref.      |
|-------------------------------------------------------------------------------------------------------------------------|-------------------|---------------------|---------------------------------------------------------------------|-----------|
| Hydrogenation                                                                                                           |                   |                     |                                                                     |           |
| [(1,3-HD)RhCl <sub>2</sub> ] <sub>2</sub> – $\beta$ -cyclodextrin                                                       |                   | H <sub>2</sub>      | ArCH <sub>2</sub> CH <sub>2</sub> R                                 | 59–61     |
| RuCl <sub>3</sub> –TPPTS–NaI                                                                                            | RC(O)H            | H <sub>2</sub>      | RCH <sub>2</sub> OH                                                 | 60, 61    |
| RhCl <sub>3</sub> –TPPTS– $\beta$ -cyclodextrin                                                                         |                   | H <sub>2</sub>      | RCH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H                  | 62        |
| CoCl <sub>2</sub> –KCN–KCl–KOH– $\beta$ -cyclodextrin                                                                   |                   | H <sub>2</sub>      | R <sup>1</sup> CH <sub>2</sub> CH <sub>2</sub> CH(OH)R <sup>2</sup> | 63        |
| [Rh(COD)Cl] <sub>2</sub> –chiral amine– $\beta$ -cyclodextrin                                                           |                   | H <sub>2</sub>      |                                                                     | 64        |
|                                                                                                                         |                   | H <sub>2</sub>      |                                                                     | 64        |
|                                                                                                                         |                   | H <sub>2</sub>      |                                                                     | 65        |
|                                                                                                                         |                   | H <sub>2</sub>      |                                                                     | 66        |
|                                                                                                                         |                   |                     |                                                                     |           |
| Hydroformylation                                                                                                        |                   |                     |                                                                     |           |
| H(CO)Rh(TPPTS) <sub>3</sub> , modified $\beta$ -cyclodextrins                                                           |                   | CO + H <sub>2</sub> |                                                                     | 35, 67–70 |
| Rh <sub>2</sub> ( $\mu$ -SBu <sup>t</sup> ) <sub>2</sub> (CO) <sub>2</sub> (TPPTS) <sub>2</sub> , $\beta$ -cyclodextrin |                   | CO–H <sub>2</sub> O |                                                                     | 35, 71–74 |
| H(CO)Rh(TPPMS) <sub>3</sub> , $\alpha$ -cyclodextrin                                                                    |                   | CO–H <sub>2</sub> O |                                                                     | 72–74     |
| PdCl <sub>2</sub> –TPPTS, modified cyclodextrins                                                                        |                   | CO–H <sub>2</sub> O |                                                                     | 72–74     |

**Note.** 1,3-HD is cyclohexa-1,3-diene, COD is cycloocta-1,5-diene, TPPTS is trisodium tris(*m*-sulfophenyl)phosphine, TPPMS is monosodium (*p*-sulfophenyl)diphenylphosphine.

The use of supramolecular catalytic systems for selective hydrogenation and reduction of substrates containing functional groups (*e.g.*, alcohols, aromatic carbonyl compounds, linear aldehydes, dienes, *etc.*) enhanced the activity of metal complex catalytic systems and selectivity of the reactions.<sup>59–72</sup>

Hydrogenation of aromatic aldehydes and ketones by hydrogen in THF in the presence of rhodium(hexa-1,3-diene) chloride results in complete deoxygenation to yield alkylbenzenes. The addition of  $\beta$ -cyclodextrin accelerates the process more than fourfold and enhances the selectivity of hydrocarbon formation.<sup>59</sup> It was demonstrated<sup>75</sup> that alkyl aryl ketones form 1 : 1 inclusion complexes with  $\beta$ -cyclodextrins. In these complexes, the benzene ring is located inside the cavity and thus is protected from the attack by the reagent. This leads to enhanced selectivity of the reaction of the carbonyl group. If  $\alpha$ -cyclodextrin is used instead, the reaction rate drops due to the low stability of the complexes formed by this receptor with aromatic ketones in THF.

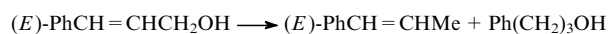
Similar effects were observed in the hydrogenation of aromatic ketones catalysed by Ir/Al<sub>2</sub>O<sub>3</sub> and Pt/C.<sup>76,77</sup> In these cases, the addition of  $\beta$ -cyclodextrin to the catalytic system abruptly decreased the yield of the hydrogenation product of the aromatic fragment. Hydrogenation of substituted pyridines catalysed by Pd/C is also decelerated in the presence of cyclodextrins.<sup>78</sup>

The rate of reduction of normal aldehydes by formate anions in the presence of ruthenium(II), rhodium(I) or iridium(I) complexes with sulfonated triphenylphosphine ligands is abruptly decreased upon addition of  $\beta$ -cyclodextrin, which is explained by steric hindrance associated with formation of the inclusion complexes of the aldehyde with cyclodextrin.<sup>60</sup> However, in the case of hydrogenation of the same aldehydes by hydrogen in biphasic systems (water–aldehyde) catalysed by ruthenium complexes with trisodium tris(*m*-sulfophenyl)phosphine (TPPTS), the addition of cyclodextrin significantly increases the yield of the product, *i.e.*, normal alcohol, as in the case of the aforementioned Wacker oxidation. Substituted  $\beta$ -cyclodextrins, *viz.*, hydroxypropyl- (**3**, **4**), hydroxyethyl- (**10**) and 2,6-dimethylcyclodextrins (**1**) are even more active. The latter compound provides the maximum reaction rate, which was explained by the lowest stability of the complex with the reaction product and faster formation of the host–guest complexes.<sup>61,62</sup>

The RhCl<sub>3</sub>–TPPTS system containing  $\beta$ -cyclodextrin is highly active in the hydrogenation of unsaturated acids in aqueous media. The use of  $\beta$ -cyclodextrin both accelerates the reaction and affects its selectivity due to structural features of the inclusion complexes formed. For instance, complete reduction of maleic and fumaric acids in the absence of  $\beta$ -cyclodextrin required 83 h and 104 h, respectively. Meanwhile, in the presence of cyclodextrin, 100% conversion of maleic acid was achieved in 17 h whereas the level of conversion of fumaric acid was still as low as 45% after 96 h. Hydrogenation of acrylic acid was slower than that of cinnamic acid in the absence of cyclodextrin. The opposite situation was observed after the receptor was added to the catalytic system. Presumably, this difference was due to formation of the inclusion complex, where the double bond of the substrate is located inside the cyclodextrin cavity and the active rhodium sites interact with the hydroxy groups of the host molecule. This suggestion also explains the fact that the difference in the hydrogenation rates for the two substrates is substantially decreased if methylated cyclodextrin **1** is used instead of  $\beta$ -cyclodextrin. Furthermore, the degree of hydrogenation of cinnamic acid using the catalytic system containing  $\beta$ -cyclodextrin was 2% after 50 h as compared to 80% after 24 h in the case of cyclodextrin **1**.<sup>63</sup>

Lee and Alper showed<sup>64</sup> that the use of cyclodextrins for the reduction of allylic alcohols to alkenes by hydrogen, catalysed by a system containing aqueous potassium hydroxide and the complex HCo(CN)<sub>5</sub><sup>3–</sup> generated *in situ*, allows one to significantly increase the activity of the catalyst and change the selectivity of the reaction. Without cyclodextrin, a mixture of *cis*- and *trans*-alkenes is obtained whereas *trans*-isomers are exclusively produced in its

presence. However, in the case of those allylic alcohols that should yield terminal alkenes, virtually no reaction occurs. Presumably,<sup>64</sup> the *trans*-selectivity of the reaction is due to formation of a host–guest complex of cyclodextrin and the catalytically active anion HCo(CN)<sub>5</sub><sup>3–</sup>, with subsequent reaction inside the cavity of cyclodextrin. Thus, it represents one of a few examples of a reaction proceeding according to the scheme depicted in Fig. 4. As in the previous cases, the activity of the system depends on the size of the cyclodextrin ring. The yields (%) of the reduction products of cinnamic alcohol in the presence and in the absence of cyclodextrins are listed below.



|                        |    |    |
|------------------------|----|----|
| No cyclodextrin        | 62 | 12 |
| $\alpha$ -Cyclodextrin | 70 | 26 |
| $\beta$ -Cyclodextrin  | 80 | 11 |
| $\gamma$ -Cyclodextrin | 3  | 15 |

Hydrogenation of dienes in a water–benzene system, like reduction of allylic alcohols, yields only *trans*-alkenes, the reaction occurs mainly as 1,2-addition due to shielding of one of the double bonds in the inclusion complex.<sup>65</sup> Hydrogenation of  $\alpha,\beta$ -unsaturated carboxylic acids and of their derivatives gives rise to the products of the C=C bond reduction.<sup>66</sup> It is noteworthy that the use of catalytic systems containing  $\beta$ -cyclodextrin made it possible to achieve high yields of reduction products in the cases of acrylic acid (81%) and methacrylonitrile (80%). Furthermore, in these cases, no dimerisation occurred due to the formation of the inclusion complexes.

Asymmetric hydrogenation of  $\alpha$ -keto esters to *R*-isomers of  $\alpha$ -hydroxy esters is catalysed by a complex of *N,N'*-dimethyl-(1*R*,2*R*)-diphenylethylenediamine with rhodium cyclooctadiene chloride.<sup>71</sup> The addition of  $\beta$ -cyclodextrin to the catalytic system enhances both the reaction rate and the selectivity. It was suggested<sup>71,79</sup> that it is the complex of cyclodextrin and the substrate that reacts; this changes the polarity of the micro-environment and increases the yield of the *R*-product.

The addition of cyclodextrins to catalytic systems containing TPPTS and palladium dichloride substantially increases the rate of hydrocarboxylation of alkenes by carbon monoxide in aqueous media.<sup>35,72</sup> A comparison of different modified cyclodextrins as regards their activities in the hydrocarboxylation of dec-1-ene showed that hydroxypropyl- (**3**, **4**) and poly(oxyethyl)cyclodextrin (**9**) are nearly as active as  $\beta$ -cyclodextrin. Meanwhile, the activity and selectivity of methylated cyclodextrin **1**, as in other reactions studied, were significantly higher. In all cases, the effect of inhibition by the reaction product was observed due to the formation of H bonds between the carboxy group of the substrate and the oxygen atoms of cyclodextrin.<sup>35</sup>

In the example of the hydroformylation reaction catalysed by rhodium complexes in biphasic systems, it was shown that the influence of cyclodextrin on the reaction rate and selectivity can differ substantially depending on the structure of the host–guest complex involved. In the case of the hydroformylation of hex-1-ene by a rhodium complex with monosulfonated triphenylphosphine [(4-NaO<sub>3</sub>SC<sub>6</sub>H<sub>4</sub>)Ph<sub>2</sub>P], *viz.*, HRh(CO)(TPPMS)<sub>3</sub>, the addition of  $\alpha$ -cyclodextrin gives rise to a decrease in the yield of aldehydes from 55% to 11%.<sup>72</sup> A similar effect was observed upon addition of  $\alpha$ -cyclodextrin to the catalytic system based on the complex HRh(CO)(PPh<sub>3</sub>)<sub>3–n</sub>(TPPMS)<sub>n</sub>. Presumably,<sup>67</sup> in this case, a complex of cyclodextrin with TPPMS is formed, which inhibits the reaction.

In contrast, in the hydroformylation catalysed by a rhodium complex with trisulfonated phosphine (TPPTS), the addition of  $\beta$ -cyclodextrin, acylated cyclodextrin **7** or 2,6-dimethylcyclodextrin **1** increased the yield of aldehydes from 6% to 19%, 45% or even 80%, respectively.<sup>35,68–70</sup> The selectivity of aldehyde formation is also enhanced from 60% (without cyclodextrin) to 95% (in the presence of cyclodextrin **1**). This system also manifests the substrate selectivity related to different stabilities of the respective

inclusion complexes: the reaction rate in the case of dec-1-ene is significantly higher than that for undec-1-ene or dodec-1-ene. Vinylcyclohexane, styrene, propenyl- and butenylbenzenes react faster than *n*-alkenes. Finally, alkenes with an internal double bond are virtually inert in this reaction since such a bond is shielded in the inclusion complex.

The increase in the activity of the catalytic system Rh–TPPTS in hydroformylation upon addition of cyclodextrins is explained by the formation of not only host–guest complexes of the substrate with the receptor molecule, but of analogous complexes of  $\beta$ -cyclodextrin with TPPTS as well.<sup>35,80</sup> The existence of the latter complexes was confirmed by several methods.<sup>73,81–84</sup> The stability constant of the complex is  $7110 \text{ M}^{-1}$  at 298 K and decreases to  $610 \text{ M}^{-1}$  with an increase in temperature to 348 K. In the case of cyclodextrin **1**, the stability constant of the 1 : 1 complex with TPPTS is  $2800 \text{ M}^{-1}$  (see Refs. 82, 84). Structural studies of these complexes revealed that the phosphorus atom therein is arranged in a way that prevents its coordination to the metal ion. The addition of cyclodextrin changes the equilibrium between the rhodium complexes in the solution thus facilitating formation of the complex with an alkene, which leads to acceleration of the reaction. It is of note that this effect is weakened with an increase in the concentration of TPPTS. Meanwhile, the activity of the catalytic system significantly increases with an increase in the concentration of cyclodextrin up to a cyclodextrin : rhodium molar ratio of 30 : 1. It was shown that at elevated temperatures, the reaction rate is limited by diffusion of the inclusion complex into the aqueous phase. The activation energy of the reaction above  $60^\circ\text{C}$  is slightly more than  $5 \text{ kJ mol}^{-1}$  (see Ref. 80).

In the hydroformylation of alkenes catalysed by  $\text{Rh}_2(\mu\text{-SBU})_2(\text{CO})_2(\text{TPPTS})_2$ , the addition of  $\beta$ -cyclodextrin to the catalytic system significantly increases their conversion into aldehydes but decreases the fraction of linear isomers.<sup>74</sup> In particular, the selectivity with respect to *n*-nonanal is 98% in the absence of cyclodextrins and decreases to 76% in the presence of  $\beta$ -cyclodextrin. With cyclodextrin **1**, the selectivity with respect to *n*-nonanal under identical conditions is 92%.

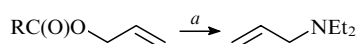
The decrease in the selectivity was rationalised assuming specific orientation of the substrate in the cavity of cyclodextrin, which favours an attack on the terminal  $\text{CH}_2$  groups of the alkene by the rhodium hydride species.<sup>74,85</sup> If cyclodextrin **1** was used, the rates of the hydroformylation were equally high for alkenes  $\text{C}_8\text{--C}_{12}$ .<sup>84,85</sup>

It should be noted that the rate of hydroformylation in the presence of  $\beta$ -cyclodextrin decreases with an increase in the number of carbon atoms in the alkene (the rate for dodec-1-ene was only 2% of the value observed for oct-1-ene).

In the case of cyclodextrin **1**, the activity of the catalytic system in an aqueous phase increases upon repetitive use. Dessoudeix *et al.*<sup>85</sup> explained this fact by the formation of supramolecular associates composed of two cyclodextrin molecules and the active rhodium complex in the solution.

### 3. Miscellaneous reactions

Decomposition of allyl carbonates catalysed by palladium complexes with sulfonylated triphenylphosphine in the presence of various modified cyclodextrins has been studied by Monflier and co-workers<sup>86,87</sup>

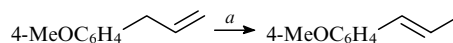


(a)  $\text{Pd(OAc)}_2$ –TPPTS, modified cyclodextrins,  $\text{NEt}_3$ ,  $\Delta$ .

The activity of these catalytic systems is several times higher than that of systems containing unsubstituted  $\beta$ -cyclodextrin. The maximum activity was found for the system containing methylated cyclodextrin **1**, then the activity decreases in the following series: permethylated  $\beta$ -cyclodextrin **2**, hydroxypropyl- (**3**, **4**) and hydroxyethyl- $\beta$ -cyclodextrin **10**. For this reaction, the depend-

ence of the reaction rate on the substrate structure was elucidated in detail. It was found that, among alkyl allyl carbonates with linear substituents, the maximum activity is manifested by the derivative having 12 carbon atoms in the alkyl chain. For allyl decyl and allyl dodecyl carbonates it was shown that the introduction of additional methyl groups into the alkyl radical virtually did not affect the reaction rate whereas the introduction of bulkier substituents decelerated the reaction. The activity of allyl  $\beta$ -naphthylbenzyl carbonate was two times higher than that of allyl  $\alpha$ -naphthylbenzyl carbonate; a similar situation was observed for allyl *p*-phenylbenzyl carbonate in comparison with allyl *o*-phenylbenzyl carbonate. These results can be rationalised in terms of correspondence between sizes of the cyclodextrin cavity and of the substrate molecule.<sup>87</sup>

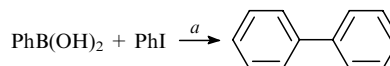
Isomerisation of *p*-allylanisole to anethole catalysed by iridium trichloride in a water–substrate system was studied by Barak *et al.*<sup>88</sup> The addition of either  $\alpha$ - or  $\beta$ -cyclodextrin led to acceleration of isomerisation several-fold and to a decrease in the energy of activation of the process. Presumably, a complex of iridium trichloride with the substrate and cyclodextrin is formed in this case.



(a)  $\text{IrCl}_3$ – $\beta$ -cyclodextrin.

Hydrosilylation of alkenes on platinum- or palladium-containing catalysts represents yet another example of an increase in the product yield upon addition of  $\beta$ -cyclodextrin to a catalytic system. Thus, the rate of hydrosilylation of styrene by triethoxysilane or trimethylvinylsilane on Pt catalysts is increased in the presence of  $\beta$ -cyclodextrin by a factor of two and more than three, respectively. In the case of Pd-containing catalysts, the rate of the last mentioned reaction is negligibly low. The increase in the reaction rate can be explained by stabilisation of the transition state due to the formation of the host–guest complex. These reactions are nearly completely inhibited by decane, which itself forms stable complexes with  $\beta$ -cyclodextrin.<sup>89</sup>

Water-soluble calixarenes (**11**, **12**, **16–18**) and  $\beta$ -cyclodextrin have been tested as components of catalytic systems for the cross-coupling of iodobenzene with phenylboronic acid (the Suzuki reaction), catalysed by a palladium complex with sulfonylated triphenylphosphine.<sup>90</sup>



(a)  $\text{PdCl}_2$ –TPPTS,  $\beta$ -cyclodextrin or modified calixarenes.

The addition of the receptors increased the yield of biphenyl more than twofold. Amino-containing calixarenes manifested the maximum activity. The stability constants for the respective inclusion complexes as well as the rates of their formation were substantially higher than those for non-substituted calixarenes (Table 3).

**Table 3.** The stability constants ( $k_s$ ) of calixarene complexes with iodobenzene and yields of products in the Suzuki reaction.<sup>90</sup>

| Calixarene                                                           | $k_s$ of the 'guest–host' complex / $\text{M}^{-1}$ | Relative yield |
|----------------------------------------------------------------------|-----------------------------------------------------|----------------|
| Tetrasodium calix[4]arene-tetrasulfonate ( <b>11</b> )               | 60                                                  | 2.4            |
| Hexasodium calix[6]arene-hexasulfonate ( <b>12</b> )                 | 56                                                  | 2.9            |
| Tetrakis( <i>p</i> -dimethylamino-methyl)calix[4]arene ( <b>16</b> ) | 402                                                 | 5.8            |

**Note.** Relative to the yield obtained in the absence of the receptor molecule.

### III. Catalysis by metal complexes with ligands based on receptor molecules

The catalysts that combine, within one molecule, properties of a metal complex and a phase-transfer reagent together with capabilities of molecular recognition, attract special attention from researchers.<sup>12, 13, 23, 26</sup> Such catalysts include a metal centre and a ligand containing one or several macrocyclic receptors (*e.g.*, cyclodextrin, calixarene, *etc.*) (Fig. 8).<sup>91–93</sup>

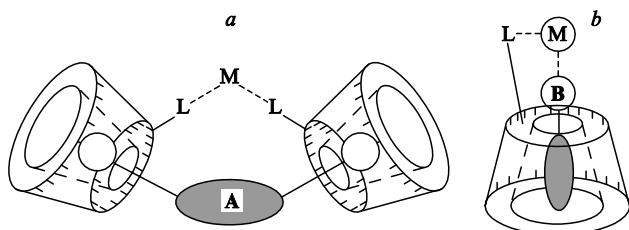


**Figure 8.** Different types of binding of a substrate by a metal complex containing fragments of receptor molecules.

L is a ligand bound to the receptor molecule; M is a metal ion; A is a group accessible for reaction; B is a group in the guest molecule.

(a) binding of two fragments of a guest molecule; (b) additional coordination of the group B in the guest molecule to the metal atom.

This combination of a host and a metal centre in one molecule not only retains all the features typical of catalytic systems discussed in the previous section but also confers new catalytically important properties. First of all, binding of a substrate by the cavity of the receptor ligand strictly defines its orientation with respect to the metal centre, which can strongly affect both the product distribution and the substrate selectivity of the reaction. The most interesting examples of this approach are enzyme models containing several host fragments in one ligand (Fig. 8 a).

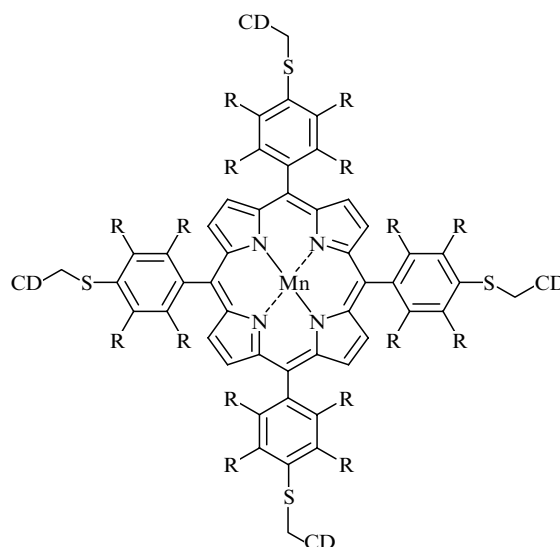
It has to be emphasised that if the substrate embedded into the host–guest complex is additionally coordinated to the metal centre in the course of reaction (Fig. 8 b), the stability of this inclusion complex, as well as of the transition state of the reaction, can be enhanced by several orders of magnitude. This effect is referred to as ‘double recognition’.<sup>92, 93</sup> Due to concerted binding of the substrate, no additional step of the interaction of the substrate inclusion complex with the metal ion (which was typical of all catalytic systems considered in Section I) is necessary. As a consequence, such catalysts provide a substantial decrease in the energy of activation and the entropy of the reaction and thus increase its rate.<sup>13, 94</sup>

Complexes with receptor molecules were initially tested as models of hydrolytic enzymes.<sup>12, 92, 93, 95–101</sup> Up to now, issues related to the design and catalytic activities of such complexes have been elucidated in biomimetic oxidation, epoxidation, hydroxylation, Wacker oxidation, oxidation of sulfides and alcohols, hydroformylation, hydrogenation and other reactions.

#### 1. Oxidation

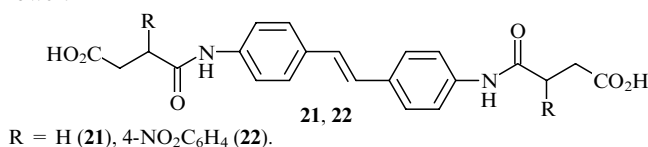
Breslow *et al.*<sup>102–107</sup> demonstrated the possibility of selective oxidation of different compounds on manganese porphyrinate complexes capable of selective substrate binding due to the presence of two or more cyclodextrin fragments.

The manganese complexes **19**, **20** enable epoxidation of unsaturated compounds by iodosylbenzene in aqueous media. The product yield is strongly dependent on the matching of the structures of the substrate and the metal complex.<sup>102</sup> In particular,

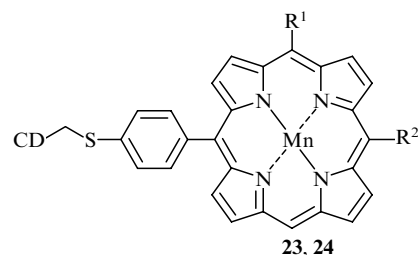


CD is cyclodextrin; R = H (**19**), F (**20**).

in the presence of complex **19**, the substrate **22** is epoxidised 50 times faster than the substrate **21** due to the presence of nitrophenyl groups, which are strongly bound by the cyclodextrin fragments. The activity of the complex **23**, in which the substrate is cooperatively bound by two cyclodextrin fragments simultaneously, is comparable to that of **19**. The activity of the catalyst **24** (where the arrangement of the receptor fragments does not correspond to the substrate shape and one of the cyclodextrin units does not take part in the substrate binding) is significantly lower.

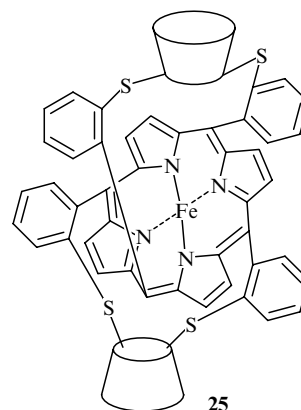


R = H (**21**), 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> (**22**).



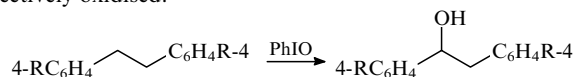
**23:** R<sup>1</sup> = H, R<sup>2</sup> = C<sub>6</sub>H<sub>4</sub>SCH<sub>2</sub>CD; **24:** R<sup>1</sup> = C<sub>6</sub>H<sub>4</sub>SCH<sub>2</sub>CD, R<sup>2</sup> = H.

The iron porphyrinate complex **25**, containing two cyclodextrin fragments above and below the porphyrin plane, manifests



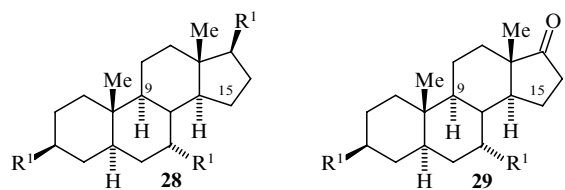
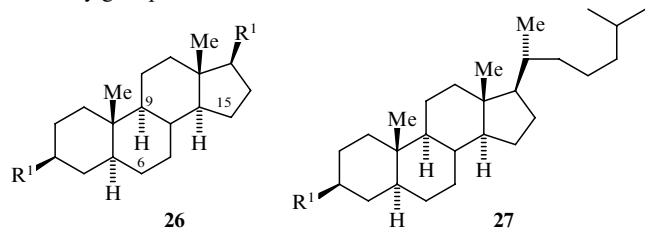
selectivity in the epoxidation of unsaturated compounds: in the case of cyclohexene, the reaction rate is several times higher than that of styrene. Furthermore, in the presence of a similar porphyrinate complex containing no cyclodextrin fragments, cyclohexene reacts significantly slower than in the presence of the complex **25**.<sup>108</sup>

The selectivity of the oxidation of C–H bonds with PhIO, catalysed by cyclodextrin-containing manganese porphyrinate **19**, also depends on the matching of the arrangement of binding centres within the ligand and the substrate structure.<sup>103–107</sup> In particular, in the oxidation of substituted 1,2-diphenylethanes, the aromatic moieties are not affected while the benzylic sites are selectively oxidised.

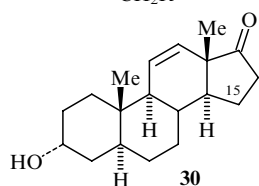


R = OCH(CO<sub>2</sub>H)C<sub>6</sub>H<sub>4</sub>Bu<sup>t</sup>-4.

Manganese porphyrinate complexes modified by cyclodextrins can catalyse selective oxidation of specific C–H bonds in steroids **26–30**. It was demonstrated that the selectivity is governed by the orientation of the substrate in the host–guest complexes due to specific binding of aromatic fragments of auxiliary groups in the steroid molecule.<sup>102–104</sup>



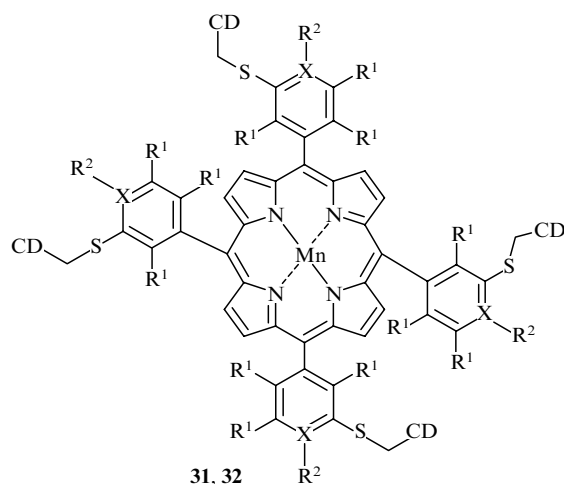
R<sup>1</sup> = 4-Bu<sup>t</sup>C<sub>6</sub>H<sub>4</sub>CHCH<sub>2</sub>C(O)O; R<sup>2</sup> = CONHCH<sub>2</sub>CH<sub>2</sub>SO<sub>3</sub>H.



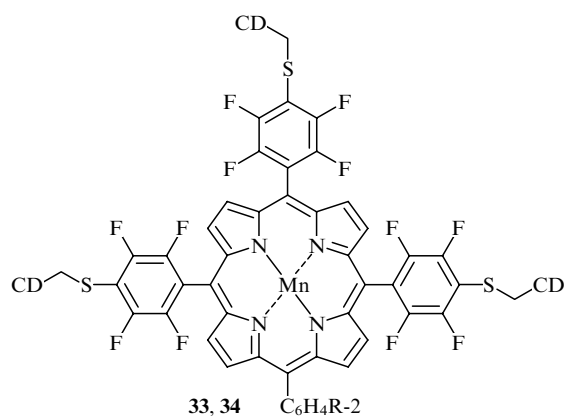
For instance, oxidation of steroid **26** catalysed by the complex **19** yields exclusively the 6- $\alpha$ -hydroxy derivative. Meanwhile, compound **27** devoid of one substituent R<sup>1</sup> yields a mixture of nine components.<sup>102</sup> The activity of manganese porphyrinates **20**, **31** and **32** containing tetrafluorophenyl groups is significantly higher.<sup>105–107</sup>

Selective oxidation of steroid **28**, catalysed by the complexes **20**, **33** and **34**, yields the 9-hydroxy derivative as the major product.<sup>107</sup> This could be due to involvement of all three cyclodextrin fragments in steroid binding. A minor hydroxylation product at C(15) is formed due to involvement of only two cyclodextrin fragments in binding. Therefore, oxidation of steroid **29** catalysed by porphyrinate **20** yields oxidation products at C(9) and C(15) in nearly equal proportions. The catalysts **31** and **32** enable strictly selective hydroxylation at C(9).

It is of note that substrate binding by only one cyclodextrin fragment allows selective introduction of a hydroxy group into a steroid molecule. In particular, oxidation of compound **30** catalysed by porphyrinate **20** yields mainly the hydroxylation product



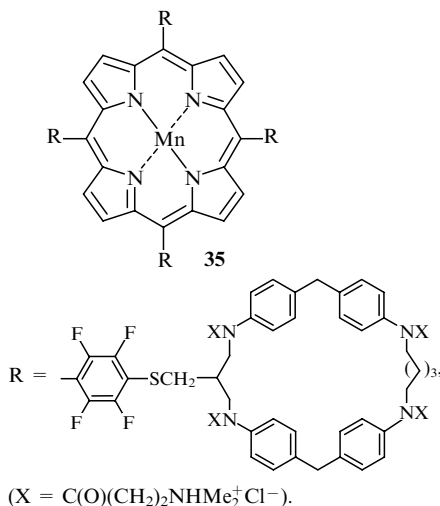
R<sup>1</sup> = R<sup>2</sup> = H, X = C (**31**); R<sup>1</sup> = F, X = N, R<sup>2</sup> is absent (**32**).



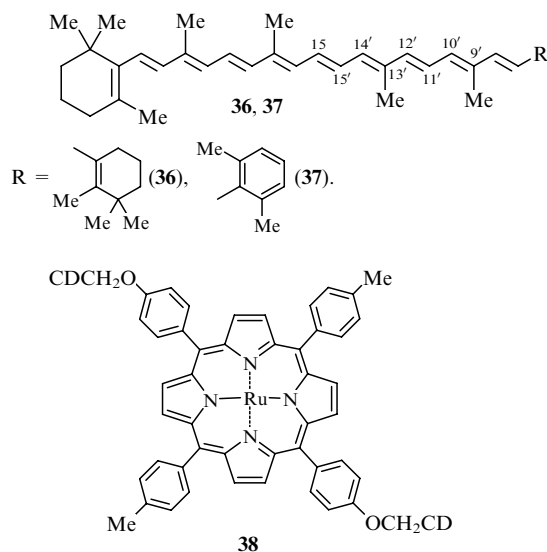
R = NO<sub>2</sub> (**33**), (**34**).

at C(15) whereas neither the double bond nor the hydroxy group are affected.

Manganese porphyrinate **35** containing cyclophane fragments<sup>109</sup> catalyses oxidation of compound **26** but the selectivity is significantly lower compared to that of the analogous complex containing cyclodextrin fragments [the ratio of the hydroxylation products at C(6) and C(15) is 3 : 1]. In the case of steroid **28**, the selectivity of hydroxylation at C(9) is only 60%. Apparently, the substrate, even bound by the cyclophane fragments, retains sufficient mobility resulting in non-oxidation.



Similar effects of the 'rigidity' of substrate binding are observed for the oxidation of  $\beta,\beta$ -carotene **36** and its analogue **37** by *tert*-butyl hydroperoxide catalysed by ruthenium porphyrinate **38** containing two cyclodextrin fragments.<sup>110–113</sup>



In this case, the stability constant of the host–guest complex is very high ( $2.6 \times 10^6 \text{ M}^{-1}$ ) due to cooperative binding of the carotene molecule by the cyclodextrin fragments. Nevertheless, oxidation of carotene proceeds non-selectively: the cleavage products of the C(15)–C(15'), C(11')–C(12') and C(9')–C(10') bonds are formed, although the two former products prevail. At the same time, if one of the cyclohexene fragments is replaced by an aromatic one (compound **37**), the cleavage product of the C(15)–C(15') bond is selectively formed. Probably, in this case both the structural 'rigidity' of the inclusion complex and binding constant are increased, the latter is  $5.6 \times 10^6 \text{ M}^{-1}$ .

The iron complex **39**, containing  $\beta$ -cyclodextrins modified by catechol groups, proved active with respect to phenol hydroxylation. Abnormally high regioselectivity was achieved in this system: the yield of catechol exceeded 90%. The use of the metal complexes results in a significant increase in the binding constant of phenol; its specific orientation in the host–guest complex owing to additional coordination provides selectivity for *ortho*-hydroxylation (Fig. 9).<sup>34, 49, 50, 114</sup> It was shown<sup>115, 116</sup> that the

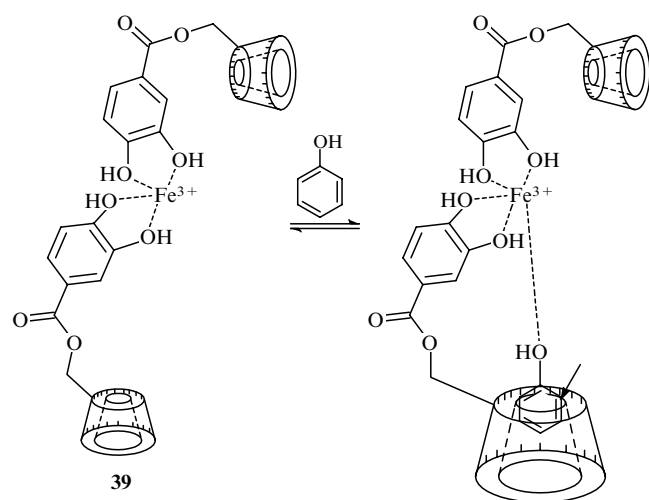


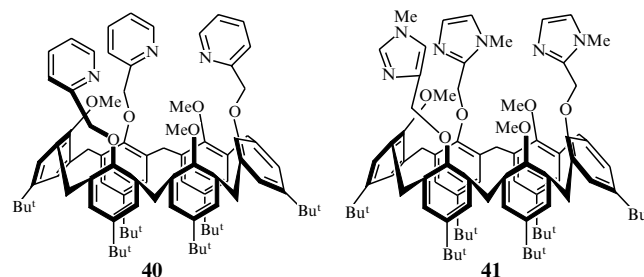
**Figure 9.** Formation of a complex of the catalyst with phenol in the hydroxylation of the latter by hydrogen peroxide. The arrow marks the site available to hydroxylation.

iron complexes formed at pH 2.5, which contain two ligands per iron ion, manifest the highest activity. The quantitative selectivity as regards catechol formation was achieved in the reaction with copper complexes containing ethylenediamine-modified cyclodextrins and, noteworthy, non-modified  $\beta$ -cyclodextrin. In the latter case, the catalytic activity is probably due to binuclear copper complexes with  $\beta$ -cyclodextrin, which, in turn, form stable complexes with phenol.<sup>117–121</sup>

Catechol is also formed as the main product in hydroxylation of benzene by hydrogen peroxide, catalysed by the complex **39**. The yield of phenol, *i.e.*, the primary hydroxylation product, being about four times lower.<sup>34, 50, 115</sup> This is explained by the fact that phenol formed upon hydroxylation of benzene remains in the cyclodextrin cavity due to cooperative binding to the metal atom and thus undergoes further oxidation to catechol. With iron complexes containing  $\beta$ -cyclodextrin modified by catechol at the primary hydroxy group, hydroquinone is predominantly formed.<sup>115, 116</sup>

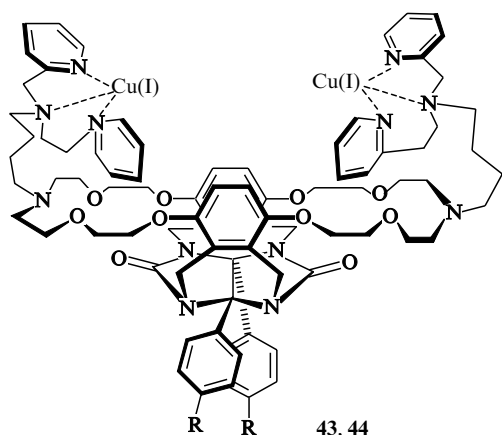
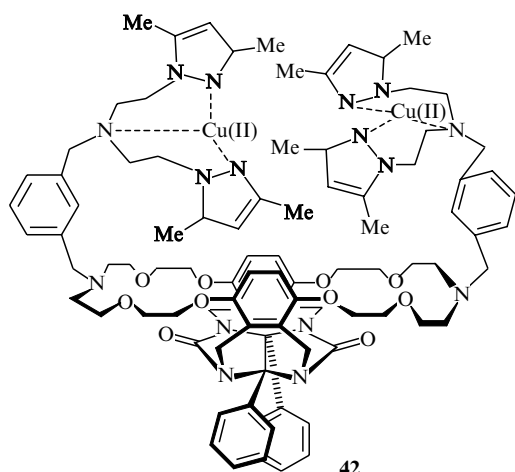
Copper complexes with cyclodextrins were used in the oxidation of isoborneol and borneol by peracetic acid and hydrogen peroxide in a acetic acid–pyridine mixture.<sup>122, 123</sup> The yield of camphor, the main product, and selectivity of the reaction were much higher than those in the process catalysed by copper sulfate. The catalytic effect is explained by specific orientation of the substrate molecule in the inclusion complex due to coordination of the alcohol group to the copper ion.

The copper complex of pyridine-modified calix[6]arene **40**<sup>124–128</sup> is active in the oxidation of benzene to quinone *via* phenol and hydroquinone. It is of note that no catechol is formed in this case. The same complex is active in the oxidation of ethylene to acetaldehyde and acetic acid.<sup>129</sup> A similar copper complex of calix[4]arene modified by the imidazole groups **41** catalyses oxidation of 3,5-di-*tert*-butylcatechol, benzene and ethanol by hydrogen peroxide to the corresponding quinone, benzoquinone and acetaldehyde, respectively.<sup>129, 130</sup>

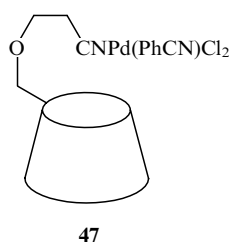
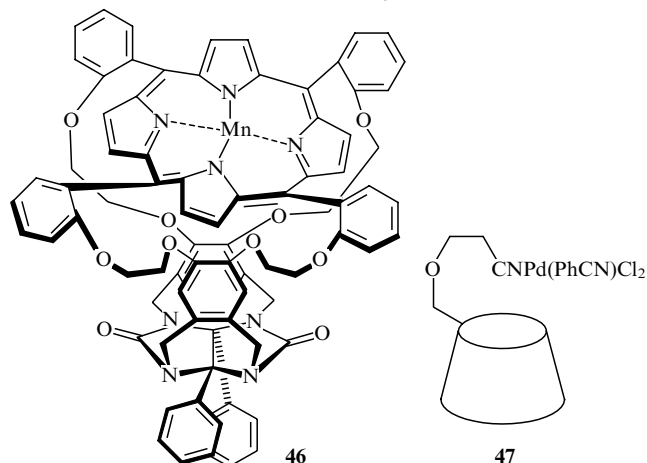
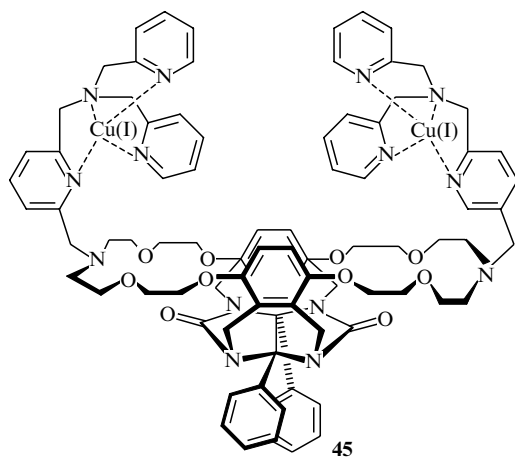


Interesting examples of supramolecular oxidation catalysts are given by compounds based on 'molecular clips'.<sup>131–136</sup> The copper complexes **42** and **43** of such molecules proved to be selective catalysts for biomimetic oxidation of alcohols to the respective aldehydes.<sup>132–134</sup> The analogous porphyrinates were efficient in the epoxidation of stilbene and pinene by hypochlorite.<sup>135</sup>

The rate of oxidation of 3-hydroxy- and 3,5-dihydroxybenzyl alcohols catalysed by the complex **42** was substantially higher than that of benzyl alcohol. Presumably, H bonds are formed between oxygen atoms of the oxy groups in the cavity and the hydroxy groups in the aromatic ring of the substrate, in addition to coordination of the benzyl group to the copper ions.<sup>132</sup> Oxidation of phenols by air in the presence of the copper complexes **43** and **45** with pyridine-containing ligands yields only polymeric products of oxidative coupling.<sup>133</sup> Martens *et al.* proposed<sup>132</sup> analogous catalysts **44** that are soluble in fluorinated solvents.<sup>134</sup> Manganese porphyrinates **46** containing pyridine as an axial ligand are unstable. The use of 4-(*tert*-butyl)pyridine made it possible to stabilise the catalyst owing to another type of ligand coordination in the active complex: in contrast to pyridine, it cannot be accommodated in the cavity of the receptor and thus is coordinated from the outer side.<sup>135, 136</sup>



R = H (43), SiMe<sub>2</sub>R<sub>F</sub> (44) (R<sub>F</sub> is perfluorinated hydrocarbon fragment).

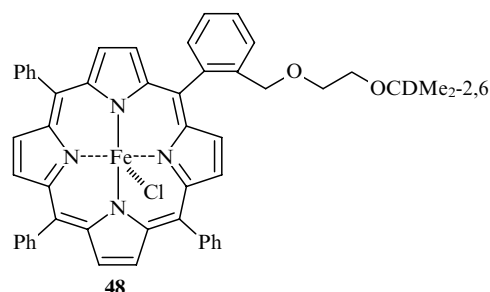


The palladium complex **47** with  $\beta$ -cyclodextrin modified by cyanoethyl group manifested significantly higher activity than the catalytic system PdCl<sub>2</sub>(PhCN)<sub>2</sub>– $\beta$ -cyclodextrin in the Wacker oxidation of higher alk-1-enes. Its activity is due to cooperative binding of the substrate and the increased stability constant of the catalyst–substrate complex. It was shown that the stability constants of the inclusion complexes significantly increase on going from non-modified cyclodextrin to the metal complexes of the type **47**. The energy of activation of the reaction decreases approximately twofold, which is explained<sup>42</sup> by additional coordination of an alkene to the palladium atom in the inclusion complex. The activity of the catalyst depends on the chain length of the alkene and is a maximum for hept-1-ene.<sup>42</sup>

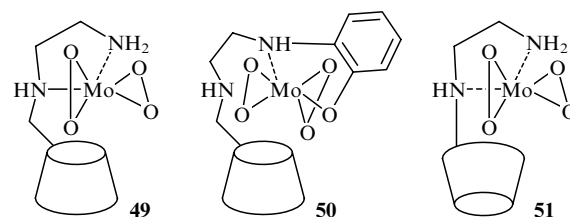
The catalyst **47** demonstrates higher activity in reactions with aromatic substrates, *e.g.*, styrene, than with linear alkenes.<sup>34, 42, 50, 137</sup> Oxidation of styrene catalysed by a system containing the palladium complex and non-modified cyclodextrin, yields acetophenone as the major product. If the cyclodextrin in the catalytic system is modified by nitrile groups, phenylacetaldehyde is formed in about the same proportion as acetophenone. This means that the regioselectivity of the reaction is altered.

Palladium complexes with sulfocalixarenes modified by nitrile-containing groups manifest higher activities in the biphasic Wacker oxidation of alk-1-enes compared to systems composed of non-modified sulfocalixarenes. The catalytic activity strongly depends on the size of the calixarene cavity: calix[4]arene and calix[6]arene are most active towards hex-1-ene and oct-1-ene, respectively.<sup>45</sup>

Catalysts based on cyclodextrins are very promising for performing enantioselective catalytic reactions. Oxidation of a mixture of (*S*)- and (*R*)-pinenes by oxygen under irradiation with visible light, catalysed by the iron complex with porphyrin modified by 2,6-dimethyl- $\beta$ -cyclodextrin (**48**), is an example of this approach.<sup>138, 139</sup> Under these conditions, the (*S*)-isomer was more reactive and the enantioselectivity was above 60%.



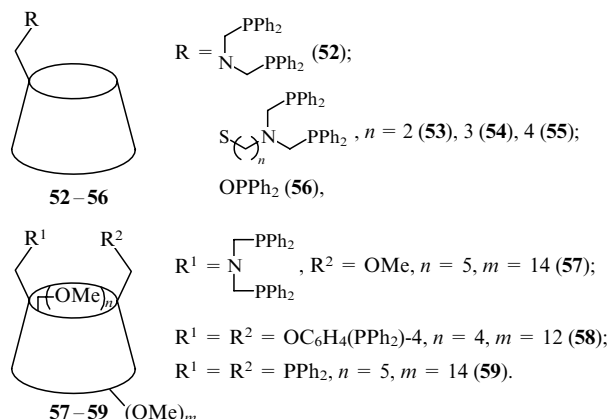
Only a few studies were aimed at the synthesis of macrocyclic receptors as catalysts of enantioselective reactions. Oxidation of aromatic sulfides to sulfoxides catalysed by the molybdenum complexes **49**–**51**, containing modified cyclodextrins as ligands, yields predominantly (*R*)-isomers. The yield of sulfoxide in the oxidation of thioanisole by hydrogen peroxide in biphasic systems, catalysed by the molybdenum complex **49** containing cyclodextrin with ethylenediamine as a substituent of one of the primary hydroxy groups, was 91% [*ee* 59% (*R*)]. In the case of the complexes **50**, containing  $\beta$ -cyclodextrin, and **51**, containing  $\beta$ -cyclodextrin with ethylenediamine as a substituent of a secondary hydroxy group, the enantioselectivities were substantially lower (from 17% to 24%).<sup>140</sup>





## 2. Hydrogenation and hydroformylation

A series of rhodium complexes **52–59** with cyclodextrins modified by various phosphine groups have been synthesised as potential catalysts for hydrogenation and hydroformylation reactions.



Reetz *et al.*<sup>94, 141, 142</sup> showed that these complexes possess substrate specificity in the hydrogenation of aromatic unsaturated compounds. Furthermore, rhodium complexes with cyclodextrin ligands are active in the hydroformylation of alkenes<sup>13, 34, 142</sup> and similar platinum, rhodium and iridium complexes are efficient catalysts for the hydrogenation of aromatic chloronitro compounds<sup>143</sup> (Table 4).

**Table 4.** Complexes with cyclodextrin-containing ligands catalysing hydroformylation and hydrogenation reactions.

| Ligand           | Reaction                        | Conditions                                                                                 | Ref.                     |
|------------------|---------------------------------|--------------------------------------------------------------------------------------------|--------------------------|
| <b>52</b>        | Hydrogenation of nitrobenzenes  | toluene – water, 20 °C, H <sub>2</sub> , 2 MPa                                             | 143                      |
| <b>52–55, 57</b> | Hydrogenation, hydroformylation | 25% DMFA in water, H <sub>2</sub> , 0.1 MPa or synthesis-gas under 10 MPa, 25 °C and 60 °C | 12, 13, 34, 94, 141, 142 |
| <b>56</b>        | Hydroformylation                | DMFA, synthesis-gas, 2 MPa, 80 °C                                                          | 144                      |
| <b>59</b>        | Hydroformylation                | methanol : water = 6 : 4, synthesis-gas, 4 MPa, 60 °C                                      | 145                      |
| <b>60</b>        | Asymmetric hydrogenation        | methanol, ethanol, THF, acetone, H <sub>2</sub> , 0.1 MPa                                  | 146                      |

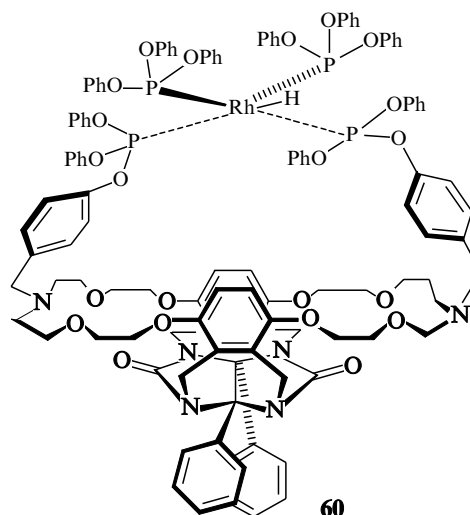
The use of rhodium complexes with the ligands **52–55** as catalysts for hydroformylation increases the rates of the reactions compared to those for catalytic systems containing non-modified  $\beta$ -cyclodextrin and  $\text{H}(\text{CO})\text{Rh}(\text{TPPTS})_3$ . Furthermore, the selectivity of formation of linear aldehyde is also increased, which is explained by specific orientation of the substrate in the supramolecular complex with the cyclodextrin fragment. In contrast to the catalytic systems based on  $\text{H}(\text{CO})\text{Rh}(\text{TPPTS})_3$ , rhodium complexes with the ligands **52–55** enable conversion, in biphasic solvent systems, of alkenes even with an internal double bond [*e.g.*, (*E*)-oct-3-ene]. The catalyst remains in the aqueous phase and can be recycled. Hydrogenation of aromatic compounds on the rhodium complexes with the ligands **52–55** and **57** is characterised by much higher reaction rates than those of linear alkenes, which suggests molecular recognition of the aromatic substrates.

In the hydrogenation of chloronitrobenzene, a platinum complex with the ligand **52** provided the best selectivity. The yield of aminochlorobenzene was > 95%. Virtually no hydrodechlorination products were observed due to shielding of the chlorine atom within the inclusion complex.<sup>143</sup> Rhodium complexes with methylated  $\alpha$ -cyclodextrin (**58**) modified by phosphine

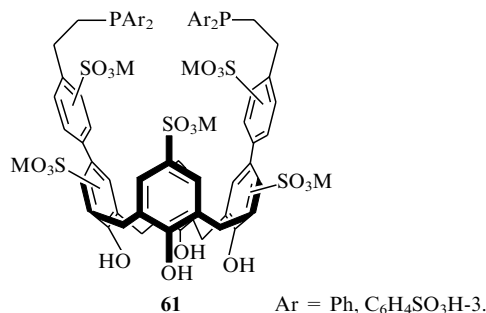
groups and with  $\beta$ -cyclodextrin (**56**) modified by phosphite groups, have been tested as catalysts for homogeneous hydrogenation.<sup>144, 145</sup> In this case, substrate selectivity was also observed: hydrogenation of aromatic compounds proceeded much faster than that of alkenes due to the higher stability of the respective host – guest complexes.

A rhodium complex with the permethylated  $\beta$ -cyclodextrin **59** modified by two triphenylphosphine groups at adjacent glucose fragments, was active in the enantioselective hydrogenation of various substituted  $\alpha, \beta$ -unsaturated acids. The enantioselectivity ranged from 49% to 92% depending on the substrate and solvent. Apparently, in this case, cooperative binding of the substrate by the ligand cavity and the metal atom defines its specific orientation and favours formation of the *R*-isomer.<sup>146</sup>

Nolte and co-workers<sup>147</sup> synthesised the rhodium phosphite complex **60** with a non-polar cavity using molecular receptors based on diphenylglycoluril. Aromatic allylic compounds can be selectively hydrogenated in the presence of this complex with a rate much higher than that in the case of catalytic systems without host fragments, due to binding of the substrate in the cavity. The activity of the catalyst towards hydrogenation of *p*-allylcatechol could be increased by addition of resorcinol, probably owing to cooperative binding of both molecules, *viz.*, the substrate and resorcinol, in the cavity of the host.<sup>147, 148</sup>



A macromolecular rhodium complex containing modified calixarene **61** as a ligand, was tested as a catalyst for hydroformylation in biphasic systems.<sup>149</sup> Hydroformylation of oct-1-ene was conducted in an alkene – water system without other organic solvents; rhodium(I) acetylacetonatodicarbonyl served as a precursor of the catalyst.

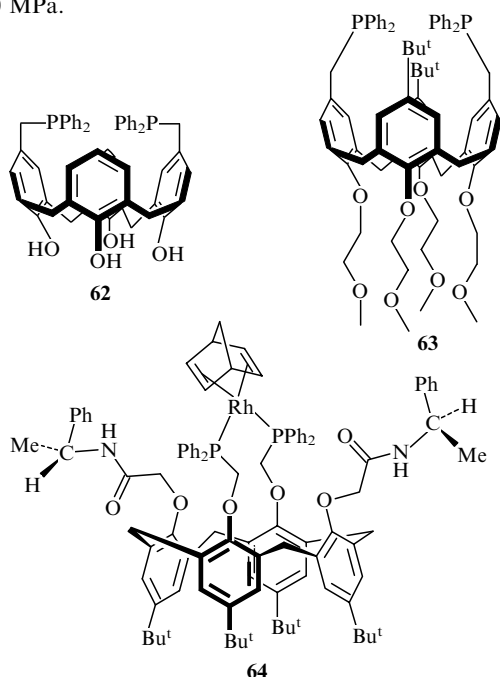


At the pressure of synthesis-gas of 4.0 MPa and 100 °C, the substrate was converted into aldehydes with normal and *iso*-carbon skeletons in a ratio of 2 : 1. The degree of conversion was 70% – 95% after 12 h. It is of note that the catalyst is active in the hydroformylation of not only alk-1-enes (*e.g.*, oct-1-ene) but of

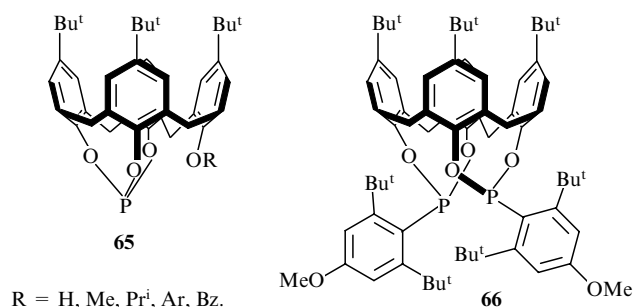
such relatively inert substrates as oct-2-ene and oct-4-ene as well. In the latter case, the reaction yielded a mixture of aldehydes.<sup>150</sup>

Complexes with calixarenes modified by phosphine and phosphite groups were also tested as catalysts for reactions with synthesis-gas under homogeneous conditions.<sup>151–159</sup> It should be noted that in this case the fragment of the receptor molecule served primarily as a template for the design of sterically hindered phosphine and phosphite ligands. Unfortunately, the process of formation of the inclusion complexes was not discussed by the authors.

Hydroformylation of styrene and oct-1-ene using rhodium complexes of calixarenes **62**, **63** was described by Bagatin *et al.*<sup>153</sup> and by Fang *et al.*<sup>154</sup> Loeber *et al.*<sup>155</sup> have employed the complex **64** in the same reaction. Quantitative conversion of styrene into 2-phenylpropanal with a selectivity of 95% took 48 h at 40 °C and 4.0 MPa.

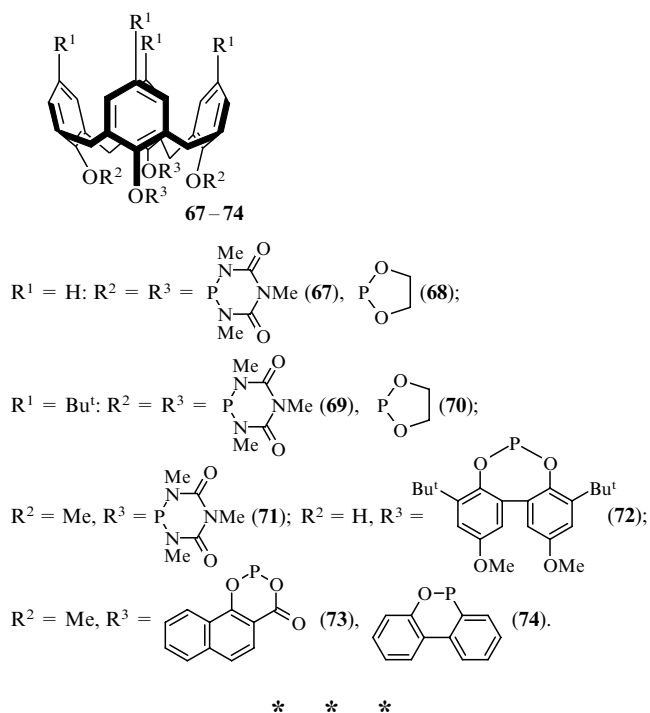


Calixarenephosphite **65** ( $R = H$ ) with a non-protected hydroxy group was used as a ligand for the rhodium-catalysed hydroformylation of hex-1-ene.<sup>156</sup> Virtually complete conversion of the starting alkene was achieved in 3 h; the yield of aldehydes was 80%–85%. Unfortunately, the selectivity was rather low: the reaction mixture contained equal amounts of linear and branched aldehydes. A series of analogous phosphites have been tested<sup>157</sup> as components of catalytic systems for the hydroformylation of oct-1-ene. It was shown that the nature and steric volume of the substituent  $R$  insignificantly affects the major characteristics of the process. In particular, the degree of conversion was 80%–90% in all cases and the selectivity of nonanal formation about 60%.



The use of chelate biphosphonite **66** gave rise to a significant increase in the regioselectivity of nonanal formation to 90%–92%.<sup>151</sup>

Hydroformylation of oct-1-ene in the presence of Rh complexes with phosphorus-containing calixarenes **67–74** was studied by Kunze *et al.*<sup>158, 159</sup> The maximum activity was observed for complexes with the ligand **73**, however, the presence of a calixarene fragment in the ligand did not enhance the catalytic activity. For instance, catalysts containing the ligands **67**, **69** and **71** provided the same activity as their analogue without calixarene whereas for complexes with the ligands **68** and **70**, the activity was even lower.



The data summarised in the present review demonstrate the rapidly growing interest of researchers in the design of supramolecular metal complex catalytic systems based on macrocyclic receptors. The number of publications in this area steadily increases.

Since it is high selectivity that becomes an increasingly important factor in chemical processes, there is no doubt that catalysts capable of molecular recognition will find broad applications in chemo-, regio- and stereoselective reactions.

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- b — *Mendeleev Chem. J. (Engl. Transl.)*
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## Chemical research at the Saint-Petersburg State University



This issue of the Journal is compiled from reviews written by researchers of the Department of Chemistry and the Research Institute for Chemistry of the Saint-Petersburg State University.

The Department of Chemistry, which celebrated its 75th anniversary in 2004, descends from the Division of Chemistry of the Physico-Mathematical Department of the Imperial Saint-Petersburg University. Teaching chemistry at the University began in the 1830s, and in 1868 the Division of Chemistry, which had expanded considerably by that time, was split into three sectors, *viz.*, inorganic, organic and analytical chemistry, headed by D I Mendeleev, A M Butlerov and N A Menshutkin, respectively. Academicians D P Konovalov, V E Tishchenko, A E Favorsky, S V Lebedev, V G Khlopin, B P Nikolsky, I I Chernyaev, A A Baikov, the Corresponding Members of the RAS M S Vrevsky, I I Zhukov, Professors L A Chugaev, S A Shchukarev, R L Müller, Ya V Durdin, A V Storonkin and other outstanding representatives of Russian science had been working at the Institute at different times.

In 1934, the Educational-and-Research Centre for Chemistry (RECC) was established on the base of the Department of Chemistry and the newly founded Research Institute for Chemistry. In 2003, the Institute for Laser Research acceded to them.

To date, the staff of the Department and the Institutes comprises Academicians A I Rusanov and M M Shults, Corresponding Members of the RAS N A Smirnova and V B Aleskovsky, 70 professors and Doctors of Science and about 300 Ph.Ds. The results of investigations carried out in the past decade and documented in more than 2400 articles and reviews in Russian and foreign periodicals, 38 monographs, 84 manuals and 33 transactions have been published and 13 patents have been granted; over 200 grants from RFBR, RFBR-DFG, RFBR-INTAS, CRDF, DAAD, INTAS, the Volkswagen Foundation, NWO, INCO-COPERNICUS and various research programmes including the NATO Science Programme, Universities of Russia and programmes of the Ministry for Education and Science and the Ministry of Defence of the Russian Federation have been obtained.

The Department of Chemistry is collaborating successfully with many classical Russian universities, institutes of the RAS, academies of sciences, research establishments and manufacturing companies in the USA, Canada, Japan, China, Korea, SAR and the majority of European countries and takes an active part in organising various conferences, symposia and seminars.

The research activities at the Department are inseparably joined with educational work. The Department is carrying out large-scale training of specialists in virtually all chemical specialties. The Department admits annually 150 students from various regions of Russia. Many of its graduates take a post-graduate course to get a Ph.D. degree and some of these continue to work for a D.Sci. degree.

At present, the Department of Chemistry and its two Institutes comprise 13 divisions and 17 sectors on quantum chemistry, colloid chemistry, physical chemistry, chemical thermodynamics and kinetics, electrochemistry, general and inorganic chemistry, analytical chemistry, organic chemistry, physical organic chemistry, polymer chemistry, chemistry of natural compounds, radiochemistry, chemistry of solids, semiconductors and laser research.

The main areas of research at the *Division and Sector of Quantum Chemistry* include development of theoretical-group methods for the study of electronic and vibrational structures of complex molecules and crystals; studies into the nature of chemical bonds in crystalline solids (transition metal oxides, high-temperature superconductors, fullerenes); studies of vibrational characteristics of complex crystals; development of methods for calculation of electronic structures, electronic spectra, valence structures and magnetic characteristics of complex transition metal derivatives; further development of the theory of atomic structures with special reference to relativistic, quantum-electrodynamic and environmental phenomena; non-empirical calculations of potential energy surfaces of ground and excited states of metastable and excimeric cations; development of the theory on atomic valence in molecules, radicals and crystals; quantum chemistry of organic compounds.



**The Division and Sector of Colloid Chemistry** are among the world leaders in many fields, *e.g.*, electrokinetic phenomena, thermodynamics of surface effects, physicochemical hydrodynamics of capillary systems, micelle formation and surface separation of compounds. The discoveries in these fields are related to the behaviour of surface layers, mechanochemistry, wetting and nucleation. Fundamental results have been obtained in the theory of micelle formation, the theory of wetting of rough surfaces taking account of linear phenomena, the theory of foams, capillary waves and currents as well as computer simulation of minor systems including clusters of polar compounds. Considerable progress has been achieved in the study of structural, adsorption, electrokinetic and filtration characteristics of real and model disperse systems and membranes of various chemical origin including porous glasses; also in the study of surface tension, surface electric charge and surface potential, surface conductivity and surface separation processes. The theory of the equation of state has been developed in recent years. This line of research has been described in the review by Academician A I Rusanov 'Novel approach to the equation of state for fluid systems, based on the concept of the exclusion factor'.

Studies on ion-exchange, ionometry and redoxometry are among the main areas of research at **the Division and Sector of Physical Chemistry**. Other trends include thermodynamics and molecular-statistical simulation of fluid systems [study of quantitative relationships between molecular characteristics of compounds and macroscopic properties of their solutions (fluid phases)]; development of novel versions of quasi-chemical models of solutions; development of a *p*-type quasi-chemical model of the fluid phase in a group variant; experimental studies and simulation of phase equilibria of fluid systems using the Monte Carlo method; thermodynamics of liquid-crystalline systems, *etc.* The review by the Corresponding Member of the RAS N A Smirnova 'Phase behaviour and self-assembly patterns of surfactant mixtures in solutions' is an overview of the state-of-the-art in solutions of surfactant mixtures.

**The Division and Sector of Chemical Thermodynamics and Kinetics** are carrying out research on heterogeneous equilibria in multicomponent systems, thermodynamics of reaction-mass-exchange processes, thermodynamics and kinetics of processes in high-temperature oxide systems, phase diagrams of water-salt systems, *etc.* Other trends include simulation of the thermodynamic behaviour of electrolyte solutions at high concentrations; thermodynamics of membrane processes; kinetics of liquid-phase reactions in strongly non-ideal concentrated media; complex intermolecular interactions (bifurcated hydrogen bonds, general acid-base catalysis, *etc.*); multimolecular intermediate reactive associates; structure and thermodynamics of aqueous solutions of organic compounds and their reactivities in aqueous media.

Studies on equilibria and kinetics of electrode processes in electrolyte solutions of variable compositions are traditional subjects of investigation at **the Division and Sector of Electrochemistry**. These include analysis of the effects of double electrical layer structures on the rates of electrode reactions and processes complicated by chemical reactions in bulk. An entirely new trend, *viz.*, electrochemistry of modified electrodes coated with conducting polymeric inorganic or organic films with mixed ion-electronic conductivities, has been developing successfully in the past decade.

Studies on coordination and cluster compounds and molecular complexes occupy a prominent place in the research carried out at **the Division and Sector of General and Inorganic Chemistry**. A general theory of the electronic structures of transition-metal clusters with weak- and strong-field ligands has been developed together with the methodology for structural-and-dynamic simulation of intramolecular electron transfer in polynuclear organo-metallic transport chains. The most important in principle achievements include the discovery of novel classes of conversions of unsaturated organic ligands on polynuclear coordinating centres; development of a model of vibrational quantum tunnel-

ling of electrons and the theory of a redoxonic mechanism for solid-phase vibrational redox reactions; rationalisation of high-temperature superconductivity, giant magnetoresistivity, electron-ionic conductivity of oxides with heterovalent atoms, *etc.* Studies on the structures and properties of aqueous solutions of salts, thermodynamics and kinetics of gas-phase reactions, nature of the donor-acceptor bonds in molecular complexes, *etc.*, are under way.

The studies at **the Department and Sector of Analytical Chemistry** are developing along several lines, *viz.*, separation methods and hybrid methods of analysis, spectroscopic methods, studies of reactivities of complexes, *etc.* The main achievements include the development of novel chromatographic methods of analysis, such as gas-liquid and gas-liquid-absorption chromatography, chromatomembrane flow techniques for continuous separation of substances, detection methods based on Zeeman modulation polarisation spectroscopy, Mössbauer and X-ray low-angle dispersion spectroscopy and discovery of new ligand reactions in complexes. Researchers at the Division are actively developing luminescent and electrochemical methods along with methods for flow-injection, vapour-phase and capillary-electrophoretic analysis including those based on the use of microchips. Each of these trends has found practical application: on-line ecological monitoring of waters has been substantiated methodologically and novel technologies for flow-injection, spectral analysis and oxygenation of blood, deoxygenation of water and homogeneous catalysis have been developed. The review by A L Moskvina and L N Moskvina 'Water and aqueous environments: on-line chemical analysis, problems and solutions' is devoted to flow-through methods of analysis, while the review by N A Bokach and V Yu Kukushkin 'Addition of HO-nucleophiles to free and coordinated nitriles' deals with novel reactions of ligands within complexes.

The main attention among other research trends developed at **the Division and Sector of Organic Chemistry** is given to the chemistry of unsaturated compounds, strained carbo- and heterocycles, study of rearrangements (including tautomeric conversions), reactions involving carbenes and reactivities of organic compounds. Novel five- and seven-membered oxygen- and nitrogen-containing heterocyclic compounds with potential biological activities have been prepared and novel approaches to the synthesis of unnatural or hardly accessible natural amino acids have been developed. The review by A F Khlebnikov, M S Novikov and R R Kostikov 'Iminium ylides from carbenes and carbeneoids: generation and synthetic applications' is devoted to various reactions of carbenes.

The main areas of research at **the Division and Sector of Physical Organic Chemistry** are studies of the mechanisms of various hetero- and homolytic reactions. Considerable progress has been achieved in the theoretical and experimental design of principles and models for identification of mechanisms of chemical reactions and control over their selectivity; in-depth studies of tautomeric conversions in the synthesis of novel anion-selective ligands, *etc.* Such areas as metal-complex catalysis, directed synthesis of heterocyclic systems and especially the novel promising trend, chemistry of ecotoxicants, *etc.*, are also developing successfully.

The activities at **the Division and Sector of Polymer Chemistry** are aimed at the synthesis and investigation of novel types of polymers with miscellaneous functions (*e.g.*, biodegradable polymers, dendritic macromolecules, *etc.*). The principles and methods for the preparation of dendritic polymers based on natural trifunctional amino acids that are promising for chromatography and the study of transport processes in biosystems have been developed. The self-assembly of dendritic macromolecules based on electrostatic interactions of a polyelectrolyte core with dendrons oppositely charged at the focal point has been carried out for the first time. A new method for the formation of porous polymeric materials for tissue engineering has been developed on the basis of biodegradable polymers.

Methods for the preparation of practically important peptides, *e.g.*, human insulin, bradykinin, vasopressin, oxytocin and its analogues, luliberin and its analogues,  $\delta$ -sleep peptide, angiotensins I and II, somnogenic peptides, neurotensin, cholecystokinin, bombesin and its analogues, *etc.*, have been developed at ***the Division and Sector of Chemistry of Natural Compounds***. Schemes for the total synthesis of steroid estrogen analogues have been developed and their crystal and solution structures have been investigated. Novel compounds manifesting selective biological activities (predominantly, antisclerotic, osteoprotective or immunosuppressive) together with low hormonal activities have been prepared; the biological properties of many natural compounds have been investigated.

***The Division and Sector of Radiochemistry*** are carrying out research in various fields of the physicochemistry of radionuclides. These investigations include studies of the nuclear prehistory and its effect on the nature of radiation-induced damage of metals; structures and migration of admixture 'hot' atoms (admixture radiation defects) formed in metals and alloys upon nuclear fission and transmutation induced by charged species, neutrons or upon radioactive decay; diffusion-thermal methods for isolation of radionuclides in the absence of substrates. Tracer methods were used to study the properties of membranes of chemical sensors [diffusion, electroconductivity, ion exchange (solution/solids) and novel chemical sensors for detecting heavy metals, *etc.*] and sensory systems of the 'electronic language' type have been developed.

Research at ***the Division and Sector of Chemistry of Solids*** is being carried out in such fields as ionics of solids, chemistry of highly organised substances, chemistry of surfaces and surface compounds, chemistry of nanostructures and nanostructured materials, UV-Vis and IR spectroscopy of surfaces and nanostructures, precision synthesis of highly organised solids and nanostructured materials, *etc.* A new line of research, *viz.*, chemistry of highly organised compounds, has appeared. Methods for the synthesis of solids and materials based on the 'backbone hypothesis' have been devised. The molecular layering method was used as a basis for the development of sorbents, catalysts, luminophores, dispersely reinforced composite materials, thin-film structures for electronic engineering, *etc.*

Medium-order studies of various processes occurring in glasses and glass-forming melts, 'semiconductor-metal' transitions and of the nature of the superionic state are being carried out at ***the Sectors for Semiconductors and Laser Investigations***. Highly effective materials for IR optical amplifiers, which represent nanostructured chalcogenide glass films doped with rare-earth ions, have been prepared for the first time by UV-laser sputtering in the framework of a novel direction of investigations, *viz.*, laser materials science. Special attention is given to the interaction of laser irradiation with a material and concomitant chemical reactions. The effect of fundamental photo-induced changes in the optical width of the forbidden gap and the refraction indices of chalcogenide films prepared by laser sputtering have been determined.

This issue includes only some of the reviews prepared by researchers of the Department of Chemistry of SPbSU. The reviews summarising the results of investigations in other areas of research will be published in the next issues of the Journal.

D V Korolkov  
Dean of the Department of Chemistry and  
Head of Educational-and-Research  
Centre for Chemistry of SPbSU

A B Valiotti  
Director of the Research Institute for Chemistry



# Novel approach to the equation of state for fluid systems, based on the concept of the exclusion factor

A I Rusanov

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**Abstract.** The review summarises the achievements in the theory of the equation of state. Novel approaches and new high-precision equations of state for one- and multicomponent fluid systems are considered. The results are given for both bulk phases and surface monolayers including two-dimensional equations. In the framework of the theory based on the exclusion factor, a hierarchy of approximations is formulated, incorporating both well-established and relatively new equations of state. The bibliography includes 79 references.

## I. Introduction

A physicochemical state of matter is characterised by some state parameters such as temperature, pressure, density and chemical composition. The significance of the equation of state consists in that it relates these parameters to one another (usually, in explicit form). Finding the equation of state is one of the central problems of the knowledge of matter, which has been under discussion in the scientific literature since 1662 (the Boyle–Mariotte law). Research on the properties of gases took two centuries but the search for a general equation of state for gases and fluids began only after proposal of the idea of continuous transition from gas to fluid (van der Waals, 1873). Interest in this problem is unabated so far. To date, a great body of experimental data has been accumulated. Complete histories of the first fifty equations of state are known<sup>1</sup> but it is impossible to count the total number of the equations of state proposed. The matters in hand are various types (cubic, logarithmic, *etc.* equations), models (*e.g.*, lattice models) and aspects of the equation of state, which have been the subject of particular reviews. The results obtained in this field by the end of the twentieth century are summarised in an incomplete collection of such reviews.<sup>2</sup> The present review is devoted to the major aspect of the equation of state, namely, the use of the concept of the exclusion factor (excluded volume or surface area).

The first equations of state for fluids were based on the Boltzmann and van der Waals concepts of excluded volume, *i.e.*,

the volume that must be subtracted from the actual volume of a system due to the fact that particles in the system have their own volumes. It is easy to understand that in an ideal gas a spherical particle of radius  $r$  and volume  $v_0 = 4\pi r^3/3$  creates an excluded (inaccessible to the centres of other identical particles) volume  $v^{\text{ex}} = 4\pi(2r)^3/3 = 8v_0$ . Now if we write the van der Waals equation

$$p = \frac{k_{\text{B}}T}{v - 4v_0} - \frac{\alpha}{v^2}, \quad (1)$$

( $p$  is the pressure,  $k_{\text{B}}$  is the Boltzmann constant,  $T$  is temperature,  $v$  is the volume per gas particle,  $\alpha$  is the attraction constant), we surprisingly see the coefficient 4 instead of 8, which contradicts van der Waals' idea. Replacement of the numerical factor 4 by 8 in this equation leads to an incorrect value of the second virial coefficient. Van der Waals tried to avoid this contradiction by assuming that collisions always occur between two molecules. This argumentation is no longer valid after Planck's equation of state.<sup>3</sup>

$$p = -\frac{k_{\text{B}}T}{8v_0} \ln \left( 1 - \frac{8v_0}{v} \right) - \frac{\alpha}{v^2}, \quad (2)$$

which contains the excluded volume  $8v_0$  in explicit form. Undoubtedly, Eqns (1) and (2) are different equations of state. But even Planck who expanded the logarithm in a series thought that he confirmed the van der Waals equation which dominated over many decades and was in essence treated as a law of nature; parameters of this equation for particular substances were published in handbooks as physical constants.

The late 1950s and early 1960s were the period when the statistical theory of scaled particles<sup>4,5</sup> was created and methods of computer simulation (molecular dynamics) of the equation of state were elaborated.<sup>6</sup> The new theory provided much more accurate equations of state, introduced a number of additional geometric notions (*e.g.*, the notion of accessible volume, which is immediately related to the equation of state). Over the years it has become a broad field which was called by Reiss (creator of the theory) statistical geometry.<sup>7–12</sup> Elaboration of methods of computer simulation permitted experiments with exactly the same models for which theory was created. By the early 1980s research on the equations of state reached a stage of steady rework, refinement and generalisation. The subject of most recent publications is generalisation of the equations of state for multicomponent systems<sup>13–24</sup> or modelling of systems comprised of aspherical particles.<sup>25</sup>

A I Rusanov St Petersburg State University, Mendeleev Centre, Universitetskaya nab. 7/9, 199034 St Petersburg, Russian Federation.  
Fax (7-812) 428 69 39, tel. (7-812) 323 41 20,  
e-mail: rusanov@AR1047.spb.edu

The two-dimensional van der Waals equation

$$\Pi = \frac{k_B T}{a - 2a_0} - \frac{\alpha}{a^2} \quad (3)$$

[ $\Pi$  is two-dimensional pressure;  $a$  is the surface area per particle;  $a_0$  is the parking area of the particle; the attraction constant,  $\alpha$ , is of course different from that which appeared in Eqn (1)] has dominated since the mid-20th century, as follows from a well-known monograph by de Boer,<sup>26</sup> which is to a great extent based on this equation. However, the scaled particle theory also provided more accurate equations in this field (they are given below). In addition, experimenters working with dense surfactant monolayers began using the logarithmic Frumkin equation (at  $\alpha = 0$ , it is known as the van Laar equation)

$$\Pi = -\frac{k_B T}{a_\infty} \ln \left( 1 - \frac{a_\infty}{a} \right) - \frac{\alpha}{a^2}, \quad (4)$$

where  $a_\infty$  is the surface area per particle at the maximum degree of coverage of the monolayer. Initially, the van Laar equation<sup>27</sup> and recently also the Frumkin equation<sup>28, 29</sup> were extended to multi-component systems.

A reference database for the two-dimensional equation of state for hard disks was created (using the molecular dynamics method and Monte Carlo simulation<sup>30</sup>) twenty-five years later than for the three-dimensional equation of state for hard spheres, being, however, characterised by the highest accuracy (0.01%). The last decade was a period of continuous research in the field of computer simulation<sup>31–33</sup> of two-dimensional systems and, as a supplement, of the scaled particle theory.<sup>34</sup> The availability of the high-accuracy database gave impetus to the development of the theory of the two-dimensional equation of state. Quite accurate but rather complex equations (*e.g.*, the Padé and Levin approximations<sup>30</sup>) based on a set of initial virial coefficients were derived. At the same time it was demonstrated that at present derivation of simple and accurate equations for hard disks<sup>35, 36</sup> using the Boltzmann concepts presents no significant difficulties.

Recently, a new approach has been elaborated to the theory of the equation of state based on the exclusion factor (excluded volume or surface area) for both bulk<sup>37–46</sup> and surface<sup>47–54</sup> systems. The approach is based on new thermodynamic relations and on a general relation of statistical mechanics for the chemical potential of a particle (molecule, ion or nanoparticle) of the  $i$ th component rather than the scaled particle theory

$$\mu_i = \mu_i^0 + k_B T \ln(c_i \Lambda_i^3), \quad (5)$$

where  $\mu_i^0$  is the chemical potential of the particle with centre of mass at rest,  $c_i$  is the concentration (particle number per unit volume) and  $\Lambda_i$  is the average de Broglie wavelength (temperature function). A traditional term including the activity coefficient is allowed for by the quantity  $\mu_i^0$ , which differs from  $\mu$  only in that it corresponds to the particle at rest.

The main parameter of the new theory is the exclusion factor (reduced excluded volume or surface area) determining the solution to the master equation that generates the equations of state. This parameter varies over a narrow range, thus providing a good accuracy of solution in different approximations. The adequacy of the approach is quite surprising. Not only does the method allow new accurate and simple (the simplicity condition is included in the computational algorithm) equations of state to be derived but it also permits reproduction of known equations that are seemingly not interrelated and establishment of some hierarchy of approximations involving these equations. On the one hand, this permits better understanding of conventional relations (we will see it below taking the van der Waals and Planck equations as examples). On the other hand, this provides a way to systematise the most important available data on the equation of state. Because of this, in the text below we use the formalism of the new approach.

## II. The equation of state for bulk phases

Now we introduce some notions and definitions used in the new theory. First of all, this is a new and rigorous thermodynamic definition of the excluded volume  $v_i^{\text{ex}}$  as the partial volume of a particle of component  $i$  with a resting centre of mass in the absence of all interactions except for the short-range interactions related to the volume of the own particle

$$v_i^{\text{ex}} \equiv v_i^0 \equiv \left( \frac{\partial V}{\partial N_i^0} \right)_{T, p, N_j, N_{j \neq i}^0}. \quad (6)$$

Here  $v_i^0$  is the partial volume of a resting particle of component  $i$  defined as the derivative of the system volume  $V$  with respect to the number,  $N_i^0$ , of particles at rest in the system provided that the temperature, pressure and the numbers,  $N_j$ ,  $N_{j \neq i}^0$ , of other particles are constant. A similar definition of the partial volume,  $v_i$ , of ordinary (moving) particles known in thermodynamics obeys the relationship

$$v_i = \left( \frac{\partial \mu_i}{\partial p} \right)_{T, \{x_i\}}, \quad (7)$$

where  $\{x_i\}$  is the set of mole fractions  $x_i$  symbolising the constancy of composition. An analogous expression for particles at rest

$$v_i^0 = \left( \frac{\partial \mu_i^0}{\partial p} \right)_{T, \{x_i\}}, \quad (8)$$

was derived as a new thermodynamic relation.<sup>38</sup> For both resting and moving particles the partial volume differs from the own particle volume  $v_{i0}$ . For instance, in gases  $v_i$  is incomparably larger than  $v_{i0}$ . Moreover, in contrast to the own particle volume, the partial particle volume can be of any sign because of competition between attractive (long-range) and repulsive forces. In the absence of long-range forces the partial volume of a particle at rest is positive and equals the excluded volume. The excluded volume is always positive, being comparable with the own particle volume. Indeed, the excluded volume is usually treated as a space inaccessible to the centres of mass of moving particles. Assuming particles to be spherical (because of Brownian rotation or simply as a model) and their concentration to be low (rarefied gas), the excluded volume can be estimated as follows. For mobile particles of the  $k$ th component of radius  $r_k$ , a resting particle of component  $i$  of radius  $r_i$  creates an excluded volume  $v_{ik}^{\text{ex}}$  in the form of a sphere of radius  $r_i + r_k$  (Fig. 1). From here it follows

$$v_{ik}^{\text{ex}} = \left( v_{i0}^{1/3} + v_{k0}^{1/3} \right)^3, \quad (9)$$

where  $v_{i0} = 4\pi r_i^3/3$  and  $v_{k0} = 4\pi r_k^3/3$  are the corresponding particle volumes [for particles of the same size relationship (9) gives  $v^{\text{ex}} = 8v_0$ , as mentioned above]. Averaging of relation (9) gives the excluded volume for a gas mixture

$$v^{\text{ex}} = \sum_{i,k} x_i x_k \left( v_{i0}^{1/3} + v_{k0}^{1/3} \right)^3. \quad (10)$$

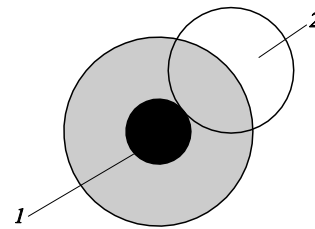


**Figure 1.** The excluded volume (shaded by gray) created by a resting particle (1) with respect to a moving particle (2).

Similarly, for the average particle volume and the average partial particle volume in a mixture one gets

$$v_0 \equiv \sum_i x_i v_{i0}, \quad (11)$$

$$v^0 = \sum_i x_i v_i^0.$$

The exclusion factor  $f$ , the most important parameter of the theory, is defined as the ratio of the average excluded volume to the average particle volume in the system

$$f \equiv \frac{v^{\text{ex}}}{v_0}. \quad (12)$$

From Eqns (10) and (11) it follows that the exclusion factor  $f_0$  for a rarefied gaseous mixture can be calculated using the relationship

$$f_0 = \frac{v^{\text{ex}}}{v_0} = \frac{\sum_{i,k} x_i x_k (v_{i0}^{1/3} + v_{k0}^{1/3})^3}{\sum_i x_i v_{i0}}. \quad (13)$$

From here for a one-component system we again get  $f_0 = 8$  (for mixtures, the  $f_0$  value can be much smaller, remaining, however, greater than two).

Passage from rarefied to the condensed state is accompanied by clustering of matter, which causes a decrease in the exclusion factor.<sup>38, 39, 42</sup> The minimum value,  $f = 1$ , is only possible for 'soft' particles capable of filling the space without cavities; for hard particles the exclusion factor is always larger than unity and depends on the packing type. Generally, the excluded volume factor varies within the limits

$$f_0 \geq f \geq \frac{v_\infty}{v_0}, \quad (14)$$

where  $v_\infty$  is the limiting volume per particle. Equality of  $v_\infty$  and  $v_0$  is only possible for 'soft' particles; otherwise, usually one has  $v_\infty > v_0$ . For instance, one gets  $v_\infty/v_0 = 6/\pi \approx 1.91$  for a cubic packing of hard spheres and  $v_\infty/v_0 = 6/\pi\sqrt{2} \approx 1.35$  for hexagonal packing. In any case the excluded volume factor varies in some narrow region within the interval  $8 \geq f \geq 1$ , whereas the pressure varies in a nearly unbounded interval. This makes the excluded volume factor a convenient tool in deriving the equation of state.

The formulation of theory begins with derivation of the master equation, that is, a rigorous thermodynamic relation to generate equations of state. We start from the Gibbs–Duhem equation

$$dp = -s dT + \sum_i c_i d\mu_i, \quad (15)$$

where  $s$  is the entropy density and  $c_i$  is the concentration of the  $i$ th component. Integration of Eqn (15) is performed at constant temperature and chemical composition (this limitation is removed after integration), so the concentration,  $c_i$ , of each component can be expressed through the overall concentration of all components

$c = \sum_i c_i$ , which becomes the exclusive integration variable.

Substitution of expression (5) into relation (15) with allowance for Eqn (8) gives

$$\frac{dp}{dc} = \frac{k_B T}{1 - cv^0}, \quad (16)$$

where  $v^0$  is the average partial volume of the particle at rest according to definition (11). As mentioned above, the behaviour of the quantity is complex owing to competition between the attractive and repulsive forces, which precludes integration of Eqn (16) in the general form. To get around this problem, we first integrate Eqn (16) in the absence of long-range interactions [in this case, according to definition (6),  $v^0$  is 'automatically' transformed

into  $v^{\text{ex}}$ ] and then add the long-range contribution  $p_1$  to the final expression. This gives the master equation in the form

$$p = k_B T \int_0^c \frac{dc}{1 - cv^{\text{ex}}} + p_1. \quad (17)$$

Expressions for  $p_1$  can be found in the literature. In particular, for the van der Waals forces one has

$$p_1 = - \sum_{i,k} \alpha_{ik} c_i c_k, \quad (18)$$

where  $\alpha_{ik}$  is the constant of attraction between particles of components  $i$  and  $k$ .

For simplicity, the master Eqn (17) can be written in a dimensionless form

$$\tilde{p} = \int_0^\varphi \frac{d\varphi}{1 - f\varphi} + \tilde{p}_1, \quad (19)$$

where  $\tilde{p} \equiv pv_0/k_B T$  and  $\tilde{p}_1$  are respectively the dimensionless pressure and its long-range part and  $\varphi$  is the total volume fraction of all components as the sum of individual volume fractions  $\varphi_i$

$$\varphi \equiv cv_0 = \sum_i c_i v_{i0} = \sum_i \varphi_i.$$

Correspondingly, Eqn (18) is transformed into

$$\tilde{p}_1 = - \sum_{i,k} \tilde{\alpha}_{ik} \varphi_i \varphi_k, \quad (20)$$

where  $\tilde{\alpha}_{ik} \equiv \alpha_{ik} v_0/k_B T v_{i0} v_{k0}$  is the dimensionless image of the constant  $\alpha_{ik}$ . In modern literature, the reduced density

$$y \equiv \frac{\sigma^3}{v} = \frac{6}{\pi} \varphi,$$

rather than the volume fraction  $\varphi$  (here,  $\sigma$  is the particle diameter) is often used. Clearly, this value corresponds to cubic packing of spheres, which, however, is not the closest packing. Having defined the reduced density in a more general form as follows

$$y \equiv \frac{v_\infty}{v},$$

(where  $v_\infty$  can also belong to hexagonal packing), one gets an alternative dimensionless form of the master equation

$$\tilde{p}' = \int_0^y \frac{dy}{1 - gy} + \tilde{p}'_1. \quad (21)$$

Here

$$\tilde{p}' \equiv \frac{pv_\infty}{k_B T},$$

$g \equiv v^{\text{ex}}/v_\infty$  is yet another exclusion factor. Correspondingly, the second dimensionless form of Eqn (18) is as follows:

$$\tilde{p}'_1 = - \sum_{i,k} \tilde{\alpha}'_{ik} y_i y_k, \quad (22)$$

where  $\tilde{\alpha}'_{ik}$  is the dimensionless attraction constant

$$\tilde{\alpha}'_{ik} \equiv \frac{\alpha_{ik} v_\infty}{k_B T v_{i\infty} v_{k\infty}}.$$

For the most dense state the exclusion factor  $g$  equals unity; therefore, it is convenient to use Eqn (21) for the condensed state. But if one starts from the gaseous state, it's better to work with Eqn (19).

To calculate the integral in Eqn (19), one must know the function  $f(\varphi)$ . Information on this function for one-component systems can be extracted from virial coefficients. If we express the exclusion factor in terms of virial expansion<sup>37, 38</sup> and restrict to the ten known virial coefficients for the system of hard spheres,<sup>55</sup> the dependence of  $f$  on  $\varphi$  is characterised by a decreasing concave

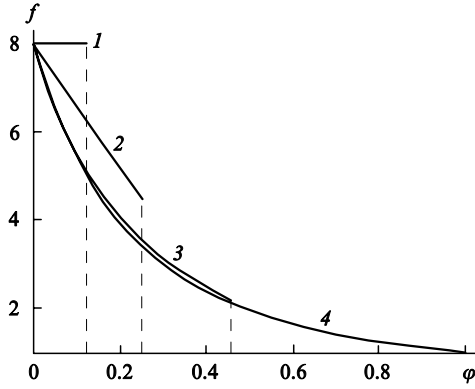


**Figure 2.** Exclusion factor plotted vs. volume fraction (solid lines) and the limits of applicability for the corresponding equations of state (dashed lines) with allowance for the short-range part only. Planck equation (1), van der Waals equation (2), Eqn (38) (3) and the line obtained from the virial expansion for hard spheres with ten known virial coefficients (4).

curve (curve 4, Fig. 2). The general form of the function  $f(\varphi)$  is still unknown. However, taking into account that the exclusion factor can vary within narrow limits, one can hope for derivation of rather accurate equations of state using realistic approximations for the function  $f(\varphi)$ .

The simplest (zeroth) approximation is to use a constant exclusion factor  $f$ . Here, the equation of state is immediately derived from Eqn (19)

$$\tilde{p} = -\frac{\ln(1-f\varphi)}{f} + \tilde{p}_1. \quad (23)$$

Particular cases of this equation are well known.

For a non-ionised monatomic gas with  $f = 8$  and allowance for Eqn (20) one has

$$\tilde{p} = -\frac{\ln(1-8\varphi)}{8} - \tilde{\alpha}\varphi^2. \quad (24)$$

This is neither more nor less than the Planck equation (2) written in a dimensionless form.

For the condensed state, taking into account Eqn (21) with  $g = 1$  and Eqn (22), we get

$$\tilde{p}' = -\ln(1-y) - \tilde{\alpha}'y^2. \quad (25)$$

This type of equation of state was derived by Temperley<sup>56,57</sup> who applied the Ising model to the lattice gas condensation theory. Later, it was often used in lattice models.<sup>58</sup>

The next (first) approximation takes into account that the exclusion factor must decrease with an increase in density (a linear dependence is assumed)

$$f = f_0 - k\varphi. \quad (26)$$

Here,  $f_0$  is the exclusion factor for rarefied gas and  $k$  is the a positive coefficient whose magnitude imposes limitations on the range of changes in  $\varphi$ . Substituting Eqn (26) into Eqn (19) gives the lattice gas equation of state in the first approximation

$$\tilde{p} = \int_0^\varphi \frac{d\varphi}{1-f_0\varphi+k\varphi^2} + \tilde{p}_1. \quad (27)$$

The form of the function resulting from the integration depends on the numerical value of the constant  $k$ ; therefore, expression (27) in fact defines a family (namely, three types<sup>37-39,41</sup>) of equations of state rather than a single equation of state. When using this approximation and higher approximations, we are guided by the principle of maximum simplicity of the solution. In this case, we take  $k = (f_0/2)^2$  and the equation of state has the form:

$$\tilde{p} = \frac{\varphi}{1-(f_0/2)\varphi} + \tilde{p}_1. \quad (28)$$

With allowance for Eqn (20) and  $f_0 = 8$ , Eqn (28) for a one-component system with van der Waals forces takes the form

$$\tilde{p} = \frac{\varphi}{1-4\varphi} - \tilde{\alpha}\varphi^2. \quad (29)$$

This is neither more nor less than the van der Waals equation (1) written in a dimensionless form.

Now we can clearly see the sense of the coefficient 4 in Eqn (1) and resolve the apparent contradiction between the van der Waals and Planck equations. Namely, the factor  $4v_0$  in the van der Waals equation is not the excluded volume. This equation does not include a constant excluded volume at all; rather, the excluded volume in this equation is variable. The van der Waals equation ranks higher than the Planck equation in the hierarchy of approximations, though the place occupied by the former is not the place of honour.

In the second approximation<sup>37-43</sup> we model the concavity of the  $f(\varphi)$  curve using a fractional-linear function

$$f = \frac{f_0 - k_1\varphi}{1 + k_2\varphi} \quad (30)$$

with two positive constants  $k_1$  and  $k_2$ . Yet another positive constant  $K$  is introduced to characterise the initial (negative) slope of the curve  $f(\varphi)$

$$\left(\frac{df}{d\varphi}\right)_{\varphi \rightarrow 0} = -K. \quad (31)$$

To calculate  $K$ , it is sufficient to know the second and third virial coefficients. For a one-component system, one has  $K = 34$ . From Eqns (30) and (31) one gets the relation

$$k_1 + k_2 f_0 = K \quad (32)$$

connecting the coefficient  $k_1$  to  $k_2$ ; as a result, only one of them can be chosen independently.

Substituting Eqn (30) into the master equation (19) leads to

$$\tilde{p} = \int_0^\varphi \frac{(1-k_2\varphi)d\varphi}{1-(f_0-k_2)\varphi+k_1\varphi^2} + \tilde{p}_1, \quad (33)$$

and its simplest form after integration meets the condition

$$k_1^{1/2} = \frac{f_0 - k_2}{2} \equiv \beta. \quad (34)$$

Taken together, this relationship and Eqn (32) unambiguously determine the coefficients  $k_1$  and  $k_2$

$$k_1 = (f_0 - K^{1/2})^2, \quad (35)$$

$$k_2 = 2K^{1/2} - f_0.$$

With  $k_1$  and  $k_2$  thus determined, the equation of state in the second approximation has the form

$$\tilde{p} = \frac{f_0 - \beta}{\beta} \frac{\varphi}{1 - \beta\varphi} + \frac{f_0 - 2\beta}{\beta^2} \ln(1 - \beta\varphi) + \tilde{p}_1, \quad (36)$$

where

$$\beta = f_0 - K^{1/2}.$$

Using Eqn (20), Eqn (36) for a nonionic system with van der Waals forces can be written in a more detailed form

$$\tilde{p} = \frac{f_0 - \beta}{\beta} \frac{\varphi}{1 - \beta\varphi} + \frac{f_0 - 2\beta}{\beta^2} \ln(1 - \beta\varphi) - \sum_{i,k} \tilde{\alpha}_{ik} \varphi_i \varphi_k. \quad (37)$$

For a one-component system, one has  $f_0 = 8$ ,  $K = 34$  and  $\beta \approx 2.169$ . In this case Eqn (37) takes the form

$$\tilde{p} = \frac{2.688\varphi}{1 - 2.169\varphi} + 0.778 \ln(1 - 2.169\varphi) - \tilde{\alpha}\varphi^2. \quad (38)$$

Equation (38) looks like a combination of the van der Waals and Planck equations, being much more accurate than both of them and provides exact values of the first three rather than two virial coefficients. This equation describes a gas–liquid phase transition and the critical point. A comparison of the critical parameters of the three equations<sup>37–39, 41</sup> revealed their improvement on going up in the hierarchy of approximations. One of the critical parameters of Eqn (38) can be treated outstandingly, *viz.*, the ratio of the Boyle temperature ( $T_B$ ) to the critical temperature ( $T_c$ ) is 2.74 (*cf.* a value of 2.75 determined from experiments).

Figure 2 shows how the range of applicability of the equation of state extends in the hierarchy of approximations. Indeed, one has  $\varphi < 0.125$  for the Planck equation,  $\varphi < 0.25$  for the van der Waals equation and  $\varphi < 0.461$  for Eqn (38); but this is much smaller than  $\varphi = 0.74$  for the closest packing of hard spheres. Therefore, all three equations are applicable to gases. Nevertheless, Eqn (36) can be adapted to the whole density range. The case in point is that this equation gives the correct value of the second virial coefficient irrespective of the parameter  $\beta$ , which thus is responsible for the correctness of the value of the third virial coefficient. Losing quality of the equation, it is possible to use a fitting parameter  $k$  instead of  $\beta$  and write the equation of state for a system of hard spheres of the same size as

$$\tilde{p} = \frac{8-k}{k} \frac{\varphi}{1-k\varphi} + \frac{8-2k}{k^2} \ln(1-k\varphi), \quad (39)$$

and then determine the  $k$  value assuming the best correspondence between Eqn (39) and the results of a molecular dynamics simulation.<sup>6</sup> This procedure can be illustrated by Fig. 3; the  $k$  and cross-correlation square  $R^2$  (this parameter characterises the quality of computer fitting) values are listed in Table 1. As can be seen, while the curve plotted using Eqn (39) passes near the ‘experimental’ points, the amplitude of deviations (1%–10%) is too large to meet modern requirements.

The third and higher approximations were derived by successively adding the terms next in order of smallness to the numerator of expression (30) while the principle of maximum simplicity was realised by choosing the coefficients reducing the denominator of the first term of the equation of state to an integer power of the difference. All coefficients were expressed through the same

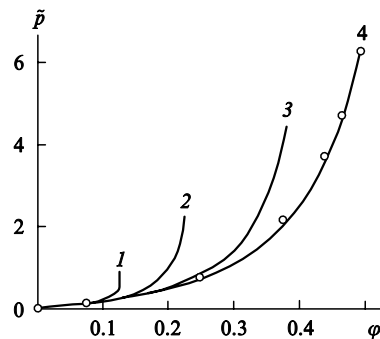


**Figure 3.** Dimensionless pressure isotherms for a fluid of hard spheres obtained in the zeroth (Planck equation, curve 1), first (van der Waals equation, curve 2) and second [Eqn (38), curve 3] approximations of the equation of state for a gas derived in the framework of the theory of excluded volume and using Eqn (39) (curve 4) for the entire density range. Points denote the results of molecular dynamics simulations reported by Alder and Wainwright.<sup>6</sup>

**Table 1.** Coefficient  $k$  and cross-correlation square  $R^2$  obtained in different approximations of the equation of state for the whole range of densities in fitting the Alder and Wainwright<sup>6</sup> and Erpenbeck and Wood<sup>59</sup> databases.

| Approximation number | Database <sup>6</sup> |          | Database <sup>59</sup> |          |
|----------------------|-----------------------|----------|------------------------|----------|
|                      | $k$                   | $R^2$    | $k$                    | $R^2$    |
| 2                    | 1.592960              | 0.994418 | 1.597202               | 0.989454 |
| 3                    | 1.283681              | 0.997342 | 1.299441               | 0.998856 |
| 4                    | 1.070709              | 0.999457 | 1.077599               | 0.999684 |
| 5                    | 0.918766              | 0.999847 | 0.921284               | 0.999920 |
| 6                    | 0.805259              | 0.999945 | 0.805372               | 0.999988 |
| 6'                   | 0.803025              | 0.999952 | 0.802941               | 0.999994 |
| 7                    | 0.717260              | 0.999946 | 0.715955               | 0.999998 |
| 8                    | 0.563023              | 0.998591 | 0.608111               | 0.999611 |

constant  $k$ . The third and higher approximations contain no logarithms and can be expressed using a general relationship

$$\tilde{p}^{(n)} = \frac{1}{(1-k\varphi)^{n-1}} \left\{ \varphi + \frac{f_0 - 2k(n-1)}{(n-1)(n-2)k^2} \times \right. \quad (40)$$

$$\left. \times \left[ (1-k\varphi)^{n-1} - 1 + (n-1)k\varphi \right] \right\} + \tilde{p}_1,$$

where  $n$  is the approximation number ( $n \geq 3$ ). It is acceptable to write the equation of state in terms of a compressibility factor (especially for the model of hard spheres)

$$Z \equiv \frac{pv}{k_B T} = \frac{\tilde{p}}{\varphi}. \quad (41)$$

Using this technique, we rewrite relationship (40) for a fluid of hard spheres of the same size ( $f_0 = 8$ ,  $\tilde{p}_1 = 0$ ) in the form

$$Z^{(n)} = \frac{1}{(1-k\varphi)^{n-1}} \left\{ 1 + \frac{8-2k(n-1)}{(n-1)(n-2)k^2\varphi} \times \right. \quad (42)$$

$$\left. \times \left[ (1-k\varphi)^{n-1} - 1 + (n-1)k\varphi \right] \right\}.$$

In this category the Carnahan–Starling equation<sup>60</sup>

$$Z = \frac{1 + \varphi + \varphi^2 - \varphi^3}{(1-\varphi)^3}, \quad (43)$$

obtained by summing the virial expansion with coefficients rounded to integers is thought to be the most accurate. Before this equation (at first, in the framework of scaled particle theory<sup>4</sup>), the Percus–Yewick equation<sup>61, 62</sup>

$$Z = \frac{1 + \varphi + \varphi^2}{(1-\varphi)^3}, \quad (44)$$

$$Z = \frac{1 + 2\varphi + 3\varphi^2}{(1-\varphi)^2}, \quad (45)$$

(in the form of the compressibility and pressure equations, respectively) and the Guggenheim equation<sup>63</sup>

$$Z = \frac{1}{(1-\varphi)^4}. \quad (46)$$

were derived. Here, we don't present well-established, more complex equations of state (Padé approximants,<sup>64</sup> Le Fevre equation,<sup>65</sup> Woodcock equation,<sup>66</sup> *etc.*) because they are not related to the approach in question and are inconsistent with the concept of maximum simplicity.

Returning to Eqn (42), we will make some comments concerning particular approximations. For the third, fourth and fifth approximations we get the following equations of state:

$$Z^{(3)} = \frac{1 + (4 - 2k)\varphi}{(1 - k\varphi)^2}, \quad (47)$$

$$Z^{(4)} = \frac{1 + (4 - 3k)\varphi + k(k - 4/3)\varphi^2}{(1 - k\varphi)^3}, \quad (48)$$

$$Z^{(5)} = \frac{1 + (2/3)(1 - k)(6\varphi - 4k\varphi^2 + k^2\varphi^3)}{(1 - k\varphi)^4}. \quad (49)$$

With  $k = 1$ , Eqn (47) is a truncated Percus–Yewick equation (45), relationship (48) is similar to the Carnahan–Starling equation (43) and the Percus–Yewick equation (44), while equation (49) coincides with the Guggenheim equation (46).

The reader can assure himself that Eqn (42) gives the correct value of the second virial coefficient irrespective of the value of  $k$ . In other words, Eqn (42) can be applied to a gas of hard spheres at any value of the constant  $k$  that can be used as a parameter of fitting to the results of numerical experiments for all densities; this is the best way to refine Eqn (42). This was done<sup>67, 68</sup> using the first database by Alder and Wainwright<sup>6</sup> (see above) and the highly accurate but covering the range of lower densities database by Erpenbeck and Wood<sup>59</sup>. Table 1 lists the  $k$  values thus found for each approximation and the cross-correlation squares  $R^2$ . As can be seen, the highest accuracy of equation (42) is achieved in the seventh approximation. Passage to higher approximations is pointless because starting from the eighth approximation the results of fitting become much poorer owing to the use of only one parameter. It should be noted that already in the third approximation the region of formally admissible changes in the volume fraction,  $0 \leq \varphi \leq 0.779$ , is broader than the region of formally admissible changes for a system of hard spheres,  $0 \leq \varphi \leq 0.74$ , which ensures coverage of all possible densities.

The sixth approximation of Eqn (42) deserves particular attention. With the  $k$  value listed in Table 1, which nearly coincides for both databases, this approximation has the numerical form

$$Z^{(6)} = \frac{1 - 0.026(\varphi - 0.805\varphi^2 + 0.324\varphi^3 - 0.052\varphi^4)}{(1 - k\varphi)^5}. \quad (50)$$

The smallness of the coefficient 0.026 allows the numerator to be truncated to unity. Having done this, one gets an approximation (denoted by 6')

$$Z^{(6')} = (1 - k\varphi)^{-5}, \quad (51)$$

which combines a very simple form with high accuracy. Indeed, after repeating the fitting procedure using Eqn (51) and getting somewhat different  $k$  values (see Table 1) we find that Eqn (51) is the most accurate among all approximations (with a maximum deviation of less than 1%) evaluated using the Alder and Wainwright database. A comparison of the accuracy of Eqn (51) with the accuracy of the Carnahan–Starling equation (43) and other equations of state (even complex equations including the most accurate Woodcock equation<sup>66</sup>) shows the advantage of Eqn (51).<sup>45, 46</sup> Evaluated with the highly accurate Erpenbeck and Wood database, Eqn (51) occupies an intermediate position between the sixth and seventh approximations, being characterised by a maximum deviation of 0.45%. Here, the Carnahan–Starling equation provides a maximum deviation of 0.31% while Eqn (42) in the seventh approximation is characterised by a deviation of only 0.20% (see Ref. 68) (the Woodcock equation was evaluated using another database and was characterised by a deviation of 0.59%).

Thus, at present Eqn (42) at  $n = 7$  is one of the most accurate equations of state (maybe, the most accurate one). It should be noted that in comparing the equations of state a question of the accuracy of the database is posed.<sup>6</sup> As it is improved, the procedure can be repeated for any other set of reference data, which allows the coefficient  $k$  in Eqns (42) and (40) to be refined.

### III. Equation of state for surface monolayers

A technique similar to that considered above was applied to the analysis of a surface monolayer formed on adsorption or spreading of a substance on the surface. The surface area was considered instead of volume. However, it is incorrect to reason that transition from the equation of state for bulk systems to the equation of state for a monolayer is reduced to trivial reduction of the equation dimension. The volume,  $v_0$ , of anisometric particles is independent while their parking area,  $a_0$ , depends on the spatial orientation, which complicates the computational procedure. The necessity of taking into account the effect of the substrate also goes beyond the two-dimensional approach. Thus, strictly speaking, description of a monolayer requires a three-dimensional theory based on the same expression (5) for the chemical potential of matter in the bulk system.

Consider a multicomponent monolayer on a planar (solid or liquid) substrate. Since only the surface characteristics are important for the equation of state, the monolayer will be thought insoluble; this will permit a rigorous treatment in terms of equilibrium thermodynamics. The main relationship in this theory is the Gibbs adsorption equation

$$d\gamma = -\bar{s}dT - \sum_i \Gamma_i d\mu_i, \quad (52)$$

where  $\gamma$  is the surface tension,  $\bar{s}$  is the entropy excess per unit surface area and  $\Gamma_i$  and  $\mu_i$  are the adsorption (excess of substance per unit surface area) and the chemical potential of particles (molecules, ions or nanoparticles) of component  $i$  in the monolayer. Summation is performed over all components of the monolayer but does not involve the substrate whose influence is included in all other parameters. For insoluble monolayers the adsorption  $\Gamma_i$  coincides with the actual amount of matter per unit surface area of the monolayer. In other words,  $\Gamma_i$  is the surface concentration of particles of the sort  $i$ , related to conventional (three-dimensional) concentration as follows

$$c_i = \frac{\Gamma_i}{h_i}, \quad (53)$$

where  $h_i$  is the average size of particles of the sort  $i$  in the direction perpendicular to the plane of the monolayer. Clearly, if we deal with aspherical particles, the parameter  $h_i$  is sensitive to their orientation.

According to the Gibbs equation of adsorption, the presence of a substrate causes a decrease in the surface tension of the monolayer. The difference

$$\Pi_0 \equiv \gamma_0 - \gamma, \quad (54)$$

( $\gamma_0$  is the surface tension of the substrate in the absence of a monolayer) is called the surface pressure; this is the main characteristic of the monolayer. Substituting Eqn (54) into Eqn (52) gives the equation

$$d\Pi = \bar{s}dT + \sum_i \Gamma_i d\mu_i, \quad (55)$$

which is similar to the Gibbs–Duhem equation (15). Equations (5), (53) and (55) serve as the basis of a theory which also operates with some geometric characteristics considered below.

The most important geometric characteristics of the particles of component  $i$  in the monolayer are the parking area  $a_{i0}$ , the minimum possible surface area per particle  $a_{i\infty}$  at  $\Pi \rightarrow \infty$ , the partial surface area  $a_i$ , the partial surface area of a particle at rest  $a_i^0$  and the excluded surface area  $a_i^{\text{ex}}$  defined as the partial area of a particle at rest in the absence of long-range forces<sup>47–49</sup>

$$a_i^{\text{ex}} \equiv a_i^0 \equiv \left( \frac{\partial A}{\partial N_i^0} \right)_{T, \Pi, N_j, N_{j \neq i}^0}, \quad (56)$$

where  $A$  is the surface area of the monolayer. The partial surface areas obey the following relations

$$a_i = \left( \frac{\partial \mu_i}{\partial \Pi} \right)_{T, \{x\}}, \quad (57)$$

$$a_i^0 = \left( \frac{\partial \mu_i^0}{\partial \Pi} \right)_{T, \{x\}},$$

where  $\{x_i\}$  is the set of mole fractions of the components

$$x_i \equiv \frac{\Gamma_i}{\Gamma}, \quad (58)$$

$$\Gamma \equiv \sum_i \Gamma_i.$$

Out of two relations (57) the latter was derived recently.<sup>47</sup>

The multicomponent monolayer is also characterised by the average geometric parameters:

$$a_0 \equiv \sum_i x_i a_{i0}, \quad (59)$$

$$a_\infty \equiv \sum_i x_i a_{i\infty}, \quad (60)$$

$$a \equiv \sum_i x_i a_i, \quad (61)$$

$$a^0 \equiv \sum_i x_i a_i^0, \quad (62)$$

$$a^{\text{ex}} \equiv \sum_i x_i a_i^{\text{ex}}, \quad (63)$$

$$h \equiv \sum_i x_i h_i. \quad (64)$$

The parameter  $h$  can be treated as the average monolayer thickness.

Integration of Eqn (55) assuming constant temperature and composition taking into account Eqns (5), (53) and (56)–(64) gives the master equation

$$\Pi = k_B T \int_0^\Gamma \frac{1 - cdh/d\Gamma}{1 - \Gamma a^{\text{ex}}} d\Gamma + \Pi_1, \quad (65)$$

where  $\Pi_1$  is the long-range part of the surface pressure. For instance, in the case of the van der Waals interaction one has

$$\Pi_1 = - \sum_{i,k} \alpha_{ik} \Gamma_i \Gamma_k. \quad (66)$$

Equation (65) is an analogue of the master Eqn (17) for bulk phases but has a more complex form owing to the orientation effect ( $dh/d\Gamma$  derivative). At a specified particle orientation or in the case of spherical particles, the derivative  $dh/d\Gamma$  vanishes and the master equation takes the two-dimensional form

$$\Pi = k_B T \int_0^\Gamma \frac{d\Gamma}{1 - \Gamma a^{\text{ex}}} + \Pi_1, \quad (67)$$

suitable for the derivation of two-dimensional equations of state.

Using  $a_0$  or  $a_\infty$ , Eqn (67) can be written in a dimensionless form in two alternative ways. The first form is

$$\tilde{\Pi} = \int_0^\varphi \frac{d\varphi}{1 - f\varphi} + \tilde{\Pi}_1, \quad (68)$$

where  $\tilde{\Pi} \equiv \Pi a_0 / k_B T$  and  $\tilde{\Pi}_1$  are respectively the dimensionless surface pressure and its long-range part,  $\varphi \equiv \Gamma a_0$  is the total surface fraction of components of the monolayer and  $f \equiv a^{\text{ex}} / a_0$  is the exclusion factor. The second form is as follows

$$\tilde{\Pi}' = \int_0^\theta \frac{d\theta}{1 - g\theta} + \tilde{\Pi}'_1, \quad (69)$$

where the dimensionless surface pressure is given by  $\tilde{\Pi}' \equiv \Pi a_\infty / k_B T$ ,  $\theta \equiv \Gamma a_\infty$  is the surface coverage degree and  $g$  is the second exclusion factor

$$g \equiv \frac{a^{\text{ex}}}{a_\infty} = \frac{f a_0}{a_\infty}. \quad (70)$$

In the case of van der Waals interactions the long-range part of the surface pressure in Eqns (68) and (69) has the form

$$\tilde{\Pi}_1 = - \sum_{i,k} \tilde{\alpha}_{ik} \varphi_i \varphi_k, \quad (71)$$

$$\tilde{\Pi}'_1 = - \sum_{i,k} \tilde{\alpha}'_{ik} \theta_i \theta_k, \quad (72)$$

where  $\tilde{\alpha}_{ik} \equiv \alpha_{ik} a_0 / k_B T a_{i0} a_{k0}$  and  $\tilde{\alpha}'_{ik} \equiv \alpha_{ik} a_\infty / k_B T a_{i\infty} a_{k\infty}$ . Of course, Eqns (68) and (69) are equivalent and the use of a particular equation is governed by convenience. Equation (68) is more appropriate for the gaseous state while Eqn (69) is better for the condensed state.

The functions  $f(\varphi)$  and  $g(\theta)$  in Eqns (68) and (69) are still unknown, but the ranges of their changes are available.<sup>48, 52–54</sup> For a gas, the average exclusion factor in the multicomponent monolayer can be calculated with ease using the relationship

$$f_0 = \frac{\sum_{i,k} x_i x_k (a_{i0}^{1/2} + a_{k0}^{1/2})^2}{\sum_i x_i a_{i0}}. \quad (73)$$

Equation (73) gives  $f_0 = 4$  for one-component and even smaller  $f_0$  for multicomponent monolayers. This is the maximum value of the exclusion factor in the absence of clustering. Analysis of two-dimensional clustering<sup>48, 52–54</sup> defines the minimum value of the exclusion factor as  $f_\infty = a_\infty / a_0$  (packing type dependent parameter). Then, in accord with Eqn (70), the minimum value of  $g$  must be  $g_\infty = 1$ . In any case the exclusion factor varies within the interval  $4 > f$ ,  $g > 1$ , which is narrower than for three-dimensional systems. Correspondingly, one can also expect a higher accuracy of the equation of state when using approximations for the functions  $f(\varphi)$  and  $g(\theta)$ .

Consider two-dimensional equations of state that follow from Eqns (68) and (69). In the zeroth approximation the exclusion factor is thought to be constant, which is possible only for a narrow interval of gas or fluid states. In this case, Eqns (68) and (69) take the form

$$\tilde{\Pi} = - \frac{\ln(1 - f\varphi)}{f} + \tilde{\Pi}_1, \quad (74)$$

$$\tilde{\Pi}' = - \frac{\ln(1 - g\theta)}{g} + \tilde{\Pi}'_1. \quad (75)$$

Equation (74) for a rarefied non-ionised gas with  $f = f_0 = 4$  and allowance for expression (71) is transformed to

$$\tilde{\Pi} = - \frac{\ln(1 - 4\varphi)}{4} - \tilde{\alpha}\varphi^2. \quad (76)$$

This is a two-dimensional analogue of the Planck equation (24), which also gives the exact value of the second virial coefficient of two-dimensional virial expansion. By replacing the factor 4 in Eqn (76) by  $f_0$  in accord with Eqn (73) we get a general expression for a two-dimensional gaseous mixture.

Equation (75) with  $g = 1$  gives two famous equations. At  $\tilde{\Pi}'_1 = 0$ , it represents the van Laar equation of state for an ideal monolayer

$$\tilde{\Pi}' = - \ln(1 - \theta), \quad (77)$$



whose form is independent of the number of components.<sup>27</sup> If (again with  $g = 1$ ) the parameter  $\tilde{H}'_1$  is expressed in the form (72), Eqn (75) represents the generalised Frumkin equation<sup>28, 29</sup> written in a dimensionless form

$$\tilde{H}' = -\ln(1 - \theta) - \sum_{i,k} \tilde{\alpha}'_{ik} \theta_i \theta_k. \quad (78)$$

For one-component systems the equation of state (78) takes the form

$$\tilde{H}' = -\ln(1 - \theta) - \tilde{\alpha}' \theta^2. \quad (79)$$

It corresponds to the Frumkin equation (4) written in a dimensionless form, which is transformed into the van Laar equation at  $\tilde{\alpha}' = 0$ .

Starting from the gaseous state, we must assume that the exclusion factor decreases as the surface density increases. To a first approximation, the exclusion factor  $f$  is a linear function of  $\varphi$

$$f = f_0 - k_1 \varphi, \quad (80)$$

where  $k_1$  is a positive constant. Substituting the dependence (80) into Eqn (68) gives a family of equations of state. The simplest of them meets the condition  $k_1 = f_0^2/4$  and has the form

$$\tilde{H} = \frac{\varphi}{1 - (f_0/2)\varphi} + \tilde{H}_1. \quad (81)$$

Substituting expression (71) into Eqn (81), we get the generalised van der Waals equation written in a dimensionless form

$$\tilde{H} = \frac{\varphi}{1 - (f_0/2)\varphi} - \sum_{i,k} \tilde{\alpha}_{ik} \varphi_i \varphi_k. \quad (82)$$

For a one-component system ( $f_0 = 4$ ) Eqn (82) takes the dimensionless form of the two-dimensional van der Waals equation (3)

$$\tilde{H} = \frac{\varphi}{1 - 2\varphi} - \tilde{\alpha}\varphi^2. \quad (83)$$

In the second approximation, a new equation of state is derived.<sup>47, 48, 51, 52</sup> The procedure is the same as that employed in the case of three dimensions [see Eqns (30)–(36)]. Starting from condition (30), we get the two-dimensional equation of state

$$\tilde{H} = \frac{f_0 - \beta}{\beta} \frac{\varphi}{1 - \beta\varphi} + \frac{f_0 - 2\beta}{\beta^2} \ln(1 - \beta\varphi) + \tilde{H}_1, \quad (84)$$

where again  $\beta = f_0 - K^{1/2}$ . Equations (84) and (36) have the same form, but all coefficients are different. In the case of van der Waals forces, substitution of Eqn (71) provides a more detailed equation of state

$$\tilde{H} = \frac{f_0 - \beta}{\beta} \frac{\varphi}{1 - \beta\varphi} + \frac{f_0 - 2\beta}{\beta^2} \ln(1 - \beta\varphi) - \sum_{i,k} \tilde{\alpha}_{ik} \varphi_i \varphi_k. \quad (85)$$

A one-component monolayer is characterised<sup>47, 48, 51, 52</sup> by  $f_0 = 4$ ,  $K = 6.616$  and  $\beta = 1.428$ . Substituting these values into Eqn (85) leads to

$$\tilde{H} = \frac{1.801\varphi}{1 - 1.428\varphi} + 0.561 \ln(1 - 1.428\varphi) - \tilde{\alpha}\varphi^2. \quad (86)$$

This is a two-dimensional equation of state in the second approximation. Unfortunately, the two-dimensional gaseous state has been studied much less than the three-dimensional state. Equation (86) can be evaluated in two ways, by comparison with the van der Waals equation (83) and by comparing the values of the virial coefficients.<sup>16, 69</sup> The applicability range of Eqn (86) ( $0 < \theta < 0.7$ ) is much broader compared to the van der Waals equation ( $0 < \theta < 0.5$ ), the former being much more accurate. If the van der Waals equation gives exact values of the first and the

second virial coefficients only, Eqn (86) exactly reproduces the first, second and third virial coefficients and provides a nearly exact value of the fourth virial coefficient (overestimated by 9%) and the fifth virial coefficient overestimated by 28%.

It is of interest to compare Eqns (38) and (86). As was expected, the two-dimensional equation is more accurate. Until recently, only the van der Waals equation simultaneously covered the three-dimensional and two-dimensional cases. Making use of the situation, de Boer showed<sup>26</sup> that for the same substance the two-dimensional critical temperature  $T_c^{(2)}$  must be half the three-dimensional critical temperature  $T_c^{(3)}$ . Evaluation<sup>49</sup> using Eqns (38) and (86) revealed that

$$\frac{T_c^{(2)}}{T_c^{(3)}} \approx 0.455. \quad (87)$$

The ratio (87) shows that the de Boer estimate  $T_c^{(2)}/T_c^{(3)} \approx 0.5$  is quite correct, being at the same time somewhat rough.

Higher approximations are derived using the same algorithm as for the bulk phases. A general formula for the  $n$ th approximation ( $n \geq 3$ ) is as follows

$$\begin{aligned} \tilde{H}^{(n)} = & \frac{\varphi}{(1 - k\varphi)^{n-1}} \left\{ 1 - \frac{2nk - 2k - f_0}{(n-1)(n-2)k^2\varphi} \times \right. \\ & \left. \times [(1 - k\varphi)^{n-1} - 1 + (n-1)k\varphi] \right\} + \tilde{H}_1. \end{aligned} \quad (88)$$

It is easy to verify that Eqn (88) gives correct values of the first and second virial coefficients irrespective of the choice of the constant  $k$ . This assures applicability of Eqn (88) to the gaseous state of the monolayer at any  $k$  value and allows  $k$  to be used as a fitting parameter for the whole density range. Here, it is convenient to use an ultrahigh-precision (to 0.01%) data array obtained by Monte Carlo simulation and molecular dynamics.<sup>30</sup> Let us demonstrate the procedure taking a model of hard disks as an example.

Let the disks be of the same size,  $\tilde{H}_1 = 0$  and  $f_0 = 4$ . Rewrite Eqn (88) using the compressibility factor  $Z = \tilde{H}/\varphi$ ,

$$\begin{aligned} Z^{(n)} = & \frac{1}{(1 - k\varphi)^{n-1}} \left\{ 1 - \frac{2nk - 2k - 4}{(n-1)(n-2)k^2\varphi} \times \right. \\ & \left. \times [(1 - k\varphi)^{n-1} - 1 + (n-1)k\varphi] \right\}. \end{aligned} \quad (89)$$

In accord with expression (89), the equation of state in the third approximation has the form

$$Z^{(3)} = \frac{1 - 2(k-1)\varphi}{(1 - k\varphi)^2}. \quad (90)$$

With  $k = 1$  Eqn (90) reproduces the equation of state known in scaled particle theory<sup>70, 71</sup>

$$Z^{(3)} = (1 - \varphi)^{-2}. \quad (91)$$

In addition, Eqn (91) is a two-dimensional analogue of the Carnahan–Starling equation (43) for hard spheres, *i.e.*, it is obtained by summing the two-dimensional virial expansion in which all coefficients are rounded to integers. Equation (91) is also similar to the Henderson equation<sup>72</sup>

$$Z = \frac{1 + (b_3 - 3)\varphi^3}{(1 - \varphi)^2} \quad (92)$$

with  $b_3 - 3 \approx 0.128$ . Equation (90) best fits the reference database<sup>30</sup> at  $k \approx 1.0145$  (cross-correlation squared is 0.999908 with a maximum deviation of  $\sim 1\%$ ) and the form of Eqn (90) is as follows

$$Z^{(3)} = \frac{1 - 0.029\varphi}{(1 - 1.0145\varphi)^2}. \quad (93)$$

Since the  $k$  values found do approach unity, expression (91) can be used as the equation of state in the third approximation. In this case a small decrease in accuracy (maximum deviation increases to 3%) is compensated for by the simplicity of the equation. Thus, we can say that scaled particle theory reproduces the third approximation to the theory of excluded area.

Going to the fourth approximation from Eqn (89) gets

$$Z^{(4)} = \frac{1 - (3k - 2)\varphi + k(k - 2/3)\varphi^2}{(1 - k\varphi)^3}. \quad (94)$$

Equation (94) best fits the database<sup>30</sup> at  $k \approx 0.876677$  (cross-correlation squared is 0.99999 with a maximum deviation of  $\sim 0.46\%$ ). With this  $k$  value Eqn (94) takes the form

$$Z^{(4)} \approx \frac{1 - 0.63\varphi + 0.184\varphi^2}{(1 - 0.876677\varphi)^3}. \quad (95)$$

The next (fifth) approximation gives somewhat poorer results (cross-correlation squared is 0.99993), which can be explained by the use of a sole fitting parameter.

Among the studies reported in the last decade, a simple equation of state<sup>35,36</sup> based on the Boltzmann concept of excluded volume must be pointed out. In our notation, the equation has the form

$$Z = \left(1 - 2\varphi + \frac{2\varphi_\infty - 1}{\varphi_\infty^2} \varphi^2\right)^{-1} = \left[1 - 2\varphi_\infty \theta + (2\varphi_\infty - 1)\theta^2\right]^{-1}, \quad (96)$$

where  $\varphi_\infty = a_0/a_\infty = 3^{1/2}\pi/6 \approx 0.9069$  is the upper limit for  $\varphi$ , which corresponds to the closest hexagonal packing, and  $\theta = \varphi/\varphi_\infty$  is the surface coverage degree. The authors of the study<sup>35</sup> compared the accuracy of their equation with the available simple and complex equations including, except for expressions (91) and (92), the equations of state by Andrews,<sup>73,74</sup> Woodcock,<sup>66</sup> Baram and Luban<sup>75</sup> and the Levin<sup>30</sup> and Padé<sup>76</sup> approximants. It was concluded that Eqn (96) is the most accurate among the simple equations. However, a comparative analysis<sup>53</sup> of Eqns (95) and (96) showed that expression (95) is even better, being the best among the simple equations; only the Levin approximant (the most accurate among the complex equations) ranks above it in accuracy.

#### IV. The orientation equation of state

Let us return to Eqn (65) and discuss the role of orientation characterised by the derivative  $dh/d\Gamma$ . To state that an increase in the surface density of a substance must lead to thickening of a monolayer as the main trend probably requires the mass balance only. But from Eqn (65) it is seen that if  $dh/d\Gamma > 0$  and the derivative is rather large in absolute value, then, possibly, the perfect derivative  $d\Pi/d\Gamma$  will be of negative sign, which means stability violation. As a result, a van der Waals loop corresponding to the first-order phase transition can appear in the two-dimensional pressure isotherm. Thus, the first important conclusion that follows from Eqn (65) is that orientation of the particles of the monolayer can induce two-dimensional first-order phase transitions. It is remarkable that this prediction is also valid in the absence of attractive forces between anisometric particles. The effect of orientation on two-dimensional condensation was demonstrated in the experiments with surfactant monolayers.<sup>77</sup>

To make Eqn (65) complete, one should know the dependence of the monolayer thickness  $h$  on the surface density  $\Gamma$ . In the general case the functional dependence

$$h = h(T, \Gamma_1, \Gamma_2, \dots) \quad (97)$$

can be called the orientation equation of state. Neither theoretical nor experimental data on such an equation are available at the moment but the first steps towards formulation of a theory have been made recently.<sup>47,51–53</sup> Of course, the cases in point are general considerations because the orientation effects strongly depend on the specific geometry of particles in the monolayer.

Apparently, the orientation effect arises in the gaseous monolayer. Since particles change their orientations by collisions, one can assume that the increase in the thickness,  $h - h_0$ , is proportional to the collision rate, which in turn is proportional to the square of the particle concentration and to the collision diameter that is determined by the linear dimension of the particles along the surface. If the parking area of particles is proportional to the square of the linear dimension mentioned above and its product by  $h$  (particle volume) is a constant, the linear dimension is proportional to the square root of the thickness. Then, one gets the orientation equation of state

$$h - h_0 = \frac{K\varphi^2}{h^{1/2}}, \quad (98)$$

where  $h_0$  is the minimum thickness of the monolayer at zero surface pressure and  $K$  is the coefficient of proportionality. Analysis and refinement of Eqn (98) should be set aside until experimental data in the field is obtained.

A model of elastic behaviour can also be applied to a condensed monolayer. This approach was used in the membrane theory<sup>78</sup> by introducing a ‘tilt modulus’ which has not been determined experimentally so far. Using the variable  $\theta$ , which is more convenient for description of the condensed state, expression (65) can be replaced by an equivalent equation

$$\tilde{\Pi}' = \int_0^\theta \frac{1 - d \ln h / d \ln \theta}{1 - g\theta} d\theta + \tilde{\Pi}'_1, \quad (99)$$

where  $\tilde{\Pi}'$  and  $\tilde{\Pi}'_1$  have the same sense as in expression (69). In particular, for a non-ionised monolayer one has

$$\tilde{\Pi}'_1 = -\tilde{\alpha}'\theta^2,$$

where  $\tilde{\alpha}' \equiv \alpha/k_B T a_\infty$  is the dimensionless attracting constant. It is reasonable to assume that the monolayer acquires elastic properties after exceeding a threshold degree of coverage  $\theta_t$ . The action of tangential stress,  $\Pi/h$ , causes the monolayer to thicken. Let us introduce the transversal elasticity modulus

$$\varepsilon = \frac{d(\Pi/h)}{d \ln h}. \quad (100)$$

Integrating relationship (100) gives the equation of state

$$\Pi = \frac{\Pi_t h}{h_t} + \varepsilon h \ln \left( \frac{h}{h_t} \right), \quad (101)$$

where the particular  $\Pi_t$  and  $h_t$  values correspond to  $\theta_t$ , i.e., to the transition to elastic orientation. Such a transition usually manifests itself as a kink point in the surface pressure isotherm (Fig. 4), so the  $\Pi_t$  can be readily determined in the experiment. In addition to the minimum thickness  $h_0$  it is also convenient to introduce the maximum thickness  $h_\infty$  corresponding to the closest packing of the monolayer at an infinite pressure. Then, Eqn (101) can be written in a dimensionless form

$$\Pi' = \frac{\tilde{\Pi}'_t \tilde{h}}{\tilde{h}_t} + \tilde{\varepsilon} \tilde{h} \ln \left( \frac{\tilde{h}}{\tilde{h}_t} \right), \quad (102)$$

where  $\tilde{\varepsilon} \equiv \varepsilon a_\infty h_\infty / k_B T$  and  $\tilde{h} \equiv h/h_\infty \leq 1$  are the reduced elastic modulus and monolayer thickness, respectively.

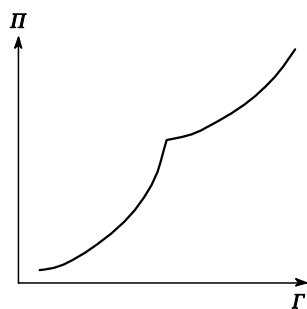


**Figure 4.** Surface pressure isotherm for the case of an orientation two-dimensional second-order phase transition.

For a dense monolayer we can assume  $a^{\text{ex}} = a$  and correspondingly

$$g^{\text{ex}} = \frac{a}{a_{\infty}} = \frac{h_{\infty}}{h} = \frac{1}{\tilde{h}}. \quad (103)$$

Substituting expression (103) into Eqn (99) with  $\tilde{\Pi}'_1 = -\tilde{\alpha}'\theta^2$  gives the equation of state for a monolayer with van der Waals interactions

$$\tilde{\Pi}' = \int_0^{\theta} \frac{1 - d \ln \tilde{h} / d \ln \theta}{1 - \theta / \tilde{h}} d\theta - \tilde{\alpha}'\theta^2. \quad (104)$$

The system of Eqns (102) and (104) completely describes the state of a non-ionised monolayer with variable orientation of particles. A general solution to this system of equations is problematic but analysis of these equations in the differential form<sup>47,51–53</sup> revealed a trend for the kink points in the surface pressure isotherm. Namely, if the kink point corresponds to an orientation phase transition, the slope of the curve must be smaller in the region of greater  $\theta$  values (see Fig. 4).

## V. Conclusion

The proposed procedure for deriving the equation of state based on the exclusion factor exhibits high creativity. This approach allows not only new highly accurate equations to be derived but also permits a better understanding of the well-established equations of state (a remarkable example is provided by the van der Waals equation). As to the use of the fitting parameter in refining the equation for the whole density range, it is appropriate to make the following comments. First, many equations of state include unknown constants that are more precisely determined in experiments. This is common practice. Second, in order to pass a curve through ten points with high accuracy using only one fitting parameter, one must have a very good equation. Eventually, third, this is a specific trick due to the fact that the problem of dependence of the exclusion factor on the density of matter is still to be solved. To solve this problem, one must know how the degree of particle clustering depends on the particle concentration. At present, this problem has been intensively studied by the researchers working in the field of physical chemistry of solutions.

It should be emphasised that the theory considers the short-range forces related to the particle size but not the long-range forces (the corresponding part of the equation of state has its traditional form). Note that in experimental studies on the role of the attraction and repulsion constants researchers deal with their combination, so knowledge of one constant facilitates determination of the other. Thus, finding the repulsion constants is also of great importance for the attractive part of the equation of state. What kind of force is more important? It is known that at temperatures above the Boyle temperature the attractive forces are insignificant so the behaviour of the gas is governed by the repulsive forces. However, recently it was suggested that near the

triple point the decisive role in molecular systems is played by the repulsive forces, the attractive forces serving to keep particles together.<sup>79</sup>

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<sup>c</sup> — *Russ. J. Phys. Chem. (Engl. Transl.)*

# Phase behaviour and self-assembly patterns of surfactant mixtures in solutions

N A Smirnova

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**Abstract.** Modern trends in studies of solutions of surfactant mixtures are discussed. The emphasis is placed on thermodynamic and molecular-statistical modelling of the phase behaviour and self-assembly patterns. The methods for prediction of properties of mixed micellar solutions based on the data for solutions of individual surfactants and the methods for calculation of the size, shape and composition distribution of micelles using the quasi-chemical models that take into account the molecular characteristics of components are analysed. Recent studies of surfactant solutions using computer experiments are surveyed. Theoretical approaches to the description of self-assembly phenomena in solutions of amphiphilic polymers and of their mixtures with low-molecular-mass surfactants are discussed. The bibliography includes 309 references.

## I. Introduction

Self-organised solutions of surfactants are the most common nanostructured liquid systems; their studies started in 1913 with the discovery of micelles by McBain. Over the last decades, the substantial progress in understanding the nature of phenomena occurring in such systems and diversity of their behaviour has been made owing to the development of novel experimental techniques, methods of theoretical simulations and computer-assisted calculations.<sup>1–3</sup> The range of surfactants under study has extended significantly. Surfactants with complex molecular architectures attract ever increasing interest, in particular, the gemini surfactants that combine two polar head groups and two non-polar tail groups linked through a bridge in one molecule.<sup>4</sup> Surfactants with fluorocarbon and siloxane hydrophobic chains, biological surfactants<sup>5</sup> and surfactants with head groups modified by introduction of specific substituents bearing chemical or biological functions<sup>6,7</sup> are the subjects of intense investigations. For instance, the self-assembly of surfactants designed by introduction of peptides and oligopeptides gives rise to structures that mimic

natural objects, such as biological membranes. Solutions containing two or more surfactants are of particular interest<sup>3,8–10</sup> since mixtures rather than individual surfactants are most abundant in practice. By combining different surfactants one can deliberately adjust properties of the system without recourse to the synthesis of new substances. Another important factor is that technological processes adopted in industry typically afford surfactant mixtures. Isolation of individual components from such mixtures can prove too time-consuming and costly and thus it is desirable to learn the effect of different admixture surfactants on the main component in order to produce formulations with optimum properties.

Mixtures of surfactants with water-soluble polymers have been attracting growing interest over the last two decades. The majority of industrial and household surfactant compositions contain polymers. Amphiphilic water-soluble polymers can be considered as modified surfactants. Such polymers can substantially reduce surface tension of the solution, be adsorbed at interfaces, form micelles in the solution, solubilise non-polar species and be assembled into liquid-crystalline structures. Furthermore, they tend to form mixed micelles with low-molecular-mass surfactants.<sup>1</sup>

The recognition of the similarity between the self-assembly phenomena in colloid systems, polymers and biological structures stimulated emergence of an interdisciplinary field of science that, in terms of physics, chemistry, materials science, biochemistry and engineering, deals with soft matter, *i.e.*, diverse systems manifesting an intermediate degree of ordering between crystalline solids and ordinary liquids. These include micellar solutions, gels and liquid crystals. Hamley, the author of one of the first books devoted to soft matter, expressed confidence that the soft-matter materials will play an ever increasing role and largely replace solid nanostructured materials in the future due to development of new design methods, which can now be only dreamed about.<sup>11</sup>

The modern applications of surfactant solutions encompass production of detergents, drugs, cosmetics, nutrition products and dyes, oil production technologies, chemical, biochemical and pharmaceutical industries where surfactants can control the rate and direction of chemical processes, perform syntheses of mesoporous materials, nanocrystals and periodic composites, produce gels with desired morphology, etc. Furthermore, surfactants are applied to affect colloids stability, emulsification, flocculation, structuring, suspension formation and rheological properties. Micellar and vesicular polymeric systems acquire growing importance in pharmacology (in particular, for encapsulation of drugs)

**N A Smirnova.** Department of Chemistry, St Petersburg State University, Universitetsky prosp. 26, Petrodvorets, 198504 St Petersburg, Russian Federation. Fax (7-812) 428 69 39, tel. (7-812) 428 67 90, e-mail: smirnova@nonel.pu.ru

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and chemical catalysis. Polymer gels with different structures are being actively investigated and widely used.

Strictly speaking, mixed micellar surfactant solutions are systems composed of two or more surfactants with each component capable of micelle formation in its own solution. In a broad sense, these are solutions where mixed micelles are formed. This definition also includes the case where only one component is capable of micelle formation, whereas the second diphilic component (*e.g.*, a fatty alcohol or acid) does not form micelles in its individual solution but can penetrate into micelles of the first component. The mixed micellar systems considered in the present review fall into the latter, extended definition. The emphasis is placed on the self-assembly in aqueous solutions of low-molecular-mass surfactants; studies of similar phenomena in solutions of block-copolymers and of their mixtures with surfactants are also cited. The review discusses results of experimental studies as well as problems of the thermodynamic and molecular-statistical modelling of mixed micellar systems.

Over the last few years, micellar solutions of surfactant mixtures have been the subject of extensive investigations, especially, in the USA, Japan and Germany. Many combinations of non-ionic, anionic and cationic surfactants have been studied as well as their mixtures with zwitter-ionic ones. The major results obtained prior to the mid-1990's have been surveyed in several monographs.<sup>2, 3, 8, 12</sup> Of particular interest are synergistic effects, which occur upon mixing of surfactants and result in an increase in the surface activity and viscosity of the solution, decrease in the critical micelle concentration (CMC) and growth of micelles.<sup>9</sup> Recent years are characterised by the increased attention of researchers to the internal structure of aggregates; the capabilities of the experimental elucidation thereof has expanded dramatically due to the modern instrumentation. Novel types of self-assembly in surfactant solutions have been discovered (for instance, formation of multilamellar vesicles). The bulk and quality of the experimental data on the sizes and shapes of aggregates,<sup>13–16</sup> micellar dynamics<sup>17</sup> and, more important, composition of micelles<sup>18–21</sup> have increased substantially. The experimental techniques of structural studies include light scattering, small-angle neutron scattering, electron microscopy, NMR and ESR spectroscopies. Of fundamental importance in the directional search for systems with desired properties is the establishment of the relationship between the molecular structure of a surfactant and its aggregation behaviour in a solution. The progress in this field relies on the achievements in the thermodynamic and molecular-statistical studies of solutions of individual surfactants,<sup>22–26</sup> but additional complications appear due to a variable composition of the micelles and complex patterns of the interparticle interactions. Computer simulation methods play an increasingly important role in studies of micellar solutions.<sup>27, 28</sup> The prediction of properties of mixed solutions based on the data for individual surfactants is of great applied significance. Semiempirical thermodynamical models are often useful in solving this problem.<sup>29</sup>

The present review does not pretend to a comprehensive coverage of the molecular-thermodynamical investigations into the aggregation and phase behaviour of surfactant mixtures. Still, it reflects the major directions of studies and the progress in the field and illustrates the interrelations between the experimental and the theoretical methods.

## II. Forms of aggregation. Synergistic effects

Highly dilute solutions of surfactant mixtures as well as solutions of individual surfactants contain the monomeric forms of the surfactant molecules. At the CMC surfactant aggregates. The region of the isotropic micellar solutions extends up to the boundary corresponding to the transition into the liquid-crystalline (mesomorphic) state (Fig. 1). Within the isotropic region, substantial structural transformations can occur, such as transition of spherical micelles to globular (ellipsoidal) and cylindrical ones (Fig. 2*a–c*), growth of the latter, emergence of worm-like

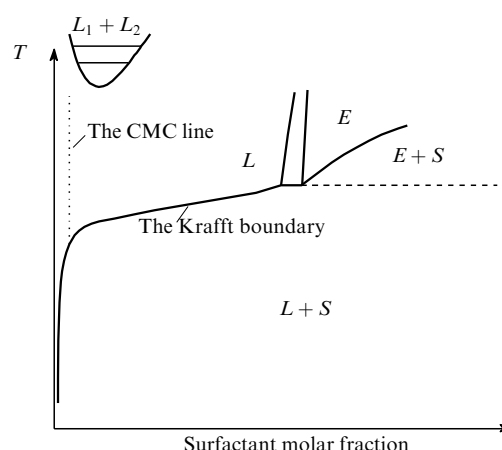


**Figure 1.** A fragment of a schematic phase diagram composition – temperature for a system surfactant – water.

*L* is a micellar solution, *S* is a solid phase, *E* is a liquid-crystalline phase, *L*<sub>1</sub> and *L*<sub>2</sub> are isotropic liquid phases.

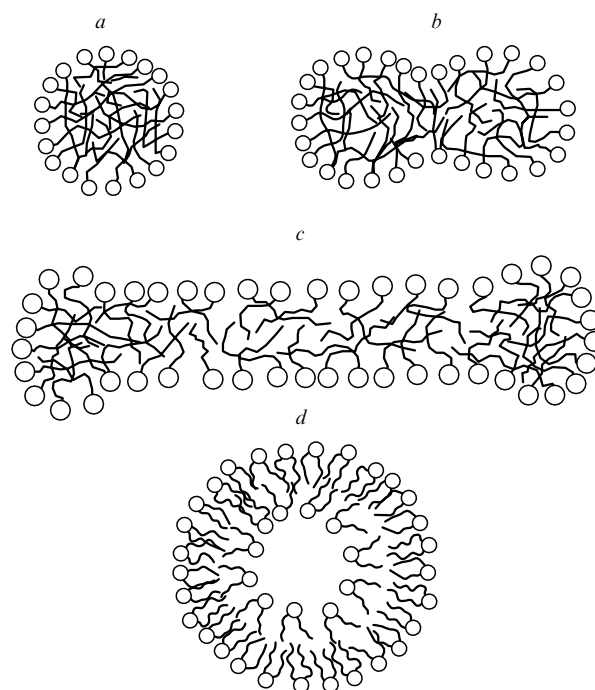


**Figure 2.** The most typical shapes of aggregates in surfactant solutions: a spherical (*a*), a globular (*b*) and a spherocylindrical (*c*) micelles; a bilayer vesicle (*d*).

micelles that form a network. Furthermore, vesicles can form, which represent closed (typically, spherical) bi- or multilayer structures with solvent incapsulated (Fig. 2*d*). Sometimes, especially in the case of non-ionic surfactants, liquid–liquid phase splitting can occur (the solubility diagram has a lower critical point). In the liquid-crystalline region, various structures, such as hexagonal, lamellar, nematic or cubic, can be realised, depending on the nature of the system, concentration of the surfactant and additives, temperature and other parameters (Fig. 3).<sup>1, 2, 30, 31</sup> In some specific cases, a bicontinuous phase is observed. The lower-temperature boundary of existence of a homogeneous surfactant solution is determined by crystallisation of the surfactant (the so-called Krafft boundary) or water. Sometimes, cooling of a micellar solution initiates gelation rather than crystallisation, but such a state is usually unstable.

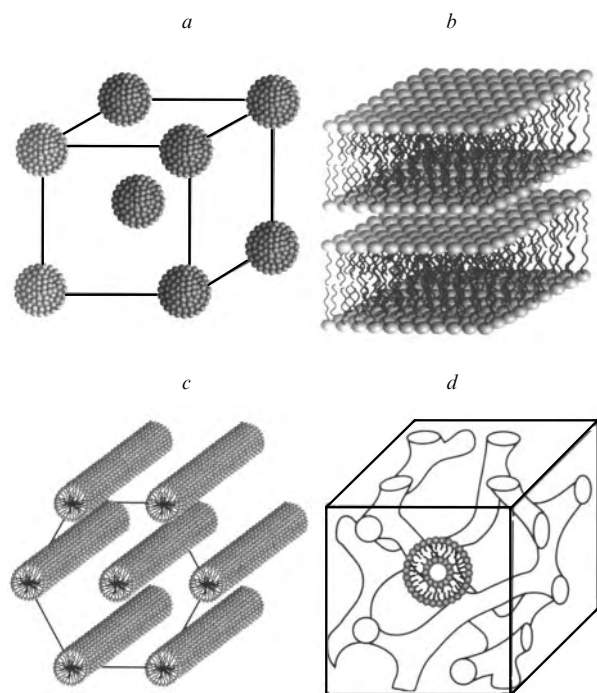


**Figure 3.** Cubic (a), lamellar (b) and hexagonal (c) liquid-crystalline structures; a bicontinuous structure (d).

In overall, the phase and aggregation behaviour of solutions containing two or more surfactants is characterised by diversity and complexity, although their major features can be observed in solutions of individual surfactants. The methods for the determination of CMC, phase boundaries and structures of aggregates and mesomorphic phases for mixed micellar systems are the same as for solutions of individual surfactants.<sup>3</sup> What is problem specific to mixed systems is the compositional analysis of aggregates. To solve the problem, such techniques as NMR,<sup>32,33</sup> small-angle neutron scattering,<sup>18</sup> ESR,<sup>34</sup> potentiometry with electrodes selective to the surfactant ions,<sup>35,36</sup> ultrafiltration through a membrane that allows monomeric molecules to pass but traps micelles,<sup>37,38</sup> etc. are typically applied.

The specificity of the behaviour of mixed solutions of two or more surfactants as compared to solutions of individual surfactants is related to the entropy of mixing (which is observed even for ideal solutions) and non-ideality effects due to differences in the interactions between identical and different molecules. The first models of micellar solutions of surfactant mixtures suggested by Lange<sup>39</sup> and Shinoda<sup>40</sup> postulated that mixed micelles behave as an ideal solution. Within the ideal solution approximation, Clint derived an equation that related the CMC of a surfactant mixture to the relative content of the individual surfactants and their CMC.<sup>41</sup> Mixtures of two surfactants belonging to one type, *i.e.*, both ionic<sup>39,40,42,43</sup> or both non-ionic,<sup>41,44</sup> behave in a way similar to that expected for an ideal solution. However, many mixtures demonstrate substantial deviations from ideality with the negative deviations due to synergistic effects. These are manifested in additional reduction of the surface tension, a decrease in the CMC, an increase in the viscosity and some peculiarities of the ternary phase diagrams (*e.g.*, extension of the region of a lyotropic liquid-crystalline phase towards lower concentrations of the surfactant, crystallisation of a 1:1 compound from surfactant mixtures with a nearly equimolar ratio of components). For instance, synergistic effects are observed in mixtures of an ionic and a non-ionic surfactants due to the fact that polar groups of the latter become incorporated between the similarly charged heads of the former thus reducing their electrostatic repulsion.<sup>45</sup> The most pronounced effects are typical of

mixtures of a cationic and an anionic surfactants, which form ionic pairs resembling a zwitter-ionic surfactant with a double tail.<sup>3,9,46</sup> This is accompanied by liberation of formerly bound counterions, which increases the ionic strength of the solution and produces the positive entropy effect. In solutions of such mixtures (commonly referred to as catanionic) at nearly equimolar concentrations, precipitation or segregation often occur at temperatures where solutions of individual surfactants are homogeneous.<sup>47</sup> Such solutions often manifest viscoelasticity. Mixtures of an anionic and a weakly basic surfactants that can be protonated (*e.g.*, alkylamine oxides, alkylamines or alkylethoxyamines) reveal strong synergistic effects that are enhanced upon acidification.<sup>48–58</sup> In an acidic medium, such a system becomes similar to a mixture of a cationic and an anionic surfactants and is characterised by very low values of CMC. For instance, CMC of aqueous solutions of sodium dodecyl sulfate and dodecyltrimethylamine oxide at 323.2 K are  $9.5 \text{ mol m}^{-3}$  and  $1.6 \text{ mol m}^{-3}$ , respectively, whereas their 1:1 mixture is characterised by CMC of  $0.65 \text{ mol m}^{-3}$  and  $0.003 \text{ mol m}^{-3}$  at normal acidity of the solution and at pH 2, respectively.<sup>58</sup> Among systems manifesting positive deviations from ideality, mixtures of hydrocarbon and perfluorinated surfactants having hydrocarbon similar polar groups are most studied. These surfactants are poorly compatible, their mixing can yield two types of micelles.<sup>59–62</sup>

Micelles with non-classical shapes (*i.e.*, other than spherical, globular and spherocylindrical) attract significant attention. In particular, tablet-shaped micelles were found in some catanionic systems using small-angle neutron scattering, although this shape is rarely encountered and sometimes appears to be non-equilibrium.<sup>63</sup> An interesting phenomenon is the network formation by long worm-like micelles. Due to this the solution can become viscoelastic (see Section VI). Vesicles are yet another type of aggregates frequently occurring in surfactant mixtures. These are also observed in solutions of many individual surfactants (*e.g.*, phospholipids, other surfactants with two tails or some surfactants with fluorocarbon radicals). The formation of vesicles is particularly typical of mixtures of a cationic and an anionic surfactants,<sup>9,64</sup> which occurs not only in water but in other polar solvents as well.<sup>65</sup> Typical vesicles are characterised by bilayer structures and sizes from *ca.* 100 nm to a few micrometers. In their local properties, vesicles are similar to planar bilayers and thus can serve as convenient models of biological membranes. For a number of surfactant mixtures, it was found that relatively small vesicles (15–40 nm) are formed in dilute solutions, which convert into multilayer onion-like vesicles with an increase in the surfactant concentration.<sup>66</sup> Another type of behaviour has recently been observed in a system sodium oleate–octanol–water: at a high surfactant concentration, small monodisperse bilayer vesicles are assembled into a hard gel that represents a densely packed ordered cubic-like phase.<sup>67</sup> According to studies of mixtures of an ionic and a non-ionic surfactants, an increase in the fraction of the ionic component favours the formation of vesicles, which is in accord with the theoretical predictions indicating the stabilisation of vesicular structures with respect to planar lamellar ones with an increase in the charge density of the bilayers.<sup>68,69</sup> The influence of the ratio of two surfactants, their total concentration, presence of additives and other factors on the transformation of vesicles into micelles and *vice versa* is currently under investigations. The conversion of vesicles into micelles can be promoted by shear stress.<sup>70</sup> For a mixture of tetradecyldimethylamine oxide with dodecylethoxysulfonic acid [ $\text{C}_{12}\text{H}_{25}(\text{CH}_2\text{CH}_2\text{O})_{2.5}\text{SO}_3\text{H}$ ], shear induced the transformation of a lamellar structure into a vesicular one.<sup>71</sup> Evidently, an assessment of the role played by the thermodynamical and kinetic factors in the formation of vesicular systems requires further investigations. Vesicular systems with polymer additives are of special interest. In particular, such additives can stabilise vesicular structures.<sup>72</sup>

The liquid crystal structures and phase boundaries were studied for a number of surfactant mixtures.<sup>2,42,55,73–79</sup> Mixing of different types of surfactants can result in the emergence of new



phases. For instance, upon mixing of tetradecyldimethylamine oxide with sodium dodecyl sulfate, the region of isotropic solutions becomes narrower and an extended region of a nematic phase appears (the total surfactant concentration at the phase boundary is less than 10 mass % at a component ratio of 1 : 1).<sup>55</sup> The available data suggest that the transition of the micellar solution into the liquid-crystalline state can be strongly affected by salts.<sup>2</sup> The phase behaviour in aqueous ethanol solutions of surfactant<sup>80</sup> and mixtures surfactant–water–oil<sup>2,81</sup> have been considered in numerous publications but these systems are beyond the scope of the present review.

### III. The critical micelle concentration and the Krafft boundary. The pseudophase model of micellar solutions

The critical micelle concentration and the Krafft boundary are two important characteristics of surfactant solutions. The former defines the tendency of a surfactant towards aggregation and the concentration of monomeric molecules in the aqueous environment of micelles. The latter represents the lower-temperature boundary of stability of homogeneous surfactant solutions, which is determined by the equilibrium between the surfactant solution and the solid phase. The temperature, at which the solid phase starts to precipitate should be sufficiently low for detergents, cosmetics, micellar solutions employed in oil production, *etc.* Therefore, a typical problem of the design of industrial surfactant formulations consists of lowering the Krafft boundary with various additives. At the same time, crystallisation is an efficient means of purification and isolation of individual surfactants from mixtures. In this case, the knowledge of the diagrams of crystallisation is required for optimising the corresponding processes. Thus, the determination of CMC and precipitation temperature for systems containing two or more surfactants based on the respective data for solutions of individual surfactants represents a topical problem. This problem can be solved within a relatively simple model that approximates a homogeneous micellar solution as a combination of two pseudophases, *viz.*, an aqueous and a micellar.<sup>82</sup> Although the pseudophase model has limitations<sup>22</sup> it appears quite useful in the description of effects of mixing. Holland and Rubingh derived the following equation for the CMC of a non-ideal mixture of two surfactants based on the pseudophase model:

$$\frac{1}{\text{CMC}} = \frac{y_1}{f_1 \text{CMC}_1} + \frac{y_2}{f_2 \text{CMC}_2},$$

where  $y_i = C_i/(C_1 + C_2)$  is the relative molar fraction,  $C_i$  is the molar concentration of the  $i$ th surfactant in the solution,  $f_i$  is its activity coefficient in a micelle ( $f_i = 1$  for a micelle composed of only the  $i$ th surfactant);  $i = 1, 2$ .<sup>83</sup>

Starting from the late 1970's, the concept of a regular solution, which enabled approximate consideration of deviations from ideality in the behaviour of mixed micelles has become widely adopted.<sup>12,83</sup> One of the basic parameters within the regular solution theory is interchange energy, which characterises the difference between the interaction energies of identical and different surfactant molecules. Typically, one uses a dimensionless parameter  $\beta$  defined as the interchange energy divided by  $kT$  ( $k$  is the Boltzmann constant and  $T$  is the temperature). For a binary regular solution, the dependence of the activity coefficients on the mole fractions ( $x_i$ ) of the components in mixed micelles is symmetrical:

$$f_1 = \exp[\beta(1 - x_1)^2]; f_2 = \exp[\beta x_1^2].$$

The value of  $\beta$  is estimated based on the CMC values for individual surfactants and at least one solution containing both surfactants. Such estimates have been obtained for many micellar systems.<sup>12,84,85</sup> Calculations of  $\beta$  using the molecular-statistical

model of mixed micelles<sup>86,87</sup> are in satisfactory agreement with the respective estimates from the experimental data. In particular, data on CMC and adsorption of aqueous solutions containing dodecylpyridinium bromide and a non-ionic surfactant have been interpreted within the regular solution model and compositions of the micelles and adsorption layers were calculated.<sup>88</sup> However, recent investigations have shown that the simple one-parameter regular solution model fails in many cases. Several two- and multi-parameter models of non-ideal mixed micelles have been proposed<sup>10,89,90</sup> that allowed the description of non-symmetrical dependences of the activity coefficients on the surfactant ratios. However, the increased number of fitting parameters diminishes the attractiveness of these, virtually empirical, models since they possess only limited predictive power.

It has been known for a long time that micelle formation in surfactant solutions is affected by the addition of salts. This effect appears as a decrease in the CMC of an ionic surfactant due to shielding of the electrostatic repulsion between the likely charged polar groups of the surfactant molecules. The dependence of CMC of an ionic surfactant on the salt concentration follows approximately the Corrin–Harkins rule, which establishes the linear correlation between the logarithms of CMC and the counterion concentration  $C$ :

$$\log \text{CMC} = -k_{\text{CH}} \log C + b_{\text{CH}}, \quad (1)$$

where  $k_{\text{CH}}$  and  $b_{\text{CH}}$  are constants specific to the surfactant.<sup>91</sup> This presumes that the surfactant and the salt contain identical ions. If both electrolytes are 1 : 1-charged, then  $C = C_s + \text{CMC}$ , where  $C_s$  is the salt concentration; the coefficient  $k_{\text{CH}}$  is taken equal to the degree of counterion binding by a micelle in the salt-free solution. Equation (1) is valid at relatively low salt concentrations. At higher concentrations, the slope of the function  $\log \text{CMC}$  vs.  $\log C$  is altered, which can be due to the change in the mean activity coefficient of the dissociated surfactant ( $f_{\pm}$ ). Taking into account the activity coefficient, the following expression can be written for a mixture of two 1 : 1-charged surfactants and a salt:

$$\log \text{CMC} + 2 \log f_{\pm}(\text{CMC}) \approx -\log(C_s + \text{CMC}) + b,$$

where the parameter  $b$  is determined by the aggregation number and the micelle formation constant.<sup>92</sup> However, this expression neglects the possibility of an incomplete binding of counterions by the micelles, *i.e.*, it assumes that the degree of counterion binding [ $k_{\text{CH}}$  in (1)] is equal to unity. A similar approximation was elaborated for surfactants and salts with arbitrary stoichiometries.<sup>22,92</sup> Simultaneous treatment of the non-ideality effects (*i.e.*, changes in the activity coefficients) and an incomplete binding of ions remains a current challenge. The validity of the Corrin–Harkins rule was discussed<sup>93</sup> on the basis of the Poisson–Boltzmann equation within the approach developed by Evans, Mitchel and Ninham.<sup>94</sup> The dependence of the degree of counterion binding on the ratio of a non-ionic and an anionic surfactants in the solution was analysed in the context of deviations from the linear equation (1).<sup>95,96</sup> Some systems, such as solutions of alkyltrimethylammonium halides with alkali-metal halides as additives, reveal an abrupt change in the slope of the  $\log \text{CMC}$  vs.  $\log C$  lines at a certain salt concentration, which is normally interpreted as the coincidence of two CMC corresponding to the starting point of micelle formation and the transition sphere  $\rightarrow$  cylinder, respectively.

A modification of the ideal pseudophase model, which takes into account the electrostatic contribution into the change in the Gibbs energy upon transfer of a surfactant ion (*e.g.*, a dodecyl sulfate anion) from the solution onto the charged surface of a micelle, was proposed to describe CMC of mixtures of anionic surfactants containing different counterions.<sup>97</sup> This approach was applied to calculate CMC of individual surfactants in the absence and in the presence of a salt as well as of mixtures of two anionic surfactants having singly and doubly charged counterions in the absence of a salt. The model was also extended to mixtures of two surfactants and a salt.<sup>98</sup> The calculations show that the depend-

ence of the CMC on the counterion concentration is mainly affected by the charge of the counterions whereas their nature is of low significance, which is in agreement with the experimental data. According to a recently suggested scheme of estimating CMC for a surfactant mixture based on the pseudophase model using the Gibbs–Duhem relation and the Poisson–Boltzmann equation, the synergistic effects upon mixing of an ionic and a non-ionic or of two ionic surfactants are dominated by the entropic contribution.<sup>99</sup> A description of CMC for mixtures of a cationic and an anionic surfactants, where the charge density on the surface of mixed micelles is strongly reduced as compared to that for the respective one-component micelles and synergistic effects are strong (within the regular solution model, the values of the parameter  $\beta$  for such systems lie between  $-20$  and  $-30$ ), remains a current challenge. The systems manifesting strong pH-dependent changes in CMC are of significant interest.<sup>100</sup>

The majority of published data concerning crystallisation from mixed surfactant solutions dealt with the phase boundaries at constant temperature (*i.e.*, the concentration of an additive as a function of the surfactant concentration in a concentrated solution). The main attention was paid to the effects of additives on the precipitation of anionic surfactants.<sup>101–112</sup> Until recently, data on the precipitation temperature as a function of the relative fraction of one of the surfactants at a constant total surfactant content, which corresponds to the Krafft boundary, were scarce and predominantly related to relatively low total surfactant concentrations, often just slightly above CMC.<sup>47, 113–116</sup> A solid phase that crystallises from a micellar solution typically has constant stoichiometry (*e.g.*, pure surfactant, its hydrate, a complex of two surfactants or ice) whereas solid solutions of surfactants are rarely formed.<sup>117</sup> Therefore, the most common type of the phase diagrams are eutectic diagrams. In the simplest case, such a diagram has two branches corresponding to precipitation of a pure surfactant (or ice) (Fig. 4a). Recently, equilibria of a variety of micellar solutions (aqueous solutions of two non-ionic, two ionic or an ionic and a zwitter-ionic surfactants, solutions of surfactants with addition of salts or alcohols) with solid phases have been elucidated.<sup>29, 44, 58, 118–125</sup> Mixtures of sodium or magnesium dodecyl sulfate [NaDS or Mg(DS)<sub>2</sub>, respectively], which are anionic surfactants, with alkyldimethylamine oxide (AO),

which is a non-ionic surfactant that undergoes protonation and acts as a cationic surfactant in acidic media, were shown to behave anomalously: a strong dependence of the solubility diagrams on pH was observed for the first time (Fig. 4b).<sup>58</sup> In the case of acidic solutions, the diagram precipitation temperature *vs.* mole fraction of AO (for a constant total surfactants content) reveals a maximum corresponding to the composition 1:1. According to chemical analysis and X-ray diffraction studies, a 1:1 cation-anionic complex (AOH<sup>+</sup>DS<sup>−</sup>) is crystallised from solutions with nearly equimolar ratios of the two surfactants, while the nature of the cation of dodecyl sulfate is not important. In addition to the 1:1 compound, complexes with other stoichiometries are likely formed at higher relative concentrations of AO.

Models allowing prediction of solubility diagrams for ternary systems based on the data for aqueous solutions of individual surfactants (*e.g.*, precipitation temperature at constant concentration of the solution, enthalpy of dissolution) are of great interest, in particular, from the practical viewpoint. The problem can be solved using the pseudophase model of a micellar solution. Equilibrium conditions can be expressed in variables of any of the two pseudophases, *viz.*, aqueous ( $x_i^W$ ) and micellar ( $x_i^M$ ). For ionic surfactants, variables describing the composition of the aqueous pseudophase and a concept of the solubility product are traditionally applied.<sup>101</sup> For instance, the solubility product ( $K$ ) of the salt A(DS)<sub>*n*</sub> can be written as

$$K = a_{A^{n+}} a_{DS^-}^n,$$

where  $a_i$  is the activity of free ions  $i$  in the saturated solution ( $i = A^{n+}, DS^-$ ). However, the application of this approach to compositions far from CMC faces difficulties in estimating the concentrations of free surfactant ions and their counterions. It was established that the applicability of the pseudophase model for predicting the phase behaviour of mixed solutions in the range of relatively high concentrations based on the data for solutions of the individual surfactants can be extended making use of the concentration variables of the micellar pseudophase (this is valid for both non-ionic and ionic surfactants).<sup>29, 118–125</sup> Since the micellar pseudophase is composed of only two surfactants (components 1 and 2) and the water (component 3) content may be neglected, the condition of the equilibrium between the ternary

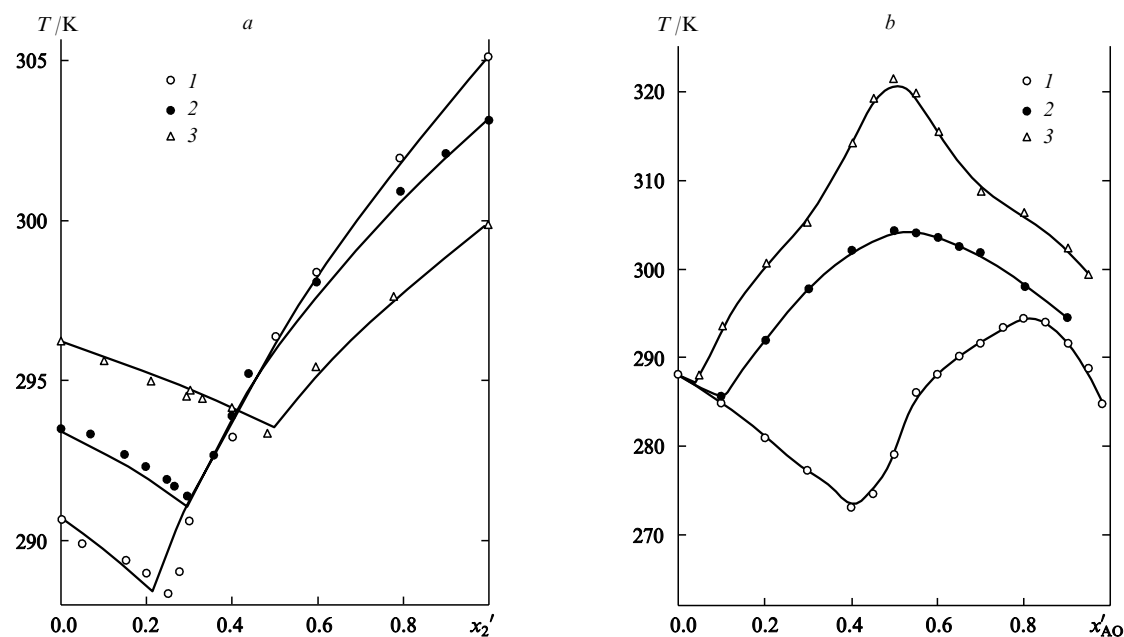


**Figure 4.** Precipitation temperature as a function of the surfactant relative content.<sup>29</sup>

(a) Water–salt solutions of NaDS and Mg(DS)<sub>2</sub>;  $x_2' = x_{MgDS} / (x_{NaDS} + x_{MgDS})$ ;  $C_{NaCl} / \text{mol litre}^{-1}$ : 0 (1); 0.1 (2); 0.3 (3); (b) aqueous solutions of NaDS and dodecyltrimethylamine oxide (AO) with variable acidities;  $x_{AO}' = x_{AO} / (x_{NaDS} + x_{AO})$ ;  $x_{HCl}' = x_{HCl} / (x_{HCl} + x_{AO})$ : 0 (1); 0.3 (2); 0.6 (3).

solution and the solid surfactant can formally be reduced to equations of the biphasic equilibrium for the two-component system 1–2. For the line of crystallisation of the surfactant 1:

$$\Delta T = \frac{RTT_0}{\Delta H_1} \ln a_1(x_1^M), \quad (2)$$

where  $\Delta T = T - T_0$ ,  $T_0$  and  $T$  are precipitation temperatures of the surfactant from its individual and mixed (at identical total surfactants concentration) aqueous solutions, respectively,  $R$  is the gas constant,  $\Delta H_1$  is the enthalpy of dissolution,  $a_1$  is the activity in a mixed micelle ( $a_1 = 1$  provided that  $x_1^M = 1$ ). If the micellar phase behaves as an ideal solution, then:

$$\Delta T = \frac{RTT_0}{\Delta H_1} \ln x_1^M. \quad (3)$$

Equations (2) and (3) are also valid for surfactant solutions containing additives that do not form micelles on their own (*e.g.*, low-molecular-mass alcohols). These equations suggest that a substantial decrease in the precipitation temperature can be induced by additives that form mixed micelles with the main surfactant, and it is the distribution coefficient of the additive between the micellar and aqueous phases that plays a decisive role. For salt-free solutions of mixtures of two non-ionic or ionic surfactants at concentrations substantially above CMC, the composition of micelles is very close to the composition of the surfactant mixture without taking solvent into account:  $x_1^M = x_1/(x_1 + x_2)$ , therefore,  $\Delta T$  depends only on the relative concentrations of the two surfactants but is independent of their total content. The eutectic-type diagrams precipitation temperature–relative concentration of the surfactant for salt-free mixtures of ionic surfactants as well as for mixtures of non-ionic surfactants can be modelled in a similar way. In the case of ionic surfactants, this approach is simpler than that based on the concept of the solubility product. For solutions of ionic surfactants in the presence of salts or low-molecular-mass amphiphilic additives, the ion exchange (for the former) or distribution coefficient (for the latter) between the micelles and the aqueous environment should be taken into account. An account for the non-ideality of mixed micelles and the aqueous pseudophase is a significant aspect of the modelling. For this purpose, approximate models developed for molecular solutions (*e.g.*, the regular solution model, the Flory–Huggins model, *etc.*) are applied.<sup>126</sup> The strong dependence of the solubility diagram for the system sodium dodecyl sulfate–alkylamine oxide–water on pH can be reproduced within a model taking into account protonation of alkylamine oxide and formation of a cation-anionic complex.<sup>29, 58</sup>

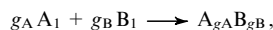
In addition to the practical importance, studies of the solubility diagrams represent an efficient means of gaining information on the thermodynamical properties of micellar solutions, the degree of non-ideality in the behaviour of mixed micelles and specific interactions between components of the mixtures. The major difficulties in the calculations of the solubility diagrams for micellar solutions of surfactant mixtures relate to the description of the non-ideality and often to the lack of data on the temperatures and enthalpies of dissolution for individual surfactants. Definitely, the extension of the experimental database is an important task.

#### IV. Molecular-thermodynamical models of aggregation

Starting from pioneering works by Tenford,<sup>23, 127</sup> Israelachvili, Mitchell and Ninham,<sup>24</sup> Ruckenstein and Nagarajan<sup>128</sup> published in the 1970's, strenuous efforts have been put into development of approximate models establishing relationships between the molecular properties of components and their aggregation behaviour (this is often referred to as the molecular-thermodynamic approach). The formation of a micelle is described as a chemical reaction, the equilibrium concentrations of monomers

and aggregates are calculated from the Gibbs energy of the aggregate formation according to the law of mass action. A detailed analysis of the quasichemical approach has been performed by Rusanov.<sup>22</sup> Numerous studies were devoted to estimating different contributions of micelle formation into the Gibbs energy, elucidation of their relationships with the molecular characteristics of the components as well as with the shapes and sizes of the aggregates.<sup>127–137</sup> The dependence of the stability of aggregates having specific shapes (spheres, cylinders or planar bilayers) on the packing of the surfactant molecules has been analysed.<sup>24</sup> Each type of the aggregates is characterised by its own range of values of the so-called packing factor  $P = v/al$ , where  $a$  is the surface area of the hydrocarbon core per surfactant molecule in the aggregate,  $v$  is the volume of the hydrocarbon radical and  $l$  is its length. The packing factor is equal to the mean cross-sectional area of the radical divided by the area occupied by a polar head of the surfactant on the surface of the hydrocarbon core. The packing factor increases in the order spherical micelles → rod-like micelles → planar bilayers ( $1/3 \rightarrow 1/2 \rightarrow 1$ ). The values of the packing factor larger than unity correspond to inverse micelles that form in non-polar media. The packing conditions were generalised to the case of aggregates with concave surfaces and vesicles with a convex and a concave surfaces simultaneously.<sup>138</sup> The effective cross-sectional area of a polar head is affected not only by the structure of the surfactant molecule but by other factors as well. In particular, addition of a salt to a micellar solution of an ionic surfactant gives rise to a decrease in the area of the polar head. This occurs because the degree of counterion binding increases, the electrostatic repulsion between likely charged heads is partially screened and thus they approach closer to each other. As a result, the addition of a salt promotes transition of spherical micelles to rod-like. If the additive forms mixed micelles with the primary surfactant, the packing conditions are mainly affected by the sizes and shapes of polar and non-polar parts of the additive molecule.

The quasichemical model for a solution of two surfactants A and B considers the process:



where  $g_A$  and  $g_B$  are the numbers of the monomers of A and B within a micelle. The following relation between the mole fractions of aggregates ( $X_g$ ) and monomers ( $X_{1A}$ ,  $X_{1B}$ ) can be obtained from the condition of thermodynamic equilibrium:

$$X_g = X_{1A}^{g_A} X_{1B}^{g_B} \exp \left[ - \left( \frac{g \Delta \mu_g^\circ}{kT} \right) \right]. \quad (4)$$

Here,  $g = g_A + g_B$  is the aggregation number;  $\Delta \mu_g^\circ$  is the standard Gibbs energy of micelle formation per molecule. The term  $\Delta \mu_g^\circ$  relates to the standard chemical potential of a mixed micelle  $\mu_g^\circ$  and the standard chemical potentials of the monomeric molecules in the solution  $\mu_{1A}^\circ$  and  $\mu_{1B}^\circ$  in the following way:

$$\frac{g \Delta \mu_g^\circ}{kT} = \frac{\mu_g^\circ - g_A \mu_{1A}^\circ - g_B \mu_{1B}^\circ}{kT}. \quad (5)$$

Equation (4) links the concentrations of the monomers and the aggregates having a specific size and composition. The value of  $\Delta \mu_g^\circ$  depends on temperature, the aggregation number  $g$ , composition and shape of the micelle. If  $\Delta \mu_g^\circ(T, \text{shape } 1, g) < \Delta \mu_g^\circ(T, \text{shape } 2, g)$ , then the aggregates with the shape 1 are more stable than those with the shape 2 at the same aggregation number. Estimating  $\Delta \mu_g^\circ$  taking into account the structure of the surfactant molecules and parameters of aggregates (*i.e.*, their sizes and shapes) is the key problem in modelling the aggregation behaviour of the system. Typically, micelles are represented as spheres, globules (ellipsoids) or rod-like aggregates (spherocylinders). The term  $\Delta \mu_g^\circ$  is expressed as the sum of several contributions:

$$\begin{aligned} \Delta \mu_g^\circ = & (\Delta \mu_g^\circ)_{tr} + (\Delta \mu_g^\circ)_{def} + (\Delta \mu_g^\circ)_{int} + (\Delta \mu_g^\circ)_{st} + (\Delta \mu_g^\circ)_{dip} + \\ & + (\Delta \mu_g^\circ)_{ion} + (\Delta \mu_g^\circ)_{mix}, \end{aligned}$$

where  $(\Delta\mu_g^\circ)_{tr}$  is the chemical potential of transfer of a hydrocarbon tail from the solution to the aggregate core, which is considered as a structureless liquid hydrocarbon;  $(\Delta\mu_g^\circ)_{def}$  is the potential of deformation of the hydrocarbon tail due to configurational confinement of the carbon skeleton imposed by the shape of the aggregate;  $(\Delta\mu_g^\circ)_{int}$  is the contribution of the surface tension at the interface between the hydrocarbon core of the micelle and aqueous environment;  $(\Delta\mu_g^\circ)_{st}$  is the term describing the steric repulsion of hydrophilic groups of the surfactant molecules located at the surface of the aggregate;  $(\Delta\mu_g^\circ)_{dip}$  is the contribution of dipole–dipole interactions between the polar groups;  $(\Delta\mu_g^\circ)_{ion}$  is the contribution of electrostatic interactions between charged hydrophilic groups and surrounding solution (for ionogenic surfactants);  $(\Delta\mu_g^\circ)_{mix}$  is the contribution due to mixing of A and B within one micelle (applicable only to mixed micelles whereas all other terms apply to both individual and mixed micelles).

The first term from the above list (the transfer potential) does not depend on the size and shape of the aggregate whereas other terms (in particular, the electrostatic contribution) are to a certain extent affected by these parameters. Expressions for the individual terms were obtained based on the theoretical estimates and some experimental data. Two of the most thoroughly developed and widely approved variants are Ruckenstein–Nagarajan<sup>26, 130–132</sup> and Blankschtein<sup>25, 86, 87, 133–137</sup> models. Their advantages include detailed assessment of the methods used to estimate the aforementioned terms, parametrisation of the model for a variety of surfactants, applicability of the models not only to description of properties of various systems but to their prediction as well, in particular, for solutions of surfactant mixtures.

The number of carbon atoms ( $n_C$ ) is an important parameter characterising a hydrocarbon radical. In addition to  $\Delta\mu_g^\circ$ ,  $n_C$  determines geometrical characteristics of the hydrophobic part of the surfactant molecule (*i.e.*, its volume and length), which in turn govern possible sizes of aggregates and, importantly, surface area of the hydrocarbon core per surfactant molecule. Several of the aforementioned contributions into the Gibbs energy of micelle formation are affected by the value of  $n_C$  through the geometrical characteristics.

The Gibbs energy of transfer of a hydrophobic tail from the aqueous solution into the hydrocarbon core (which is the major driving force of micelle formation) can be estimated from the experimental data on the solubility of hydrocarbons in water assuming the additivity of contributions from groups constituting the molecule. In the case of *n*-alkyl radicals:

$$(\Delta\mu_g^\circ)_{tr} = (n_C - 1)(\Delta\mu_g^\circ)_{tr(CH_2)} + (\Delta\mu_g^\circ)_{tr(CH_3)},$$

where  $(\Delta\mu_g^\circ)_{tr(CH_2)}$  and  $(\Delta\mu_g^\circ)_{tr(CH_3)}$  are contributions of a methylene and a methyl group estimated from solubilities of alkanes in water.<sup>26, 127</sup> Within this homologous series,  $(\Delta\mu_g^\circ)_{tr}$  is linearly dependent on  $n_C$ . The potential of transfer of a hydrocarbon with one double bond can be written as follows:

$$(\Delta\mu_g^\circ)_{tr} = (n_C - 3)(\Delta\mu_g^\circ)_{tr(CH_2)} + (\Delta\mu_g^\circ)_{tr(CH_3)} + 2(\Delta\mu_g^\circ)_{tr(CH)}.$$

The contribution of a CH group, which is significantly smaller than that of a CH<sub>2</sub> group in absolute value, was estimated from solubilities of saturated and unsaturated hydrocarbons.<sup>139</sup> According to the model estimates, a decrease in the absolute value of the negative transfer potential  $(\Delta\mu_g^\circ)_{tr}$  is the primary reason for an increase in CMC upon introduction of multiple bonds in hydrocarbon radicals whereas other contributions change only insignificantly.<sup>140</sup> When estimating the transfer free energies, the above formulas are sometimes modified by reduction of the number of carbon atoms by 1–2 with respect to the actual number to account for partial penetration of water molecules into the hydrocarbon core of micelles.

Within the model, a polar group is characterised by two parameters. The first one is the effective cross-section  $a_{eff}$ , which is used in the expression for the steric repulsion of head groups of the surfactant molecules:

$$(\Delta\mu_g^\circ)_{st} = -kT \ln \left( 1 - \frac{a_{eff}}{a} \right),$$

where  $a$  is the surface area of the hydrocarbon core per surfactant molecule. The second parameter is screening cross-section  $a_{scr}$ , which represents the surface area of the micelle core screened by the polar group from contacts with the solution. This parameter influences the term  $(\Delta\mu_g^\circ)_{int}$  according to the following relation:

$$(\Delta\mu_g^\circ)_{int} = \sigma_{wc}(a - a_{scr}),$$

where  $\sigma_{wc}$  is the surface tension at the interface between a solution and the hydrocarbon core.

The deformational contribution relates to the conformational confinement of the hydrocarbon tail with one end connected to the polar group located at the surface of the aggregate, while the distribution of segments inside the core corresponds to a density of liquid hydrocarbon. The value of  $(\Delta\mu_g^\circ)_{def}$  depends on the length of the hydrocarbon chain, the shape of the micelle and its composition (in the case of a surfactant mixture). The estimate of the deformational contribution adopted in the Blankschtein model is based on the conformational characteristics of individual and mixed aggregates with various shapes (*e.g.*, bilayers, spheres and cylinders) analysed within the mean-field approximation.<sup>141, 142</sup> Within such an approach, distribution functions of segments for chains with different lengths in a mixed aggregate were obtained by minimising the free conformational energy of the system. In particular, it was found that longer chains tend to stretch towards the centre of the hydrophobic core with an increase in the fraction of short chains. The conformational entropy of flexible hydrocarbon chains in curved films of surfactants can be related to their elasticity constants.<sup>143</sup> The energy required to bend a film is substantially reduced when short-radical molecules within the film are replaced by longer ones. Nagarajan and Ruckenstein derived expressions for the deformational contribution in the cases of spheres, globules and spherocylinders using the theoretical results obtained by Semenov for microdomains of copolymers.<sup>144</sup>

The difficulties in estimating the electrostatic term, which depends on the sizes and shapes of the aggregates and is strongly affected by the salt background, are due to the fact that no exact analytical solution of the non-linearised Poisson–Boltzmann equation has been obtained for curved charged surfaces in a salt solution. Typically, an approximate solution of the Poisson–Boltzmann equation for spherical and cylindrical surfaces obtained by Evans and Ninham is used in the aggregation models to describe the electrostatic term.<sup>145</sup> The nature of the polar group of the surfactant molecule and counterion is normally taken into account through the parameter  $\delta$  that characterises the distance from the surface of the hydrophobic core to the centre of a bound counterion. A serious drawback of this approximation is that it fails in the region of low surfactant and salt concentrations (*i.e.*, for large radii of the ionic atmosphere). The influence of curvature on the profile of the electrostatic potential have been considered more stringently by Mitchell and Ninham.<sup>146</sup> However, the necessity of numerical integration impedes applicability of this approximation to calculations of the size and shape distribution of micelles. An approximate analytical solution of the Poisson–Boltzmann equation for spherical colloidal particles in a salt-free solution has been obtained by Ohshima.<sup>147</sup> MacKintosh, Safran and Pincus<sup>148</sup> proposed a method for estimating the electrostatic term, which enabled successful description of the influence of the surfactant and salt concentrations on the growth of rod-like micelles including the region of dilute solutions.<sup>149, 150</sup> Other approximations have also been considered,<sup>137</sup> a search for new solutions<sup>151</sup> and refinement of the existing description of the electrostatic term for mixed micelles composed of an ionic and a non-ionic or a zwitter-ionic surfactants<sup>86</sup> are currently underway. The nature of a counterion is usually taken into account through the hydrated ion radius. This approach gives satisfactory results in many cases, which was demonstrated, in particular, for a number

of mixtures of an ionic and a non-ionic surfactant. However, it neglects a specific binding of counterions, which should also be taken into consideration.<sup>152, 153</sup> The specific binding increases according to the Hoffmeister series (for instance, in the case of cationic surfactants, the specific binding strengthens in the series  $\text{AcO}^- < \text{NO}_3^- < \text{Br}^- < \text{ClO}_3^- < \text{Sal}^- < \text{HNC}^-$ ). An increase in the degree of binding favours growth of micelles. The specificity of ions depends largely on dispersion forces; thus, the dispersion contribution has to be included into the potential of mean force when estimating the Boltzmann distribution of ions around an ionic micelle.<sup>154</sup> Differences in CMC for different pairs surfactant ion – counterion can also be due to polarisation of the boundary between the hydrocarbon core and the polar outer shell of a micelle.<sup>155</sup> However, the aforementioned factors were considered only in a few studies. A number of possible methods to account for the influence of the counterion nature on the transition sphere  $\rightarrow$  cylinder through the electrostatic term have been discussed elsewhere.<sup>156</sup>

The calculations performed within the Nagarajan – Ruckenstein and Blankshtein models for solutions of various types of individual surfactants and mixed systems have been reported.<sup>44, 140, 157</sup> The models adequately describe the influence exerted by the size of the hydrophobic part of the surfactant molecule on CMC and micelle growth. Furthermore, they make it possible to take into account the nature of the polar groups and effects of salt additives, describe solubilisation and reproduce synergistic effects in mixed systems. Model estimates of CMC are more successful than the estimates of concentrations of transitions sphere  $\rightarrow$  cylinder or of mean aggregation numbers in the micelle growth since changes in the sizes and shapes of micelles depend on finer effects than CMC. Determination of model parameters requires experimental data on CMC for a system of the type under study. However, as soon as the model is parametrised, it can be used for predicting properties of systems based on other surfactants with the same polar group. The Nagarajan – Ruckenstein model was applied to systematic studies of relationships between the molecular parameters of surfactants and characteristics of their aggregation (including CMC, mean aggregation number and polydispersity).<sup>140</sup> In particular, factors favouring the micelle growth (elongation of the hydrocarbon radical, addition of a salt, the size of the polar group) were evaluated. A modification of the Nagarajan – Ruckenstein model was used in the development of a colloidal model describing precipitation of asphaltenes from oil.<sup>158–160</sup> Different versions of the molecular-thermodynamic models have been proposed to describe surface tension of solutions of surfactant mixtures and adsorption.<sup>161, 162</sup> Model approaches to the study of stability of vesicles with respect to planar bilayer and micellar structures in catanionic systems have been developed.<sup>163–166</sup>

The interactions between aggregates, which become significant at high surfactant concentrations, can be accounted for using the virial equation of state or more rapidly converging  $y$ -expansion.<sup>167</sup> The McMillan – Mayer theory and calculations of the potential of mean force were used to describe non-ideal solutions of non-ionic micelles. The repulsive interactions between micelles were estimated through the excluded volume.<sup>168</sup> The electrostatic repulsion between micelles strongly affects deviations of solutions of ionic surfactants from the ideal behaviour. The experimental light scattering and viscosity data for a number of solutions composed of mixtures of an ionic and an anionic surfactants were interpreted with consideration of only the electrostatic contribution calculated according to the Derjaguin – Landau – Verwey – Overbeek theory.<sup>136</sup> A variant of the osmotic equation that takes into account the van der Waals and long-range electrostatic interactions has been proposed to describe micellar solutions, emulsions and microemulsions in a wide range of compositions.<sup>169</sup>

The molecular-thermodynamic approach gives optimal possibilities of using modern theoretical achievements in the search of regularities in relationships between the chemical architecture of

surfactants and aggregation behaviour. This approach is mostly suitable for solving applied problems in the field of surfactant systems. In this regard, it can be considered as the optimum theoretical tool. Meanwhile, further developments and improvements of the models are currently needed. In particular, this relates to evaluation of various contributions into the Gibbs energy of micelle formation. The factors complicating correct estimates of the electrostatic term and thus representing a challenge to modern theories have already been mentioned. Furthermore, a correct account of penetration of water molecules into the micelle core (which is typically neglected), the effects of the surface curvature and salt background on the surface tension at the interface between the hydrocarbon core and aqueous environment is highly desirable. A problem of an adequate description of the mixing functions arises in the case of mixed micelles, the systems revealing specific interactions being particularly interesting.

Several issues of interest were considered in the drop and quasidrop models developed by Rusanov *et al.*<sup>170–173</sup> for spherical micelles of individual surfactants. The canonical drop model, which assumes flexibility of the hydrocarbon chains and their complete immersion into the aggregate core, like the Nagarajan – Ruckenstein model, accounts for the surface effects in a more rigorous way. The electrostatic term is estimated according to the model of a spherical capacitor, while the deformational term is calculated using the Semenov formula.<sup>144</sup> The quasidrop model allows partial exit of undistorted hydrocarbon chains from the core. These models were applied to study the dependence of the work of formation of premicellar and micellar aggregates on the aggregation number and concentration of the surfactant monomers in the solution; the analytical approximations were derived.

The lattice theories are often used in studies of micellisation.<sup>174–181</sup> The self-consistent field lattice theory originally developed by Scheutjens and Fleer for polymer adsorption<sup>174, 175</sup> was generalised by Leermakers for the case of surfactant aggregation.<sup>176, 177</sup> In particular, this approach successfully reproduces the diffuse structure of the micellar core – corona boundary. Nevertheless, the Gaussian statistics of chains adopted in the model can give rise to errors in the estimation of the density profiles of micelles for relatively short diphilic molecules.<sup>178</sup> The lattice theories in the single-chain mean-field (SCMF) variant are free of this drawback. A simple model ‘a diphilic molecule (a diblock-chain composed of two types of units) – solvent (one unit)’ correctly reproduced the dependence of CMC on the length of the hydrocarbon chain and changes in the morphology of aggregates.<sup>180, 181</sup> The molecular structure of aggregates obtained from the theoretical calculations is in qualitative agreement with that found by computer simulations, yet the model represents surfactant molecules in a quite simplified manner.

Studies combining the molecular-thermodynamic modelling and computer simulations for evaluation of certain characteristics of micelles are of special interest.<sup>182–187</sup> This approach was applied to study solutions of cetyltrimethylammonium bromide containing sodium salicylate and describe penetration of salicylate anions inside micelles.<sup>182</sup> The molecular packing, structure and interactions within the corona of a micelle as well as the contribution of the corona to the Gibbs energy of micelle formation were obtained using the Monte Carlo method whereas other contributions were calculated according to the Blankshtein model.<sup>133, 134</sup> The computer experiments (*e.g.*, Monte Carlo and molecular dynamics) can prove extremely useful in parametrisation of model theories based on the molecular structure of surfactants.

## V. Computer simulations of surfactant solutions

Results of computer simulations of surfactant solutions have recently been surveyed.<sup>27, 28, 188</sup> Computer simulations of biological lipid membranes are especially numerous, but these studies represent a special field. The structure and interactions between the particles constituting a surfactant solution can be described at different levels, depending on the purpose of the study. All atoms

or ions constituting the system and interactions between them are explicitly taken into account in the atomistic models, although several atoms can be combined into one pseudoatom, such as methyl group. In the so-called coarse grain models, atoms are grouped into larger species, *i.e.*, represented more roughly. Furthermore, the electrostatic and torsion potentials are normally neglected, in contrast to the atomistic approach. Simulations commonly referred to as mesoscopic are undertaken using various methods including dissipative particle dynamics, calculations within the lattice gas model and dynamic mean-field density functional approach. The time scales of different events occurring in solutions of aggregated surfactants are estimated as follows:  $10^{-10}$  s for shape fluctuations,  $10^{-6}$  s for exchange of surfactant molecules between micelles and the surrounding solution, hundreds of seconds or longer for such macroscopic events as shear-induced changes. The typical time and spatial scales for the atomistic calculations are 1 ns and 1 nm, respectively. So far, simulations of the equilibrium structures of ordered surfactant solutions are impossible at this level, but still computer experiments can yield detailed information on the local structure and some kinetic aspects of the self-assembly process. In the majority of cases, it is the premicellar surfactant aggregates that are the subject of the studies, and the conformations and arrangement of the molecules at a distance scale on the order of 1 nm are obtained as outcome. As a rule, solutions of individual surfactants are studied.<sup>27, 28, 183, 189–193</sup>

Extended molecular dynamics (MD) calculations at the atomistic level have been performed for aqueous solutions of nonyltrimethylammonium chloride and erucylbis(2-hydroxyethyl)methylammonium (50 surfactant molecules and 3000 water molecules);<sup>191</sup> the mechanism and kinetics of micelle formation were studied for time scales up to 3 ns and the effects of sodium salicylate addition were simulated (the salicylate anions can incorporate into micelles between the polar groups of the cationic surfactant and thus promote growth of rod-like aggregates). Among other systems, for which atomistic calculations have been accomplished, mixtures of surfactants with lipids are worth noting.<sup>194</sup> Computer simulations of inverse micelles,<sup>195</sup> hexagonal and lamellar phases and interface layers in surfactant-containing systems have been performed. MD-simulations of bilayers of cationic surfactants in water using the software package GROMACS<sup>196, 197</sup> were reported. The simulations included 242 and  $\sim 4000$  surfactant and water molecules, respectively. The radial distribution functions, density profiles, surface areas per surfactant molecule and diffusion coefficients were estimated; it was revealed that water molecules and counterions penetrate into the hydrophobic core to a significant extent,<sup>198</sup> which was not observed for anionic surfactants.<sup>199</sup>

The coarse grain models enable calculations in wider time and spatial ranges as compared to the atomistic approach, which makes it possible to investigate equilibrium sizes of aggregates, growth of rod-like micelles, formation of vesicles, kinetics of the aggregation processes, solubilisation, phase transitions in two- and three-component systems and adsorption. However, these calculations take into account the chemical nature of the system under study only qualitatively, and their main goal consists of establishing general regularities in the aggregation and phase behaviour (in particular, for systems surfactant–water–oil)<sup>200, 201</sup> and verification of the results of approximate analytical theories, such as the mean-field theory.<sup>202</sup> The models can be formulated in the lattice and non-lattice versions.<sup>203</sup> Implementation of the latter is usually based on the methods proposed by da Gama, Gubbins and Smit *et al.*<sup>204, 205</sup> A model proposed by Larson<sup>206, 207</sup> is a prototype for many lattice models. Within the lattice approach, the Monte Carlo method was applied to study films of diphilic compounds<sup>208, 209</sup> and simulate conformational transitions in a three-component mixture solvent–diphilic compound–polymer.<sup>210</sup> Capabilities of the theoretical description of the self-assembly processes in surfactant solutions and prediction of the phase diagrams and dynamical properties can be extended

by utilisation of mesoscopic simulations using the dissipative particle dynamics method<sup>211, 212</sup> and the lattice gas model<sup>213, 214</sup> as well as dynamic mean-field density functional approach.<sup>215</sup> Many aspects of the behaviour of real systems and specific influence of the molecular structure on the macroscopic parameters have been successfully reproduced by relatively simple models at the coarse grain and mesoscopic levels. However, only qualitative matching has been reached so far and further developments of the models are required to adequately reflect the chemical identity of the components constituting the system under study. Bridging the gaps between the models of different levels, including atomistic, is a current challenge.

## VI. Viscoelastic surfactant solutions

Surfactant solutions manifest diverse rheological properties owing to the self-assembly of diphilic molecules in aqueous solutions and formation of various mesoscopic structures. The viscosities of many solutions even at high concentrations is only slightly larger than that of water so that they behave as ordinary Newtonian liquids. On the other hand, some solutions reveal viscoelastic properties at low surfactant concentrations.<sup>51, 53, 216–222</sup>

Dilute solutions where micelles are independent of each other are characterised by small changes in viscosity as a function of the surfactant concentration. In the case of spherical micelles, this dependence is represented by the Einstein formula:

$$\eta = \eta_0 (1 + 2.5 \varphi), \quad (6)$$

where  $\eta_0$  and  $\eta$  are viscosities of the pure solvent and the solution with a volume fraction of micelles  $\varphi$  (calculated with account of hydration of the surfactant molecules), respectively. The nearly linear correlation (with a slightly different coefficient) is also held for dilute solutions of monodisperse ellipsoids of revolution. The contribution of the intermicellar interactions into the viscosity of dilute solutions is proportional to the concentration squared and is relatively small. Even in the case of strong hydration of micelles (which can give rise to an increase in their apparent volume fraction by a factor of 2–3), the viscosity of a 10% solution will not exceed that of pure solvent more than twice, according to (6). This however is valid only provided the dilute solution approximation remains applicable. There are many systems manifesting a dramatic change in the viscosity vs. composition and a transition into the viscoelastic state, at a certain (sometimes low) concentration. As a rule, the reason for such a transition is the emergence of long worm-like micelles forming a network. In a sense, worm-like micelles are analogous to polymer macromolecules, although the size distribution of the latter is constant for a specific sample whereas the micelles are dynamic entities of a changing size and shape. These structural parameters of micelles strongly depend on the surfactant concentration, nature of counterions, presence of electrolytes and temperature. Growth of micelles can result in their branching under certain conditions. Long micelles can easily break down or coalesce with each other. These properties of micellar systems determine their more complex behaviour as compared to polymeric systems and make additional difficulties in the interpretation of the experimental data.<sup>223, 224</sup> Viscoelastic systems can be prepared by mixing two ordinary dilute micellar solutions (say, of a cationic and an anionic surfactants) or a micellar and a salt solutions with viscosities close to that of water, whereas the resultant solution resembles a gel. Solutions of some non-ionic and zwitter-ionic surfactants also manifest the viscoelastic behaviour. An increase in viscosity can be caused by addition of salts, especially with hydrophobic counterions capable of incorporating between the polar groups of the surfactant.<sup>53, 222, 225–228</sup> For instance, this is typical of mixtures of cetyltrimethylammonium bromide (CTAB) and sodium salicylate, the maximum effect is observed upon mixing of equal volumes of CTAB and the salicylate with concentrations of  $0.05 \text{ mol litre}^{-1}$  and  $0.03 \text{ mol litre}^{-1}$ , respectively (see Ref. 51).

Solutions of some cationic surfactants with unsaturated hydrocarbon tails manifest the viscoelastic properties (even at high temperatures) in the presence of salts.<sup>218</sup> An intense search for new surfactants and mixed systems forming viscoelastic solutions is currently underway. These studies are to a large extent stimulated by strong practical demand, since viscoelastic surfactant solutions are widely employed in the production of cosmetics and detergents, in some oil production technologies, as thickening agents and lubricants. It is often desirable to have viscoelastic behaviour appearing already at low surfactant concentrations and persisting over a wide temperature range. Numerous recent publications and reviews<sup>219–221</sup> devoted to viscoelastic surfactant solutions clearly demonstrate an increasing interest of researchers in this field.

According to the experimental results, the viscosities of surfactant solutions beyond the point of viscoelastic transition (at concentration  $c^*$ ) change with concentration ( $c$ ) obeying a power law  $\eta \propto (c/c^*)^x$  with  $x = 1.5–8.5$ ; higher values of  $x$  are typical of systems containing charged non-shielded micelles whereas lower values are observed for shielded or non-ionic micellar systems near the liquid-crystalline region. The power law usually holds in a wide composition range. In some systems the viscosity passes through maximum and then starts to decrease with increasing surfactant concentration or upon salt addition. For instance, such a behaviour is observed for solutions of cetylpyridinium chloride upon an increase in the concentration of sodium salicylate.<sup>53</sup> The non-monotonic dependence of viscosity on composition can be due to a decrease in the contour length of linear micelles or formation of branched aggregates.<sup>224, 229–231</sup> Theoretical approaches to the description of viscoelastic micellar solutions postulate two basic mechanisms ensuring flexibility of rod-like aggregates, *viz.*, reptation<sup>232–234</sup> and scission–recombination.<sup>223, 229</sup> Probably, both mechanisms can operate simultaneously. Exponents in the scaling correlation viscosity *vs.* volume fraction of the surfactant ( $\phi$ ) for the two mechanisms are different:  $\eta \propto \phi^{5.25}$  if the reptation prevails and  $\eta \propto \phi^{3.5}$  if the scission–recombination plays the dominant role (see Ref. 223).

In the analysis of factors favouring the micelle growth, the molecular-thermodynamical models described in Section IV are useful as well as alternative approaches, which allows estimation of the concentration of a transition sphere  $\rightarrow$  cylinder (the second CMC), growth of rod-like micelles and dependence of the mean aggregation number on composition. According to the general equations (4) and (5), long rod-like micelles can form spontaneously only if the decrease in the combinatorial entropy corresponding to the process is exceeded by the decrease in the Gibbs energy associated with the transfer of a surfactant molecule from the spherical cap to the cylindrical part of the micelle. The tendency of micelles to transform from spheres to spherocylinders is quantified by the parameter  $K$ , which is defined as:

$$\ln K = g_{\text{cap}} \left( \frac{\Delta\mu_{\text{cap}}^\circ - \Delta\mu_{\text{cyl}}^\circ}{kT} \right). \quad (7)$$

Here,  $g_{\text{cap}}$  is the number of surfactant molecules in the terminal spherical caps of a rod-like micelle,  $\Delta\mu_{\text{cap}}^\circ$  and  $\Delta\mu_{\text{cyl}}^\circ$  are the Gibbs energy of micelle formation per surfactant molecule in the spherical cap and infinite cylinder, respectively. The right part of Eqn (7) can be defined as a dimensionless free energy (expressed in  $kT$  units) of scission of a rod-like micelle. The values of the parameter  $K$  have been estimated experimentally for a number of systems,<sup>156, 235, 236</sup> their dependences on temperature and salt content have been measured ( $K$  increases with an increase in the salt concentration). Typical values of  $K$  for systems that form rod-like micelles lie in the range of  $10^8–10^{12}$ . If long micelles are abundant and the solution concentration significantly exceeds CMC, the dependence of the number-average ( $g_n$ ) and weight-average ( $g_w$ ) aggregation numbers on the total mole fraction of the surfactant in the solution ( $X$ ) are given as:

$$g_n \approx K^{1/2} X^{1/2}; g_w \approx 2 K^{1/2} X^{1/2}.$$

The size distribution of rod-like micelles is broad in contrast to that of spherical aggregates. In the case of non-ionic surfactants or strongly screened ionic micelles (*i.e.*, at high salt concentrations), the dependence of  $K$  on the solution composition can be neglected. Therefore, the dependence of the average aggregation number (and, respectively, the average micelle length) on the surfactant concentration under conditions of growth of rod-like micelles obeys a power law. Two other distinct modes are possible for ionic surfactants at low salt concentrations, *viz.*, the dilute mode where the micelle growth is insignificant and the semidilute mode, which is characterised by a rapid growth. Only with a further increase in concentration, the growth starts to obey the power law typical of strongly screened micelles.<sup>148, 149</sup>

According to the formula (7), the parameter  $K$  characterising the transition sphere  $\rightarrow$  cylinder is determined by the difference in the Gibbs energy between the two parts of a micelle having different geometries. The difference is substantially smaller than the energies themselves since it is caused by relatively weak effects.<sup>152</sup> Thus the results of modelling of the micelle growth are substantially more sensitive to errors in  $\Delta\mu_{\text{cap}}^\circ$  and  $\Delta\mu_{\text{cyl}}^\circ$  determination than estimates of CMC. Although the values of  $K$  calculated within theoretical aggregation models differ from the experimentally measured ones,<sup>26</sup> the model calculations make it possible to follow the effects of the chemical structure of the surfactant and the composition of the solution on the micelle growth. A model proposed for worm-like polymer molecules in solutions<sup>237–239</sup> adopted to long micelles in a combination with a micelle formation model. Calculations fairly reproduced viscosities of dilute solutions of hexaethylene glycol *n*-dodecyl ether (a non-ionic surfactant) and afforded an estimate for the concentration of the transition to semidilute solutions where long micelles start to form a network.<sup>240</sup> However, recent calculations for solutions of ionic surfactants accomplished within a similar model were only in qualitative agreement with the experiment.<sup>241</sup> The major difficulties associated with the simulations relate to the adequate description of the size distribution of worm-like micelles and to estimates of their flexibility.

## VII. Self-assembly phenomena in solutions of amphiphilic polymers and of their mixtures with low-molecular-mass surfactants

The self-assembly phenomena giving rise to mesostructures of various morphologies occur in many polymeric solutions and melts and strongly affect the behaviour of these systems. Properties of many polymeric materials and nanocomposites are determined by the structures of the intrinsic microheterogeneities.<sup>242</sup> Investigations into self-assembled polymeric structures represent a huge independent field and thus we mention here only a few relevant directions.

Self-assembly processes in solutions of low-molecular-mass surfactants bear a remarkable resemblance to those of amphiphilic polymers. A prerequisite to self-assembly of macromolecules (as well as of low-molecular-mass surfactants) is the presence of chemically different groups. A simple example is a diblock-copolymer AB composed of a sequence of monomer units A covalently bound to a sequence of units B. There are diverse more complex systems, such as linear triblock copolymers of the types ABA or ABC, multiblock copolymers (AB)<sub>*n*</sub>, comb-like polymers (in which side chains B are grafted to the backbone chain A), star-like polymers and various mixed structures. Polymeric melts or solutions composed of poorly compatible copolymer blocks can undergo microphase segregation resulting in the formation of nanosized areas having various morphologies and containing predominantly blocks of only one type. However, the self-assembly of low-molecular-mass surfactants is only possible if the molecules have a non-polar and a polar (or charged) groups simultaneously, whereas the self-assembly of a macromolecular system can occur even at small differences in the polarity of



blocks. In particular, copolymers of two low-polar organic blocks (*e.g.*, copolymers of styrene and butadiene) form micelles in organic solvents. A difference between micelles formed by high- and low-molecular-mass compounds consists of the larger size of the former. The radius of a micelle often increases with the length of the block that forms the micelle. Flexibility of long chains imparts a number of features (which are, in particular, manifested in dilute solutions) to micelles formed by macromolecules.

Nanostructures that can be formed by amphiphilic polymers in solutions and melts are diverse, they include spherical, cylindrical and disk-shaped micelles, vesicles, several types of liquid-crystalline microphases and complex bicontinuous structures.<sup>1,243</sup> Many amphiphilic block copolymers form micelles in dilute aqueous solutions with cores composed of non-polar blocks and polar coronas.<sup>244–246</sup> Other structures (*e.g.*, cylinders or disks) can be formed, depending on the polymer concentration, solvent nature and presence of additives. Comb-like copolymer macromolecules with strongly self-attracting side chains can form associated networks above a certain concentration and collapse in dilute solutions.<sup>247,248</sup> Mixtures of a hydrophobically modified polymer and a low-molecular-mass surfactant tend to form mixed micelles, like mixtures of two surfactants. With an increase in the solution concentration, a spatial network (*i.e.*, a micellar gel) can form due to binding of one polymeric chain to many micelles simultaneously. A similar phenomenon, which leads to an abrupt increase in the viscosity, is observed upon mixing of a polyelectrolyte solution with an oppositely charged ionic surfactant. The addition of a non-ionic surfactant yields a significantly smaller increase in viscosity whereas the addition of a similarly charged ionic surfactant does not virtually affect the viscosity. This can be illustrated with experimental data on the addition of cationic, non-ionic and anionic surfactants to hydrophobically modified polyacrylate.<sup>249</sup> Copolymers containing ionic hydrophilic blocks bind the oppositely charged low-molecular-mass surfactant and assemble into small vesicles with a neutralised polyion surrounded by the hydrophilic blocks of the copolymer.<sup>250–255</sup> In micellar solutions of copolymers with additives solubilisation can occur. The experimental data on the solubilisation capacity of micelles formed by different copolymers have recently been surveyed.<sup>256</sup>

In theoretical studies of the self-assembly phenomena in solutions of polymers the dominant role is played by the self-consistent mean-field theories<sup>144,242,257–277</sup> and the phenomenological scaling approach.<sup>278,279</sup> The driving force of the microphase segregation is a difference in the interaction energies of identical and different blocks  $\varepsilon_{ij}$  ( $i, j = A, B$ ), which is quantified by the Flory–Huggins parameter:

$$\chi_{AB} = \frac{z}{kT} \frac{\varepsilon_{AB} - (\varepsilon_{AA} + \varepsilon_{BB})}{2}.$$

The parameter  $\chi_{AB}$  (expressed in the  $kT$  units) determines the change in the free energy upon formation of  $z$  mixed contacts A–B between the monomeric units instead of identical contacts A–A and B–B;  $z$  is the number of the nearest monomer neighbours in the configurational cell of the copolymer. Positive values of  $\chi_{AB}$  suggest the tendency of the blocks A and B to segregate, whereas negative values indicate their tendency to mix with each other. Systems revealing no specific interactions are typically characterised by small (significantly smaller than unity) positive values of  $\chi_{AB}$  (for instance,  $\chi \approx 0.1$  for a pair styrene–isoprene). The degree of segregation (weak or strong) is characterised by the product  $\chi_{AB}N$ , where  $N = N_A + N_B$  is the total number of units in the polymeric chain. Since the blocks within a copolymer are bound by covalent bonds, a copolymer melt with a negative value of  $\chi_{AB}$  can undergo only microphase rather than macrophase segregation. The tendency of the blocks A and B to segregate is opposed by the entropy factor since the formation of microphases imposes restrictions on possible configurations of the polymer chains with concomitant decrease in entropy. The

changes in entropy due to configurational restrictions are associated with the elasticity of polymeric chains and networks. Within an approximation that the elasticity is of the purely entropic origin, it can be calculated from the configurational statistics of independent Gaussian chains.<sup>280,281</sup> The balance between the energetic and entropic factors (*i.e.*, between the interface tension and the entropy expenses to straightening of polymeric coils) determines the equilibrium sizes and geometries of the microdomains. In the case of a copolymer AB with similar volume fractions of blocks A and B, the microphase segregation gives rise to a lamellar structure formed by straightened polymer chains. According to estimates made within the mean-field theory, the transition from a completely disordered structure to the lamellar one occurs for a copolymer containing  $N$  units at  $\chi_{AB}N \approx 10.4–10.5$  (see Ref. 242). In the case of a diblock copolymer with the compositional asymmetry (*e.g.*, due to different degrees of polymerisation of the two components), the interface tends to bend thus giving rise to different morphologies of the microphases. A transition of a diblock copolymer from the lamellar structure to hexagonal or cubic structures depending on the composition was predicted in early analytical mean-field theories developed by Semenov<sup>144</sup> within the strong segregation limit ( $\chi_{AB}N \rightarrow \infty$ ) and by Leibler<sup>258</sup> within the weak segregation limit ( $\chi_{AB}N$  slightly exceeds the threshold for the order–disorder transition). A spectral method for the numerical solution of equations of the self-consistent mean-field theory developed later<sup>260–269</sup> made it possible to describe microphases with quite complex structures and demonstrate the diversity of possible patterns of the phase behaviour in the intermediate segregation regime. For instance, a change in the fraction of the units A in the diblock copolymer AB from 0.5 to 0 or 1 at  $\chi_{AB}N = 20$  gave rise to the following sequence of microphases: lamellar L, bicontinuous G (gyroid), hexagonal C (hexagonally packed cylinders), cubic S (spheres packed into a body-centred cubic lattice). According to the calculations, a perforated lamellar phase (PL), in which layers composed of the blocks present in the copolymer in a lower concentration are perforated with hexagonally arranged channels, becomes nearly stable in the proximity of the phase boundary L–G, which is supported by the experimental results. The enhanced segregation between blocks of a diblock copolymer gives rise to a change in the shape of the micellar structures formed from spherical to cylindrical and disk-like.<sup>271,272</sup> The stable gyroid phase of block copolymers was successfully described within the self-consistent field theory corrected for fluctuations either in the weak<sup>270,273</sup> or strong<sup>274</sup> segregation limit. A theory of the microphase segregation in mixtures of block copolymers and homopolymers was developed;<sup>275,276</sup> another theory predicting formation of secondary-domain structures in disordered multiblock copolymers was proposed.<sup>277</sup>

Birshtein *et al.*<sup>282</sup> performed extensive theoretical investigations into the so-called polymeric brushes (*i.e.*, grafted polymeric monolayers). A numerical self-consistency procedure for the mean-field equations originally proposed by Scheutjens and Fleer<sup>175</sup> and developed in further studies<sup>174,283</sup> proved to perform well for various systems. The scaling method was used to elucidate the influence of the solvent selectivity on the morphology of microphases and sizes of domains.<sup>282,284–286</sup> In particular, bicontinuous structures were considered. The self-consistent field theory was applied to concentrated solutions of copolymers in low-molecular-mass solvents,<sup>287,288</sup> although concentrated solutions remain less explored as compared to dilute ones. A model for the analytical description of swelling of a bicontinuous gel in a selective solution was formulated based on the mean-field theory in the strong segregation limit.<sup>289</sup> A theory of gelation of associating polymers was developed.<sup>290,291</sup>

Important regularities of the influence exerted by the structures of macromolecules, their lengths and rigidities, the character of the segment–segment and segment–solvent interactions and component concentrations on the self-assembly processes were

established within the framework of the mean-field theories and scaling approach. Nevertheless, these approaches afford a qualitative picture rather than quantitative description of the behaviour of specific systems taking into account the chemical structures of components and potentials of the interparticle interactions. A description at the microscopic level is required to solve the problems. This level of detailisation is approached in the theory of associating polyelectrolytes developed by Khokhlov *et al.*<sup>292,293</sup> for macromolecules composed of a hydrophilic backbone and hydrophobic side chains that are distributed along the backbone and can aggregate with each other in polar solvents. Within this theory viewing various contributions into the free energy of association such phenomena as stabilisation of finite-size aggregates, abnormal gelation upon a decrease in the number of associating groups, microphase segregation in semidilute solutions, shear-induced thickening of solutions, adsorption of polyelectrolytes on oppositely charged surfaces, *etc.* can be described.

The method of integral equations opens wide prospects in explicit accounting for structural features of specific macromolecules and intermolecular interactions. The integral equation RISM (Reference Interaction Site Model) proposed by Chandler and Andersen as a generalisation of the Ornstein–Zernike equation for systems with multi-site interactions<sup>294</sup> was applied to various self-assembling polymer-containing systems (the RISM equation applied to polymers is referred to as PRISM). Systems containing macromolecules and disperse particles,<sup>295–297</sup> charged copolymers with different types of distribution of monomeric units over a macromolecule (protein-like and statistical copolymers composed of two types of monomeric units, *viz.*, associating neutral hydrophobic and charged ones),<sup>298,299</sup> self-assembling comb-like polymers, polyelectrolytes in bad solvents, *etc.* were studied.

Substantial progress has been achieved in computer simulations of the aggregation in polymeric systems using the Monte Carlo, molecular dynamics and Brownian dynamics methods.<sup>234,300–305</sup> Simplified models of molecules are often used in numerical simulations of polymeric systems. An amphiphilic polymer can be represented as a sequence of two types of beads (hydrophilic and hydrophobic ones). Specific arrangements of the beads mimic a block copolymer or a comb-like copolymer. Using such a model, it has been shown that a collapse of comb-like macromolecules with associating side chains is accompanied by the microphase segregation.<sup>306</sup> The side chains then form spherical micelles and the backbone is located at the surface of these micelles twining between them. A combination of the Brownian dynamics (*i.e.*, a variant of the mesoscopic approach) and self-consistent mean-field algorithms applicable to polymeric brushes was developed.<sup>307,308</sup> Simulations of the microphase segregation in the brushes capable of liquid-crystalline ordering<sup>300</sup> confirmed the major conclusions of the analytical study accomplished earlier.<sup>282</sup> The results of calculations of the thermodynamic parameters for a simple model system, *viz.*, a rigid-chain polymer, obtained using the integral equations RISM and the Monte Carlo method were systematically compared. A self-consistent hybrid approach combining the atomistic Monte Carlo method and the numerical solution of the integral equation RISM was elaborated and adopted to the description of polymer chains in the presence of colloidal particles.<sup>309</sup>

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There is no doubt that investigations into the solutions of surfactant mixtures will develop intensely and converge with studies devoted to the self-assembly processes in other soft-matter systems. A substantial progress in the field might be anticipated owing to combined application of the theoretical studies, physical and computer experiments.

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<sup>f</sup> — *Polym. Sci. (Engl. Transl.)*  
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# Water and aqueous environments: on-line chemical analysis, problems and solutions

A L Moskvina, L N Moskvina

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**Abstract.** General approaches to the automation of chemical analysis and to the design of systems for on-line monitoring of aqueous environments are considered. The advantages of flow analysis techniques in the development of these systems are substantiated. Merits and demerits of the existing versions of flow analysis, namely flow-injection and sequential injection analysis, as well as continuous flow analysis and combined versions of these two methods, are discussed. The bibliography includes 108 references.

## I. Introduction

The chemical control of aqueous environments is needed in many branches of human activity. The most important include the environmental monitoring of natural waters and the monitoring of industrial processes that use water as the operating environment (for example, in thermal and nuclear power engineering). Unfortunately, most researchers still have to consider data obtained in the laboratory analyses of samples taken at intervals. An important drawback of such off-line arrangements of analytical control is the substantial time delay before the information on the monitored object is obtained and, hence, late decisions concerning the intervention into the monitored process for preventing an undesirable development. This is especially important for the monitoring of potentially hazardous engineering processes.

The ecological monitoring of natural waters brings about specific problems, as sampling and sample transportation require more time and labour. This is responsible for errors caused by contamination of samples or degradation of the analytes during sampling, transportation, and storage. When abnormal values are obtained for the parameters under control, verification of the results requires additional time and facilities or may not be

possible at all, because one cannot take two identical samples even from the same water area. The selection of the spatial and temporal coordinates of sampling points is largely random. Therefore, the results are scattered and often do not allow one to draw correct conclusions even on the basis of repeated observations.

The need for alternative ways of monitoring the processes taking place in aqueous environments whose composition changes spontaneously is obvious. The purpose of this review is to analyse the general trends in the development of on-line methods for continuous analysis of water environments which appeared recently.

## II. Alternatives to the traditional off-line analysis scheme

The search for alternative solutions has resulted in new schemes of chemical analysis. In medicine, '*in situ*' analysis is used most often, i.e., determination of the analyte directly within the analytical control object. This is done by monitoring easily measurable physical parameters: temperature, pressure and flow rate.<sup>1</sup> The '*on site*'<sup>2</sup> plan has found application in the solution of ecology-related analytical problems. This analysis is performed directly on the site where the monitored object is located. Both schemes imply the development of special methods of analysis as applied to the conditions under which they are performed. In the case of the '*in situ*' analysis, these are chemical sensors, while in the case of '*on site*' analysis, they are test methods.

The most versatile scheme is on-line analysis, which implies creation of a continuous sampling line from the monitored environment and installation of continuously functioning analyser(s).<sup>3</sup> In the on-line scheme, the range of applicable methods of analysis is virtually endless. Algorithms for the selection of an adequate analytical method and, correspondingly, the appropriate analyser have been proposed.<sup>4</sup> To date, up to a hundred methods can be used for continuous ecological and in-process monitoring of aqueous environments.<sup>5</sup> Information on the commercially available analysers has been covered in the *Anadata Analyser Encyclopedia*;<sup>6</sup> and a system of priorities has been outlined.

If it is necessary to monitor simultaneously a large number of impurities, high performance liquid chromatography (HPLC) is a convenient choice. However, the instrumental complexity of liquid chromatographs and, hence, their higher cost for lower reliability, and also the necessity of using flammable and toxic

**A L Moskvina** Joint-Stock Corporation Research and Production Association 'Granit-NEMP', Gospitalnyi per. 3, 191014 St Petersburg, Russian Federation. Fax (7-812) 274 01 26, e-mail: ap2005@rosanalyt.ru

**L N Moskvina** Department of Chemistry, St Petersburg State University, Universitetsky prosp. 26, Petrodvorets, 198504 St Petersburg, Russian Federation. Fax (7-812) 428 69 39, tel. (7-812) 428 68 33, e-mail: moskvina@pobox.spbu.ru

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solvents as eluents hamper broad use of HPLC in the automated systems for continuous in-process monitoring. During the period of vigorous development of HPLC, forecasts were made concerning fast extension of the scope of its application in in-process control, and special liquid chromatographs were manufactured for this purpose (for example, the Optichrom series produced by the Applied Automation company).<sup>5</sup> However, liquid chromatographs, except for ionic ones, have not found wide use in in-process control.<sup>7</sup> Whereas gas chromatography is almost irreplaceable in analysis of hydrocarbon mixtures, in the case of liquid chromatography, there exist alternative solutions. In those rare cases where HPLC is still used for in-process control, conventional laboratory instruments are employed in automated systems. For example, SAMOS (System for the Automatic Measurement of Organic micropollutants in Surface water) designed for the monitoring of organic pollutants in the Rhine collecting area is based on HP 1090 liquid chromatographs.<sup>8–10</sup>

In recent years, rapid separation-free methods of analysis have appeared in the optical and electrochemical technology (for example, those using rapid-scanning spectrophotometers on photodiode lines with computer processing of the spectra).<sup>11</sup> When photodiode lines are used as detectors, a full spectrum composed of 200–1000 points is recorded in several milliseconds.<sup>12,13</sup>

Ion chromatography, which does not require hazardous solvents and operates at much lower pressures, is still used in thermal and nuclear power engineering. Actually, one can hardly propose equally efficient and relatively inexpensive methods for determination of anions.<sup>14–18</sup>

After a period of moderately successful attempts at the development of on-line automated monitoring systems based on HPLC, flow-injection analysis (FIA) has now become the method of choice for the design of such systems.<sup>19</sup>

### III. How can chemical analysis be automated?

The problem of automation of chemical analysis involves two aspects: the automation of proper analytical procedures in the traditional off-line chemical analysis and the integrated automation of the analytical control including sampling, sample processing and data collection and display stages. The problem of integrated automation of the in-process monitoring where the composition of the monitored material spontaneously varies includes automation of analytical procedures for particular methods as a part of continuous on-line analysis.

A monograph<sup>20</sup> presents an attempt to describe the general approaches to the automation of laboratory analysis based on electrochemical, colorimetric, spectroscopic, thermal, radiometric (X-ray) and chromatographic analysis and sample preparation procedures involving separation techniques. The technical solutions proposed for any of the above methods and especially for the processing of analytical information, described in the monograph, are now essentially out-of-date. However, everything concerning the general concepts of automation of chemical analysis remains actual.

In solving the problem of automation of proper chemical analysis, two basically different approaches are possible. The first one, robotic, implies the design of mechanical devices that copy the operation of an analytical chemist when performing analyses. These devices are to measure the required amounts of samples and reagent solutions, mix them, fill the measuring cell or take aliquot portions and inject them into the analyser, measure the analytical signal, and so on. The major advantage of this approach is versatility. Almost any chemical analysis technique (for example, laboratory liquid chromatographs operating in the automated mode<sup>10</sup>) can be automated using the robotic approach. However, analysers of this type have a common drawback: high cost and low reliability caused by complexity of mechanical units.<sup>20</sup> The design of these analysers does not comply with an important requirement of automated systems for chemical analysis, in particular, the principle of minimisation of the number of moving parts.<sup>5</sup>

The second approach implies, instead of the direct imitation of the operator's action, its mimicking under conditions most susceptible to automatic control. This approach is embodied in flow analysis.

### IV. Flow analysis as a general approach to the automation of chemical analysis

This group of methods opens up the most extensive opportunities for the automation of analysis. They were first implemented as continuous flow analysis (CFA) whose history and key principles have been outlined in certain books.<sup>21,22</sup> The hydraulic flow diagram of CFA is presented in Fig. 1a. The flows of the sample and a solution of a reagent capable of producing an 'analytical form' with the analyte detectable by the flow detector are continuously pumped by a peristaltic pump, mixed in the mixing helix, and routed to the detector. This version is used if the detector cannot catch the analytical signal directly from the analyte. Otherwise, the reagent and the mixing helix are not required. A drawback of this flow chart is the fact that correctness of the detector reading cannot be checked during the measurements. This is due to elimination of the boundary between the consecutive samples of different compositions in hydraulic lines caused by mixing; this precludes the possibility of checking the detector readings due to mixing of the test and reference samples.

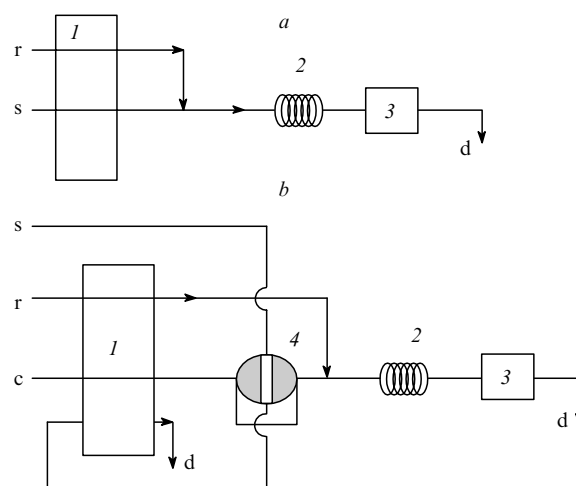


Figure 1. Hydraulic block diagrams of CFA (a) and FIA (b).

(1) Peristaltic pump, (2) mixing helix, (3) flow detector, (4) measuring valve. Inlet lines: s — for the sample, r — for the reagent, c — for the carrier solution; d — for the discharge.

The FIA scheme<sup>23</sup> implies the introduction of discrete batches of the sample into a moving laminar flow of the carrier solution to form a controlled concentration gradient of the analyte (Fig. 1b). The flow of the carrier solution is combined with the flow of the reagent solution in the mixing helix and the mixture enters the flow detector, which records concentration peaks, the peak width being determined by the dispersion of samples as they move along the hydraulic lines. Thus, FIA is the flow analysis with a 'controlled sample dispersion'.<sup>24</sup> The carrier solution, the flow of which carries the test sample, can serve additionally as the correcting medium, which creates conditions (for example, stabilises the pH) needed for the formation of 'analytical forms' of the analyte upon mixing with the sample. The amplitude and the area of the obtained peaks are related to the analyte concentration. The FIA principles and equipment have been described in the literature.<sup>23,25–27</sup> Specific problems of the application of FIA for the continuous on-line process control have been considered.<sup>28–33</sup>

The major advantage of FIA is the possibility to perform almost all known operations included in the sample preparation<sup>†</sup> — dilution,<sup>35</sup> preconcentration and isolation of the analyte by extraction,<sup>36–42</sup> dialysis<sup>43–47</sup> and sorption<sup>27, 41, 46, 48</sup> in the on-line mode. In addition, quantification can be carried out using almost any of the known detection techniques ranging from simple sensors to mass spectrometers.<sup>19, 27, 49</sup>

Yet another important advantage of FIA is the possibility of calibrating instruments with a specified scale unit directly under operating conditions,<sup>50–56</sup> which is especially important for monitoring systems. The automated taking into account of the drift of the base line and the possibility of correcting the calibrating curves ensures the reliability of the results.

Flow-injection analysis can be considered as a set of instrumental techniques that ensure the automation of the routine analytical procedures of sample preparation and measuring of the analytical signal for most methods used to quantify the analytes. The indisputable advantages of this approach resulted in a growth of the number of companies engaged in the manufacture of flow-injection analysers for process control. The information on the equipment for FIA can be found in the publication.<sup>57</sup> Flow analysers and automated multichannel systems for the on-line analytical control based on them have now been developed.<sup>58</sup>

To eliminate the loss of information concerning the monitored process during the periods between FIA cycles, a combined flow method joining the advantages of CFA and FIA has been proposed.<sup>59</sup> This approach implies alternation of different modes of operation of a flow analyser according to a specified algorithm. To obtain analytical information on even short-term fluctuations of the sample composition, if spontaneous changes are possible, the analyser operates most of the time in the CFA mode, and to verify the detector readings, the analyser is switched to the FIA mode with periodic supply of reference solutions to the inlet. This provides the opportunity to check the position of the detector base line and the response to a particular analyte concentration. Figure 2 shows the form of the analytical signal recorded with alternation of the CFA and FIA modes. During the time period from 0 to  $t_1$ , the analyser operates in the CFA mode with the supply of the test sample to the inlet. At the instant  $t_1$ , the analyser is switched to the FIA mode with the same sample being supplied to the inlet, as indicated by equal amplitudes of the peaks and the magnitudes of the continuous signal. At time instant  $t_2$ , a standard solution of the analyte starts to be supplied, and at time instant  $t_3$ , the analyser is switched again to the CFA mode and the test sample moves through the system.

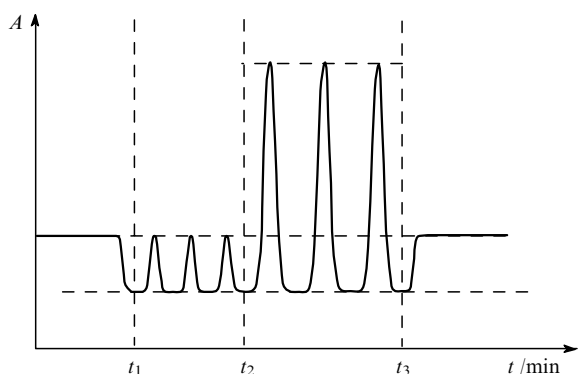


**Figure 2.** Form of the analytical signal recorded upon consecutive operation of the flow analyser in the CFA and FIA modes.

<sup>†</sup> It should be noted that in automated on-line monitoring systems, the most critical problems arise at the sample preparation stage.<sup>34</sup>

## V. Extension of the analytical potential of flow-injection analysis

Among the advantages of FIA as a versatile method for performing chemical analysis in the on-line mode, worthy of note is the possibility of incorporation of preconcentration and isolation of analytes into the analysis sequence; in some cases, this compensates for the insufficient sensitivity of widely used detectors. The separation and preconcentration methods used in FIA have been surveyed in a collection of papers<sup>28</sup> and in a monograph.<sup>46</sup> The most widely used methods include gas diffusion through porous hydrophobic membranes, extraction and sorption.

In flow analysis, the separation methods based on gas diffusion through a membrane perform two functions in sample preparation.<sup>60</sup> The first one is the isolation of analytes in the aggregative state most convenient for the subsequent determination by flow detectors. Depending on the aggregative states of the source and receiving phases, the analyte can be converted from a gas into a liquid and *vice versa*. Liquid absorption is normally used in FIA and CFA for the analysis of atmospheric air,<sup>46, 61</sup> while gas extraction is used more often in vapour analysis of aqueous media.<sup>62</sup> Another study describes<sup>63</sup> the use of membrane gas diffusion cells for the reaction gas extraction in FIA in which the analyte is intentionally transferred into a volatile form (for example, in the determination of  $\text{NH}_4^+$  in sewage water).

The second function of gas diffusion methods in FIA is to change deliberately the composition of the test medium (for example, the pH) in order to create the optimal conditions for the formation of 'analytical forms' of the substances to be determined.<sup>64–66</sup>

Liquid extraction, like gas diffusion, is used in FIA not only as a preconcentration method but also for the isolation of substances in the aggregative state most convenient for their subsequent determination. An example is extraction of petroleum products and phenols into hexane or carbon tetrachloride.<sup>67</sup> The use of extraction in FIA has required the development of special flow extraction apparatus. Extraction in segmented flows has gained the widest use.<sup>39–42, 68</sup> For this purpose, portions of an extractant are introduced at intervals into the flow of the test solution (after pre-adjustment of the composition of this solution to ensure the optimal conditions for extraction). As a result, the homogeneous flow of the solution is converted into a two-phase segmented flow in which segments of the aqueous solution alternate with segments of the extractant whose length in the capillary tube (about 0.5 mm in diameter) is 1–6 mm. The segmented flow passes through the extraction helix, which intensifies the phase transfer, and enters the separator in which the phases are separated. The organic phase is routed to the flow reactor.

The most severe drawback of these systems is the fact that it is impossible to control the ratio of phase volumes over broad ranges, which stipulates a limitation for the attainable preconcentration factor even when the distribution coefficient in the extraction system used is high.

### 1. New methods in liquid and gas flow extraction

New possibilities for the flow extraction appeared owing to the chromatographic-membrane mass exchange processes in liquid–liquid and liquid–gas systems.<sup>69</sup> The idea of chromatographic-membrane processes is based on the use of capillary effects in hydrophobic porous media.<sup>70</sup> The mass exchange between two phases differing in polarity takes place in a capillary porous medium from a hydrophobic material containing two types of pores with different sizes. The capillary pressure arising in micropores prevents water and aqueous solutions from getting inside. In turn, the aqueous solutions that enter, according to experimental conditions, the biporous system under a higher pressure fill macropores and prevent non-polar phases from entering the macropores. Thus, the two phases can move independently within the mass exchange space formed by the hydrophobic biporous medium. The diagram of a chromatographic-membrane cell

(CMC), shown in Fig. 3, corresponds to the case where the flows of two phases intersect at right angle. The mass exchange takes place in conformity with the rules of a chromatographic process, as the porous structure of the mass exchange layer in the CMC is similar to the structure of a stationary non-polar packing in an extraction-chromatographic column. The differences are manifested only as an increase in the phase transfer rate compared to that in a conventional chromatographic process (in which one phase is stationary) due to the convective movement of both phases at the interface.

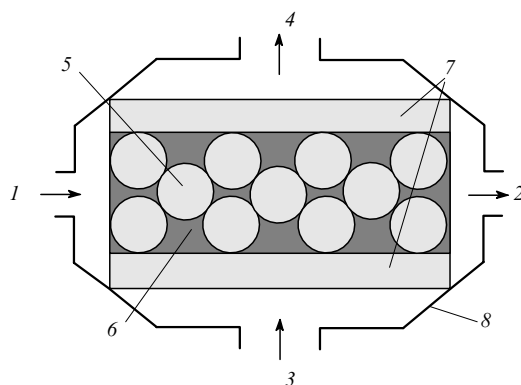


**Figure 3.** Block diagram of a chromatographic-membrane cell. (1, 2) Polar liquid inlet and outlet; (3, 4) non-polar liquid or gas inlet and outlet; (5) biporous hydrophobic matrix (microporous filler); (6) macro-pore space; (7) microporous hydrophobic membranes; (8) cell casing.

A flow of a non-polar liquid or a gas is introduced into the mass exchange space and leaves this space through hydrophobic microporous membranes, in which the pore size is close to the size of micropores in the biporous matrix. The material of the membranes and the pore size should ensure the impermeability of the membrane for the aqueous phase under conditions of the mass exchange process.

The chromatographic-membrane liquid or gas extraction is an alternative to not only extraction in segmented flows but also to the isolation by gas diffusion, because it provides intensification of phase transfer both in the liquid-liquid and liquid-gas systems. Instead of the slow diffusion through a porous membrane, the gas-diffusion membrane processes involve the delivery of phases to the interface.

Numerous examples of the use of the chromatographic-membrane liquid and gas extraction in FIA have been reported.<sup>60</sup> A number of combined protocols of sample preparation are possible. For example, for the determination of arsenic, the chromatographic-membrane reaction gas extraction is combined with gas liquid chromatography;<sup>71</sup> petroleum products and phenols are determined in water using an extraction chromatographic column for the preconcentration and isolation of the analytes into the organic phase.<sup>67</sup> After these have been eluted by the extractant, the resulting two-phase flow is separated in a chromatographic-membrane separating vessel.

## 2. Sorption preconcentration in the flow-injection analysis

Sorption techniques for sample preparation actively compete in FIA with the extraction methods and, in some occasions, the former are even preferred.<sup>27, 46, 48</sup> This is the case where it is necessary to attain the limiting preconcentration factors (for example, to determine beryllium in natural water<sup>72</sup>) or to exclude the use of organic solvents. Sorbents with chelating functional groups have found the most extensive use in FIA.<sup>48</sup> As regards minimising the time required for the sorption preconcentration, sorbents with fibrous structure are most efficient, as they ensure the highest rate of sorption equilibration.<sup>72</sup> In this case, it is expedient to incorporate a high-speed peristaltic pump into the

hydraulic circuit for sample filtration through a column containing the sorbent (Fig. 4). When the position of the switching valve corresponds to the route shown by the continuous lines, a mixed flow of the sample and a buffer solution is filtered through a column at the highest permissible rate. Simultaneously, the eluent is mixed with the reagent solution and passes through the flow detector, which records the base line. After the valve has been switched into the position corresponding to the dashed lines, the sample is routed to the discharge and the eluent is fed to the sorption column. At the column outlet, the eluate is mixed with the reagent solution and flows to the detector, which records the analyte peak against the base line obtained in the previous cycle.

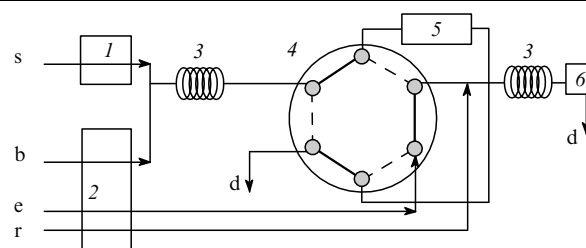


**Figure 4.** Hydraulic diagram of FIA with sorption preconcentration on a fibrous sorbent.

(1) Single-channel high-speed peristaltic pump, (2) multichannel peristaltic pump; (3) mixing helices, (4) six-way switch valve, (5) sorption column, (6) flow detector.

Inlet lines: s — for the sample, b — for the buffer solution; e — for the eluent; r — for the reagent, d — for the discharge.

## VI. Practical use of on-line chemical analysis based on the principles of flow-injection analysis

Most publications devoted to FIA describe procedures of off-line analysis in stationary laboratories. Much fewer papers have been devoted to the applications of FIA in the on-line mode. The attention is focused on the continuous determination of products either formed in the processes of biotechnology (during operation of fermenters) or supplied to the reaction medium. The publications consider both the general aspects of the on-line analytical monitoring of biochemical processes<sup>73–79</sup> and particular issues of continuous monitoring of the concentration of separate components: proteins,<sup>80</sup> enzymes,<sup>81</sup> amino acids,<sup>82</sup> antibiotics,<sup>83, 84</sup> glucose,<sup>85, 86</sup> lactate and so on.

The publications devoted to analysis of various types of water — subsurface, rain, river, sea and potable water — refer mainly to procedural aspects of the off-line determination of particular impurities. The data on flow-injection analysers operating in the on-line mode on real water environments are summarised in Table 1. Most of them provide monitoring of some single parameter of water contamination, *i.e.*, making use of automated single-channel analysers adjusted to determination of one analyte in the on-line mode.

Among interesting, although disputable solutions,<sup>‡</sup> worth noting is the SCANNER analyser, which is an example of using FIA for *in situ* control.<sup>100</sup> It is designed for determination of  $\text{SiO}_3^{2-}$  and  $\text{S}^{2-}$  in sea water directly from the ship and can operate at depths of up to 2500 m.

To perform automated chemical monitoring of several quality parameters of a water medium in the on-line mode, two systems are possible: (i) the design of *n* independent parallel channels, each

<sup>‡</sup> The point that seems disputable is overcoming of sealing problems when working under high pressures, instead of using (designing) a simple and more reliable system for continuous sampling of water from a required depth.

**Table 1.** Application of FIA for impurity analysis in the aqueous environments of real objects (in the on-line monitoring mode).

| Impurity                                         | Object of analysis                          | Detector                                                     | Detection limit<br>/ $\mu\text{g litre}^{-1}$ | Range of linearity<br>/ $\mu\text{g litre}^{-1}$ | Operation time <sup>a</sup><br>/day | Ref. |
|--------------------------------------------------|---------------------------------------------|--------------------------------------------------------------|-----------------------------------------------|--------------------------------------------------|-------------------------------------|------|
| $\text{PO}_4^{3-}$                               | natural water                               | photometer, $\lambda = 660 \text{ nm}$                       | 12 <sup>b</sup>                               | 0–1000                                           | –                                   | 87   |
| $\text{NO}_3^-$                                  | the same                                    | photometer, $\lambda = 565 \text{ nm}$                       | 24                                            | 0–12000                                          | 4                                   | 88   |
| $\text{NO}_3^-$                                  | hydroponics solutions                       | photometer, $\lambda = 542 \text{ nm}$                       | –                                             | –                                                | –                                   | 89   |
| $\text{NO}_3^-$                                  | natural water                               | photometer, $\lambda = 550 \text{ nm}$                       | –                                             | –                                                | 7 <sup>c</sup>                      | 90   |
| $\text{F}^-$                                     | the same                                    | ionometric electrode                                         | –                                             | –                                                | 7                                   | 91   |
| $\text{NH}_4^+$                                  | water from biological treatment plants      | photometer, $\lambda = 590 \text{ nm}$                       | –                                             | 500–50 000                                       | –                                   | 92   |
| $\text{NO}_3^-$                                  | the same                                    | the same                                                     | –                                             | 500–20 000                                       | –                                   | 92   |
| $\text{PO}_4^{3-}$                               | "                                           | "                                                            | –                                             | 500–30 000                                       | –                                   | 92   |
| $\text{F}^-$                                     | natural water                               | fluorimeter                                                  | –                                             | 0.2–20                                           | –                                   | 93   |
| $\text{H}_2\text{O}_2$ , $\text{H}_3\text{BO}_3$ | solutions of neutron moderators             | amperometric                                                 | –                                             | –                                                | –                                   | 94   |
| $\text{NH}_4^+$                                  | natural water                               | photometer, $\lambda = 635 \text{ nm}$                       | 17                                            | 0–5000                                           | 3                                   | 95   |
| $\text{NH}_4^+$                                  | sewage water                                | the same                                                     | 600                                           | 0–40 000                                         | 7                                   | 96   |
| $\text{SO}_3^{2-}$                               | KCl brines (up to 18%)                      | fast-scanning spectro-photometer, $\lambda = 412 \text{ nm}$ | –                                             | 0–20 000                                         | 7                                   | 97   |
| Al(III)                                          | natural water                               | photometer, $\lambda = 538 \text{ nm}$                       | < 45                                          | 0–1000                                           | 14                                  | 98   |
| V(V) <sup>d</sup>                                | alkaline solutions of the Sulfoline process | photometer, $\lambda = 550 \text{ nm}$                       | –                                             | $(5–150) \times 10^4$                            | –                                   | 99   |

<sup>a</sup> Duration of the continuous autonomous operation. <sup>b</sup> For phosphorus. <sup>c</sup> The total testing time is 2 years of operation. <sup>d</sup> In the presence of excess V(IV).

being tuned for determination of one of  $n$  monitored parameters, and (ii) the design of a system containing additional units for switching the flows in order to adjust channels for determination of one or another parameter.

The experience of design and operation of an automated system according to the principle of  $n$  parallel channels to monitor the quality of the outside water from a moving ship <sup>58</sup> has shown that such a system ensures a sufficient reliability when up to 14 parameters are simultaneously determined (Table 2). Therefore, in the design of a ship system for real-time ecological analytical monitoring, an  $n$ -channel system was preferred over the adjustable system. This provides higher reliability of the equipment due to minimisation of the number of mechanical units <sup>5</sup> and elimination of the necessity of combining units of flow-injection analysers that implement different methods of analysis. Evaluating objectively the potential of FIA, the authors <sup>101</sup> noted that these devices function efficiently in a laboratory but are not always suitable for industrial conditions. The need to use sets of different units for each analytical method and the relative complexity of operation of peristaltic pumps are the general drawbacks of FIA as regards the design of on-line monitoring systems. The former drawback is

important for the  $n$ -channel configuration of a multiparametric control system, <sup>58</sup> which is less favourable for economic reasons than a system with adjustable analysers.

## VII. Sequential injection analysis as the next step in the automation of on-line chemical analysis

The search for an alternative to FIA has given rise to a new approach in the flow analysis techniques, namely, sequential injection analysis (SIA). <sup>101</sup>

In flow-injection analysis, the analytical process takes place in a system of tubes along which the sample or calibrating solutions and solutions of reagents move in one direction. After combination of the flows, the sample or the calibration solution is mixed with the reagent, and the flow of the carrier with the reaction products moves toward the detector. Therefore, for inducing the flow along each inlet tube (the sample, the reagent solution, and auxiliary solutions), a separate pump is required. The multi-channel peristaltic pump, which is usually employed for this purpose, is actually a set of pumps operating in parallel. In addition, a measuring valve is required for introducing aliquot portions of the sample or a reagent solution into the flow of the carrier.

In the sequential injection analysis, a single liquid line is used, instead of the set of tubes, in which a syringe pump operating according to a definite schedule induces a flow of solutions moving alternately into two directions (Fig. 5). The piston of the syringe pump moves in discrete strokes in order to suck in the wash solution (1), the solution of the sample (2) and the solution of the reagent (3) into the liquid channel composed of the reaction helix, flow detector and the holding helix. The distributive valve ensures the sequential injection of solutions into the channel by switching the valve outlets synchronously with pumping. During the reverse stroke of the piston, the mixed solution of the sample and the reagent passes through the detector to the discharge and the hydraulic line is washed. Among the important advantages of SIA, noteworthy is the option to stop the flow, which allows this method to be used for measuring the rates of chemical reactions. <sup>102</sup> The possibility of stopping the flow is also useful for adjusting the conditions of analysis as regards the time for the formation of the 'analytical forms' of the analyte.

**Table 2.** List of controlled parameters of water quality and ranges of quantifiable concentrations (RQC) by systems of the flow monitoring of water quality. <sup>58</sup>

| Component                              | RQC / $\text{mg dm}^{-3}$ | Component          | RQC / $\text{mg dm}^{-3}$ |
|----------------------------------------|---------------------------|--------------------|---------------------------|
| $\text{NO}_3^-$                        | 0.3–5.0                   | $\text{SO}_4^{2-}$ | 25–250                    |
| $\text{NO}_2^-$                        | 0.05–2.0                  | $\text{Zn}^{2+}$   | 0.01–0.1 <sup>b</sup>     |
| $\text{Cl}^-$                          | 3–3500                    | $\text{Mn}^{2+}$   | 0.01–0.1 <sup>b</sup>     |
| $\text{F}^-$                           | 0.03–7.0                  | $\text{Fe}^{3+}$   | 0.05–1.0                  |
| $\text{PO}_4^{3-}$ (see <sup>a</sup> ) | 0.5–10.0                  | dissolved          | 0.02–1.0 <sup>c</sup>     |
|                                        | 0.025–1.0                 | petroleum          |                           |
| $\text{Cu}^{2+}$                       | 0.02–1.0                  | products           |                           |
|                                        | 0.001–0.02 <sup>b</sup>   | anionic surf-      | 0.03–1.5 <sup>c</sup>     |
| $\text{NH}_4^+$                        | 0.05–0.8                  | actants            |                           |
|                                        |                           | phenol             | 0.001–0.1 <sup>c</sup>    |

<sup>a</sup> Calculated for P; <sup>b</sup> with sorption preconcentration; <sup>c</sup> with chromatographic-membrane extraction concentration.

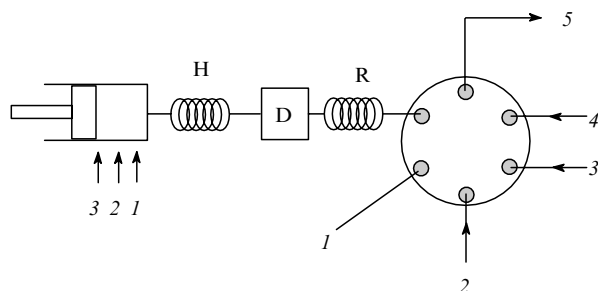


**Figure 5.** Block diagram of the sequential injection analysis.

(1) Wash solution, (2) a solution of the sample, (3) a solution of the reagent, H is the holding helix, R is the reaction helix, D is detector, (4) standard solution, (5) discharge.

The authors of SIA<sup>101</sup> stipulated the use of a pump having a 'zero time lag' and a 'zero elasticity,' which requires replacement of a peristaltic pump by a computer-controlled plunger pump. The MilliGAT plunger pump,<sup>103</sup> which completely rules out flow pulsation, is the most successful engineering solution. However, peristaltic pumps are also used in some cases.<sup>104</sup>

Sequential injection analysis has a number of advantages over FIA (especially in the on-line mode), in particular, minimisation of the consumption of the reagent solution and a better adaptability to computer control in the case of SIA.<sup>101</sup> Moreover, the SIA version no longer requires the measuring valve (which is considered to be a trouble spot in FIA instruments),<sup>105</sup> the selection of every next solution being accomplished by means of a multiway valve. The authors of the method believe that the replacement of the measuring valve eliminates the problems related to the operation of mechanical units of the analyser; however this is not self-evident. The description of the software for the automation of flow analysis systems in SIA is documented.<sup>106</sup>

The attraction of SIA as a new approach to the automation of chemical analysis is indicated by numerous publications: more than 200 papers, several patents and a review<sup>105</sup> have now been published on this topic.

The discussion of on-line analysis would be incomplete without considering the problem of continuous sampling. According to different estimates, 70% to 85% of malfunctions in on-line analysis systems refer to this stage.<sup>107</sup> The sampling problem is solved rather easily in the case of the in-process control of the aqueous media circulating or occurring in the controlled object under an elevated pressure. Connection of the sampling line requires a choke with a controlled flow rate made of an inert material.

The information on the development and functioning principles of continuous sampling systems (CSS) for natural and sewage water is very limited. The Fathom Oceanology Ltd company (Canada) has designed a CSS having a fluoroplastic hose 8 mm in diameter and a pump for water supply to the ship (with a productivity of up to 40 dm<sup>3</sup> min<sup>-1</sup> at a ship velocity of up to 12 knots). Similar systems have also been designed by the Japanese companies Morikawa and Progress Trading. Direct measurements of contaminants in a sea water flow are also performed.<sup>108</sup> Determination of nitrates and nitrites was carried out by reverse flow-injection analysis (with injection of reagents); sea water was pumped directly through the tubes of a flow-injection analyser. Later, analyses of sea water for sulfates, phosphates, silicates and a number of metals (cobalt, manganese, copper, iron) have been carried out. Analyses were performed from a drifting ship, i.e., no monitoring of water basins, which requires on-line analysis, was involved.

All the CSS systems mentioned above are meant for taking representative samples into sampling vessels for their subsequent chemical analysis in the laboratory (off-line mode). However, an experience in the design and operation of CSS in combination with

a multiparametric system of on-line analysis has been reported.<sup>58</sup> The block diagram of the CSS is shown in Fig. 6. To minimise the time delay between obtaining the data on the sample composition and the real time, a two-step pattern of sample supply to the analyser was chosen. The first step is a main channel with a membrane pump operating for the discharge of the main bulk of water overboard. The main channel includes a unit for splitting of the sample flow, some of the flow being routed to the inlet of analysers. To ensure the sample representativity, polytetrafluoroethylene and stainless steel were chosen as the main structural materials for the CSS. The removal of mechanical impurities was attained by three-step filtration. The design of water intake devices includes coarse filters manufactured from a stainless-steel grid, which separate particles larger than 1 mm. The flow splitting unit installed in the main channel of the CSS includes a fine filter for water with a filter cell made of porous stainless steel for separating particles larger than 0.1 mm. At the inlet of each analyser, except that for petroleum products, fine filters made of porous polytetrafluoroethylene are installed additionally. The filters are expected to protect the hydraulic lines and flow measuring cells of the analysers from plugging with coarse suspensions of either mineral or organic origin, which are always present in natural waters. At the same time, the filters do not influence the chemical composition of the sample.

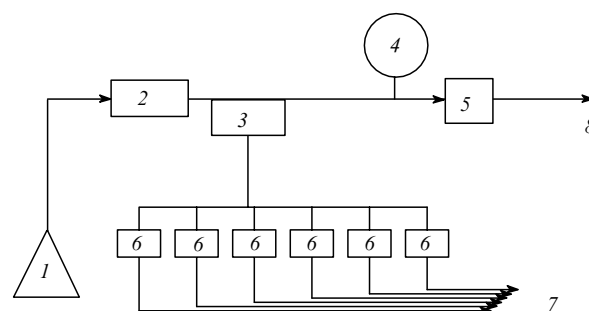


**Figure 6.** Block diagram of the continuous sampling system for natural water: (1) water intake device; (2) main pump; (3) coarse filter; (4) manometer; (5) controlled choke; (6) fine filters; (7) sample inlet channels of the monitoring system; (8) discharge line.

The presented block diagram of CSS and the diverse types of flow analysers considered above demonstrate the presence of a methodical and instrumental base for the design of automated on-line chemical analysis systems for the industrial process control and ecological analytical control of aqueous environments.

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<sup>a</sup> — *Russ. J. Anal. Chem. (Engl. Transl.)*

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# Addition of HO-nucleophiles to free and coordinated nitriles

N A Bokach, V Yu Kukushkin

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**Abstract.** The review surveys data on the addition of HO-nucleophiles (water, oximes, hydroxylamines, hydroxamic acids, alcohols) to nitriles. Main methods for  $C\equiv N$  bond activation in nucleophilic addition reactions are discussed. Particular attention is given to activation of nitriles through coordination to metal centres. The bibliography includes 191 references.

## I. Introduction

Nitriles are widely used in preparative chemistry due to their ability to be involved in nucleophilic and electrophilic addition and  $[2+3]$ -cycloaddition reactions. In particular, these reactions are used to synthesise amides and carboxylic acids [for example, acrylamide, nicotinamide and *S*-(+)-ibuprofen], which are of considerable practical importance, and a wide range of heterocyclic compounds containing one or more nitrogen atoms. The addition of various nucleophiles at  $C\equiv N$  bonds giving rise to compounds containing new  $C-N$ ,  $C-O$ ,  $C-S$ ,  $C-C$  or  $C-P$  bonds is most generally employed in nitrile chemistry.

Nitriles containing activating electron-withdrawing groups, for example, perfluoroalkyl groups, can react with various nucleophiles without additional  $C\equiv N$  bond activation, whereas the addition reactions to nitriles containing electron-donating or weak electron-withdrawing groups require that the electrophilicity of the carbon atom in the RCN molecule be additionally enhanced. In organic chemistry, activation of nitriles and nucleophilic addition reactions are often carried out with the use of acid catalysis (Pinner reaction;<sup>1</sup> see also Refs 2–10) or alkylation giving rise to nitrilium salts.<sup>11–13</sup> Another efficient method for activation is based on coordination of  $RC\equiv N$  to the metal centre. Nowadays, numerous reactions involving the activated  $C\equiv N$  bond are known: metal-mediated and metal-catalysed hydrolysis and alcoholysis of nitriles,<sup>†</sup> nucleophilic addition reactions of amines, imines and sulfimides and addition reactions of halo- and

aminoalcohols.<sup>14–24</sup> Coordination to metal can not only activate the  $C\equiv N$  bond but also promote reactions accompanied by  $\alpha-C-H$  and  $C-C$  bond cleavage in nitriles.<sup>25–28</sup>

The body of literature on metal-mediated reactions of nitriles published in recent years is too large to be reviewed here. Hence, this review covers the reactions of nitriles with one particular group of nucleophiles, *viz.*, HO-nucleophiles, accompanied by their addition at the  $C\equiv N$  bond to form imidoates  $HN=C(R)O-$ . HO-Nucleophiles include a wide range of compounds of various classes, which differ in reactivity.

In the last few years, data on reactions of nitriles with particular classes of HO-nucleophiles have been summarised in several publications (for example, hydrolysis of RCN involving various metals was considered in the reviews,<sup>19,29–38</sup> reactions with nitrile hydratases and mimetic complexes of these enzymes were surveyed in publications<sup>33–48</sup>). However, in none of these publications were the addition reactions of different classes of HO-nucleophiles with nitriles compared. Moreover, abundant new data on the reactions of nitriles with such HON-nucleophiles as oximes, hydroxylamines and hydroxamic acids have been reported in the very recent past.

The aim of the present review is to survey the available data and perform comparative analysis of the data on interactions of the  $C\equiv N$  group of free and coordinated nitriles with HO-nucleophiles. The review provides an overview of recent studies of the reactions of nitriles with water and alcohols in the presence of metal centres and reveals the main factors responsible for these reactions. Considerable attention is given to reactions with poorly known nucleophiles (in particular, with HON-nucleophiles), which have been investigated rather recently. It should be noted that the present review is a continuation of a series of articles published in this journal<sup>12,13,49–52</sup> and devoted to reactions of nitriles in organic and coordination chemistry.

## II. Metal-mediated and metal-catalysed hydrolysis of nitriles

Hydrolysis of nitriles proceeds in two steps to form carboxamide, which is then transformed into acid. In most cases, the rate of the second step of hydrolysis is higher than that of the first step.<sup>53</sup>

N A Bokach, V Yu Kukushkin Department of Chemistry, St Petersburg State University, Universitetsky prosp. 26, Petrodvorets, 198504 St Petersburg, Russian Federation. Fax (7-812) 428 69 39, tel. (7-812) 428 45 82, e-mail: nadia-bokach@yandex.ru (N A Bokach), kukushkin@VK2100.spb.edu (V Yu Kukushkin)

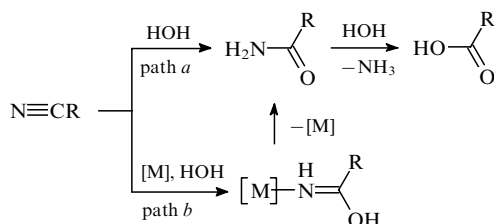
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<sup>†</sup> Hydrolysis and alcoholysis of nitriles with stoichiometric (metal-mediated) or catalytic (metal-catalysed) amounts of metal complexes.

Hence, the reaction affords carboxylic acid as the major transformation product (Scheme 1, path *a*).<sup>53, 54</sup>

Scheme 1



A specific feature of metal-mediated hydrolysis is that, as a rule, the reaction stops at coordinated amide  $[M]-NH=C(OH)R$  (Scheme 1, path *b*). This reaction pathway is favoured by mild reaction conditions, under which the resulting free or coordinated amide is not subjected to the transformation into  $RCO_2H$ .

Metal-mediated and metal-catalysed transformations of nitriles into amides were examined in numerous experimental studies, which have been surveyed in sufficient detail in several reviews.<sup>11–24, 32</sup> Hence, here we consider only the main factors responsible for hydrolysis and give selected examples of unusual hydrolytic transformations of coordinated nitriles, which have been reported in the last few years.

**The intra/intermolecular character of the reaction.** The rate of hydrolysis of metal-coordinated nitriles by an intramolecular mechanism (unlike hydrolysis proceeding by an intermolecular mechanism) was found<sup>55–70</sup> to be substantially higher than that of uncoordinated nitriles. In this case, the reaction can be accelerated by a factor of  $10^{18}$  (the rate of reactions proceeding by the intermolecular mechanism increases by a factor of  $10^6–10^9$ ).<sup>55–70</sup> Apparently, the efficiency of the reaction proceeding by the intramolecular mechanism is achieved mainly due to an increase in the 'local' concentration of an  $H_2O/OH^-$  nucleophile in the vicinity of coordinated nitrile.

**The nature of the metal.** The position of the metal in the Periodic table influences substantially the reaction rate and is also responsible for the either catalytic or stoichiometric character of the process. Analysis of the reactivities of related complexes with metals varying within a single subgroup allows one to compare adequately the results of investigations and reveal the corresponding correlations. For example, the rate of hydrolysis of coordinated benzonitrile in the  $[M(NH_3)_5(NCPh)]^{3+}$  complexes ( $M = Co, Rh, Ir$ ) increases with decreasing ionic radius in the series  $Co(III) > Rh(III) > Ir(III)$ .<sup>65</sup> The same tendency is observed for hydrolysis of nitriles in  $Pt(II)$  and  $Pd(II)$  complexes [ $Pd(II) > Pt(II)$ ].<sup>71</sup> If the metal has several oxidation states a higher rate of hydrolysis is observed in complexes, in which the central atom exists in a higher oxidation state. For example, hydrolysis of acetonitrile coordinated to the  $Ru^{III}(NH_3)_5$  group proceeds  $10^8$  times more rapidly than hydrolysis of uncoordinated nitrile, whereas coordination to  $Ru^{II}(NH_3)_5$  has virtually no effect on the reaction rate.<sup>66</sup>

In most cases, metal-mediated hydrolysis of nitriles affords stoichiometric amounts of amide complexes, whereas examples of catalytic reactions are scarce.<sup>18, 19, 32, 54, 72–106</sup> Systems based on platinum(II) phosphinite complexes (see Section VI)<sup>32, 54, 72, 73</sup> and zinc(II) salt–oxime systems (see Section III)<sup>74</sup> proved to be most efficient in metal-catalysed hydrolysis. In both cases,<sup>32, 54, 72–74</sup> hydrolysis involves nitrile activation in one of the initial steps followed by the intramolecular reaction with  $HOP-$ ,<sup>32, 54, 72, 73</sup> or  $HON$ -nucleophiles.<sup>74</sup> Among other catalytic systems used in hydrolysis of nitriles, let us mention  $Ni(II)$  and  $Cu(II)$  complexes with ethylenediamine,<sup>75, 76</sup>  $Co(III)$  sulfenato complexes,<sup>77, 78</sup>  $Hg(II)$  salts in acidic solutions,<sup>79, 80</sup> low-valent ruthenium<sup>27, 81–84</sup> and iridium<sup>26, 27</sup> hydride complexes, systems based on  $[Rh(\mu-Cl)(cod)]_3$  and  $P(C_6H_4SO_3Na-m)_3$ ,<sup>85</sup>  $Ir(I)$  phosphine complexes,<sup>86</sup> mixtures of  $Rh(III)$  or  $Ir(III)$  halides with  $(PhO)_3P$  or

$Ph_3P$  and their derivatives,<sup>87–89</sup> mixtures of  $RuCl_3$  with phenanthroline or  $Na_2[PdCl_4]$  with 2,2'-bipyridyl,<sup>90</sup>  $Pd(II)$  aqua and hydroxo complexes,<sup>91–97</sup>  $Pd(II)$  thiolate complexes,<sup>98, 99</sup>  $Pt(0)$  and  $Pt(II)$  phosphine complexes<sup>100–104</sup> and clusters with a  $Pt_4$  core.<sup>105, 106</sup>

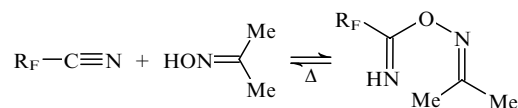
It should be noted that hydrolysis of nitriles in the coordination sphere of the metal affords not only amides but also other products of hydrolytic transformations, for example, the metallacycles  $[RuCl(CO)\{NH=C(p-MeC_6H_4)N=C(p-MeC_6H_4)O\} \cdot (PPh_3)_2]$ ,<sup>107</sup>  $[PtCl\{O=C(CCl_3)NC(CCl_3)=O\}(Me_2SO)]$ <sup>108</sup> and  $[PtCl_4\{NH=C(NR_2)OC(NR_2)=NH\}]$  ( $R = Me, Et$ ;  $R_2 = C_5H_{10}, C_4H_8O$ )<sup>109</sup> (hereinafter, atoms bound to metals are underlined). These complexes are generated in multistep processes involving hydrolysis of one of the nitrile molecules in the coordination sphere of the metal followed by the reaction of the hydrolysis product with another nitrile. The formation of amidines and coordinated imidoyl amidines is considered in Section III. It is believed that these transformations also involve hydrolysis of nitrile in the coordination sphere of the complex as one of the initial steps.

Therefore, the use of metal complexes in reactions of nitriles with water leads to a substantial increase in the rate of the first step of hydrolysis (due to electrophilic activation of the nitrile through its coordination) and provides the possibility of stopping hydrolysis selectively at the formation of amide (due to its stabilisation as a result of coordination and milder reaction conditions).

### III. Reactions of oximes with free and coordinated nitriles

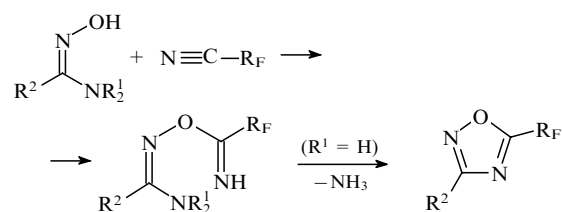
#### 1. Nucleophilic addition of oximes to free nitriles and nitrilium salts

In organic chemistry, only a few examples of the nucleophilic addition of oximes to nitriles are known. These reactions proceed exclusively with activated nitriles, for example, with those containing a perfluoroalkyl group.<sup>110, 111</sup> The reactions of perfluorocarbonitriles with acetone oxime were investigated.<sup>110</sup>



$R_F = CF_3, C_3F_7$ .

These reactions are reversible: *O*-imidoyl oxime that formed in good yield is unstable and decomposes on heating to give the starting compounds.<sup>110</sup> Kabakchi *et al.*<sup>111</sup> prepared 1,2,4-oxadiazoles by the reaction of perfluorocarbonitriles [ $R_F = C_6F_{13}, CF_3O(CF_2CF_2O)_4CF_2, (O(CF_2)_3CF)CF_2$ ] with aromatic amidoximes  $HON=C(NR_2)R^2$  (benzamidoxime, substituted and unsubstituted terephthalamidoximes).



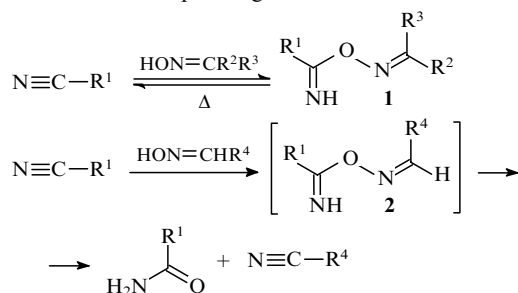
$R^1 = H$ ;  $R^2 = Ph, p-HON(NH_2)CC_6H_4$ ;

$NR_2 = N(CH_2)_4, N(CH_2)_5, R^2 = p-HON(NH_2)CC_6H_4$ .

The first step of the synthesis of 1,2,4-oxadiazoles also involves the formation of *O*-imidoyl oximes. In the study,<sup>111</sup> the authors noted that, although the addition of unsubstituted amidoximes to nitriles could, in principle, occur in two different ways, *viz.*, the addition of either the amide or oxime group could take place, exclusively the latter situation was experimentally observed. It should be noted that *O*-imidoyl oximes were prepared

under mild conditions in good yields. In the reactions with perfluorocarboxylic acid fluorides, *O*-imidoyl oximes are transformed into 1,2,4-oxadiazoles with elimination of ammonia.

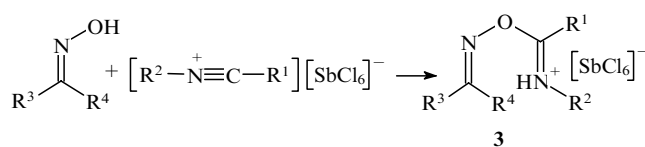
Activation of nitriles with electron-withdrawing groups, such as  $\text{CCl}_3$  and  $\text{CCl}_2\text{CN}$ , is also sufficient for them to react with oximes. For example,  $\text{Cl}_3\text{CC}\equiv\text{N}$  and  $(\text{N}\equiv\text{C})\text{Cl}_2\text{CC}\equiv\text{N}$  readily react with oximes to give unstable *O*-imidoyl oximes.<sup>112, 113</sup> Imines **1** produced by the reactions with ketoximes  $\text{R}^2\text{R}^3\text{C}=\text{NOH}$  can be isolated, whereas unstable *O*-imidoyl oximes **2** formed in the reactions with aldoximes  $\text{R}^4\text{CH}=\text{NOH}$  are rearranged to give halogenated carboxamide and nitrile  $\text{R}^4\text{CN}$  as a dehydration product of the corresponding aldoxime.<sup>113</sup>



$\text{R}^1 = \text{CCl}_3, \text{CCl}_2\text{CN}$ ;  $\text{R}^2 = \text{Me}$ ;  $\text{R}^3 = \text{Me, Ph, 4-HOC}_6\text{H}_4$ ;  
 $\text{R}^2 = \text{R}^3 = \text{Ph}$ ;  $\text{R}^4 = 2\text{-C}_4\text{H}_7\text{O, Pr}^n, \text{Pr}^i, \text{Ph, 4-MeC}_6\text{H}_4$ ,  
 $3,4\text{-(MeO)}_2\text{C}_6\text{H}_3$ , 1-naphthyl,  $\text{PhCH}=\text{CH}$ .

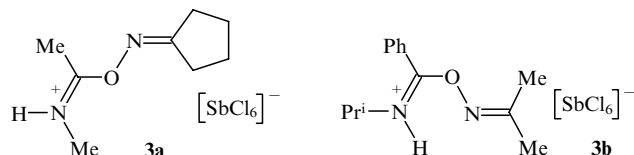
In the study,<sup>112</sup> dehydration of aldoximes with trichloroacetonitrile was proposed for use for the preparation of aromatic nitriles, which are difficult to synthesise (dehydration of aldoximes with coordinated nitriles is considered in Section III.3).

Nitriles can be activated also by alkylation of the nitrogen atom of the nitrile group to form nitrilium salts.<sup>114, 115</sup> For example,  $[\text{R}^1\text{C}\equiv\text{N}^+\text{R}^2][\text{SbCl}_6]^-$  salts can be involved in the addition reactions to oximes  $\text{R}^3\text{R}^4\text{C}=\text{NOH}$ . The initiating role of nitrilium salts in the Beckmann rearrangement in anhydrous aprotic solvents was examined in the studies.<sup>114, 115</sup> The reactions of the  $[\text{R}^1\text{C}\equiv\text{N}^+\text{R}^2][\text{SbCl}_6]^-$  salts with oximes were demonstrated to afford imidoyl compounds as unstable intermediates.

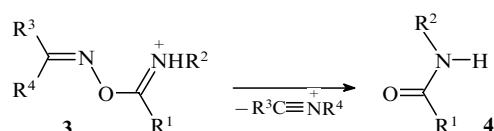


$\text{R}^1 = \text{Me, Pr}^i, \text{Ph}$ ;  $\text{R}^2 = \text{Pr}^i$ ;  $\text{R}^1-\text{R}^2 = \text{Me}_2, (\text{CH}_2)_5$ ;  
 $\text{R}^3-\text{R}^4 = \text{Me}_2, (\text{CH}_2)_n$  ( $n = 4-7, 12$ ),  $\text{Ph}_2$ .

Addition products **3** exist in solution as mixtures of *E* and *Z* isomers. Compounds with  $\text{R}^1 = \text{R}^2 = \text{Me}$ ,  $\text{R}^3-\text{R}^4 = (\text{CH}_2)_4$  (**3a**) and  $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{Pr}^i$ ,  $\text{R}^3 = \text{R}^4 = \text{Me}$  (**3b**) were characterised by X-ray diffraction. It was established that compounds **3a** and **3b** have *Z* and *E* configurations, respectively.



Iminium salts **3** can be subjected to the Beckmann rearrangement to form the corresponding carboxamides **4**.<sup>114, 115</sup>



Hence, for the nucleophilic addition of oximes to nitriles to occur, it is necessary either to use nitriles  $\text{RCN}$  containing strong electron-withdrawing *R* groups or to activate nitriles by alkylation of the nitrogen atom of the nitrile group. A considerable drawback of the first method is that the field of its application is limited to a relatively small set of perfluorocarbonitriles and some other nitriles containing the chlorine atoms and/or a pseudohalide group in the activating fragment. This method can be used to prepare only derivatives containing electron-withdrawing groups at the carbon atom. The second method can be employed to synthesise nitrile derivatives containing electron-donating groups at the carbon atom (in this case, acylation of oximes affords salts). It was noted<sup>110-115</sup> that imidoyl compounds formed upon addition of nitrilium salts to oximes are unstable. In some cases, they were characterised only in a reaction mixture and were not isolated as individual products.

## 2. Reactions of 'simple' oximes with coordinated nitriles

The nucleophilic addition of 'simple' ‡ oximes to coordinated nitriles was investigated in much more detail. The reaction of oxime with nitrile in the presence of a metal centre giving rise to a stable imino complex was described for the first time in 1990.<sup>116</sup> In this study, the authors performed the reaction of the palladium complex  $[\text{PdCl}_2(\text{PhCN})_2]$  with  $\text{HON}=\text{CMeBu}^t$  to prepare the  $[\text{PdCl}_2\{\text{NH}=\text{C}(\text{Ph})\text{ON}=\text{CMeBu}^t\}]$  complex as one of products and characterised the latter. More than ten studies devoted to the addition of oximes to nitriles in the presence of V(IV), Re(IV), Rh(III), Ni(II), Pt(II) and Pt(IV) complexes were published by the mid-1990s.<sup>117-132</sup> In all these studies (see below), the reactions of oximes with nitriles proceed under mild conditions to give coordinated imines  $\text{HN}=\text{C}(\text{R}^1)\text{ON}=\text{CR}^2\text{R}^3$ . It was reported that even nitriles containing electron-donating substituents, such as  $\text{MeCN}$  and  $\text{EtCN}$ , which do not react with oximes in the free state, are involved in nucleophilic addition to oximes in the presence of metal complexes (see Section III.1).<sup>117-126</sup> Evidently, the metal centre plays a decisive role in these reactions. The metal centre not only activates nitrile but also stabilises the resulting imino ligand.

In spite of the diversity of the starting compounds and reaction conditions, there are several factors influencing the nucleophilic addition of oximes to nitriles in the presence of metal.

### a. Effect of the central metal atom on the reactivity of nitrile

*The nature of the central atom.* In accordance with the logic of the discussion, let us first consider the role of the central metal atom in activation of nitrile followed by consideration of the role of the metal centre in stabilisation of coordinated imines  $\text{HN}=\text{C}(\text{R}^1)\text{ON}=\text{CR}^2\text{R}^3$ .

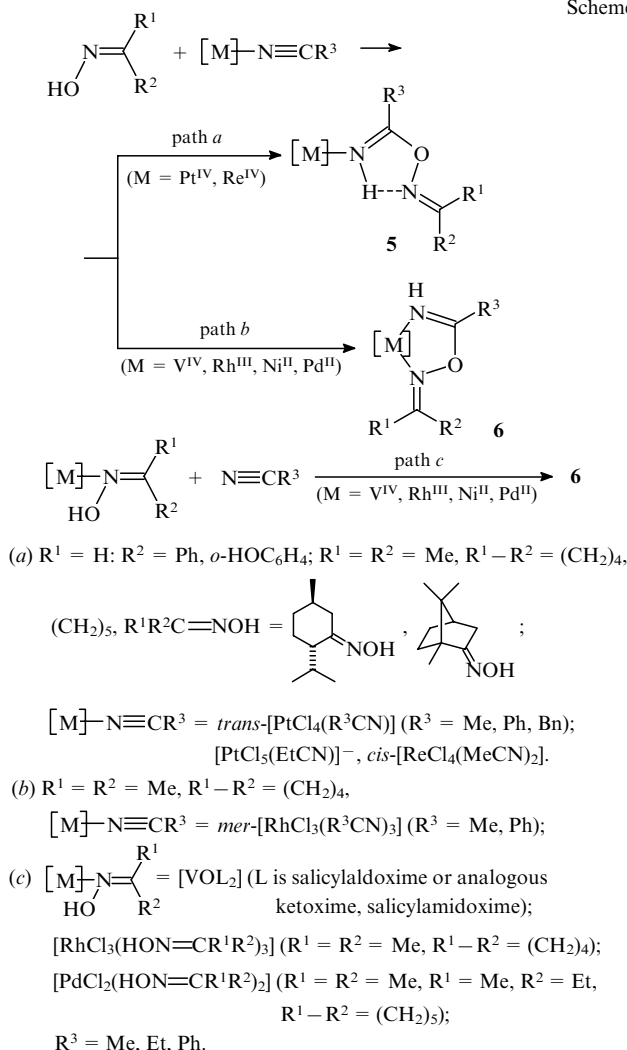
The way of performing the reaction and the character of the reaction products depend on the nature of the central atom. For example, the reactions of oximes  $\text{R}^1\text{R}^2\text{C}=\text{NOH}$  with nitrile complexes of platinum(IV)<sup>117-119</sup> and rhenium(IV),<sup>120</sup> viz., *trans*- $[\text{PtCl}_4(\text{R}^3\text{CN})_2]$ ,  $[\text{PtCl}_5(\text{EtCN})]^-$  and *cis*- $[\text{ReCl}_4(\text{MeCN})_2]$ , respectively, proceed under mild conditions to give complexes **5** with monodentate imino ligands in nearly quantitative yields (Scheme 2, path *a*). These complexes exist in the *E* form stabilised by hydrogen bonding between the hydrogen atom of imine and the nitrogen atom of oxime.

It was demonstrated<sup>117-120</sup> that free nitrile is not involved in these reactions even under more drastic conditions (on refluxing and/or in the presence of a large excess of  $\text{R}^3\text{CN}$ ).

Another way of performing metal-mediated reactions of nitriles with oximes is based on the use of relatively labile V(IV), Rh(III), Ni(II) and Pd(II) complexes (Scheme 2, paths *b* and *c*). Imines  $\text{NH}=\text{C}(\text{R}^3)\text{ON}=\text{CR}^1\text{R}^2$  formed in the course of the reaction are coordinated to the metal atom in a bidentate fashion

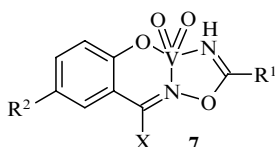
‡ By 'simple' oximes is meant compounds containing only one functional (oxime) group.

Scheme 2



through two nitrogen atoms. In the presence of 'labile' metal complexes,<sup>8</sup> the addition of oximes to nitriles can occur by two mechanisms, *viz.*, either as the addition of the nitrile complex to free oxime (path *b*) or as the addition of the oxime complex to free nitrile (path *c*)<sup>¶</sup> giving rise to the same product **6**. It is believed that the first step of the reaction of an oxime complex with nitrile involves coordination of nitrile at the *cis* position with respect to complexed oxime followed by the reaction of the adjacent oxime and nitrile ligands, the latter being activated as a result of its coordination.

Dissolution of the oxovanadium oximate complexes [VOL<sub>2</sub>] (L is salicylaldehyde or analogous ketoxime and salicylamidoxime) by heating in nitriles<sup>121, 122</sup> affords complexes **7** with the tridentate imino ligand.



$\text{X} = \text{H, Me, Et}; \text{R}^1 = \text{Me, Ph, C}_6\text{H}_4\text{NO}_2\text{-}p, \text{C}_6\text{H}_4\text{Me-}p, \text{MeC}(\text{O})\text{CH}_2;$   
 $\text{R}^2 = \text{H, Cl, Bu}^t;$   
 $\text{X} = \text{NH}_2, \text{R}^1 = \text{Me}, \text{R}^2 = \text{H}.$

§ The metal centre is labile with respect to substitution reactions.

¶ It should be noted that the reaction does not occur in the presence of Pt(IV) or Re(IV) complexes.<sup>117, 118</sup>

In both studies,<sup>121, 122</sup> the authors noted that the imino ligand cannot be prepared by the direct reaction of oximes with nitrile and, consequently, the reaction is promoted by metal. It was suggested<sup>121</sup> that the reaction mechanism involves coordination of nitrile to V(IV) as the initial step followed by nucleophilic addition of oxime to the nitrile to form a tridentate ligand. In addition, the reaction is accompanied by oxidation of the central atom to V(V). It was hypothesised that one of the inner-sphere oximes in the starting complex serves as the oxidiser.<sup>121</sup> The structure of complex **7** (X = NH<sub>2</sub>, R<sup>1</sup> = Me, R<sup>2</sup> = H) is shown in Fig. 1.

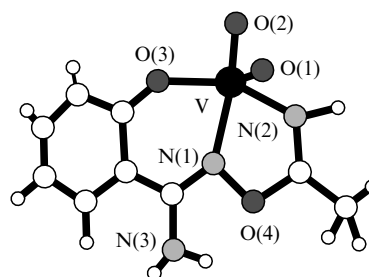
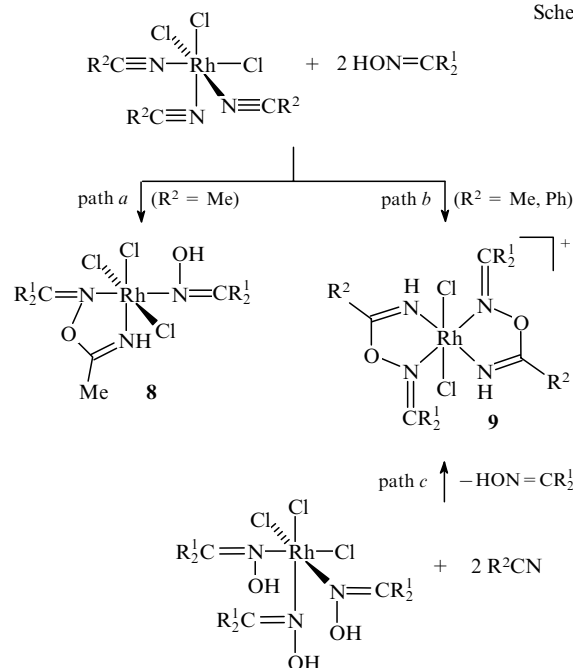


Figure 1. Molecular structure of complex **7** (X = NH<sub>2</sub>, R<sup>1</sup> = Me, R<sup>2</sup> = H).

In the studies of the reactions of R<sub>2</sub>C=NOH with the rhodium(III) nitrile complexes *mer*-[RhCl<sub>3</sub>(R<sup>2</sup>CN)<sub>3</sub>] (R<sup>2</sup> = Me, Ph) (Scheme 3, paths *a* and *b*), several imino complexes were isolated and characterised: [RhCl<sub>3</sub>{NH=C(R<sup>2</sup>)ON=CR<sup>1</sup>}]<sub>3</sub>·[HON=CR<sup>1</sup>]<sub>2</sub> (**8**, R<sup>2</sup> = Me) and [RhCl<sub>2</sub>{NH=C(R<sup>2</sup>)ON=CR<sup>1</sup>}]<sub>2</sub>·[ON=CR<sup>1</sup>]<sub>2</sub>Cl (**9**, R<sup>2</sup> = Me, Ph).<sup>123, 124</sup>

Scheme 3



R<sup>1</sup> = Me<sub>2</sub>, (CH<sub>2</sub>)<sub>4</sub>; R<sup>2</sup> = Me, Ph.

In the resulting compounds **8** and **9**, the imino ligand is coordinated to Rh(III) through two nitrogen atoms. The rhodium complexes [RhCl<sub>2</sub>{NH=C(R<sup>2</sup>)ON=CR<sup>1</sup>}]<sub>2</sub>Cl (**9**, R<sup>1</sup> = Me<sub>2</sub>, (CH<sub>2</sub>)<sub>4</sub>; R<sup>2</sup> = Me) were also prepared by independent synthesis by the reaction of the rhodium oxime complexes [RhCl<sub>3</sub>{HON=CR<sup>1</sup>}]<sub>3</sub> with acetonitrile (Scheme 3, path *c*).<sup>123</sup> It was suggested that the reaction proceeds in two steps and involves the initial coordination of MeCN and its activation followed by

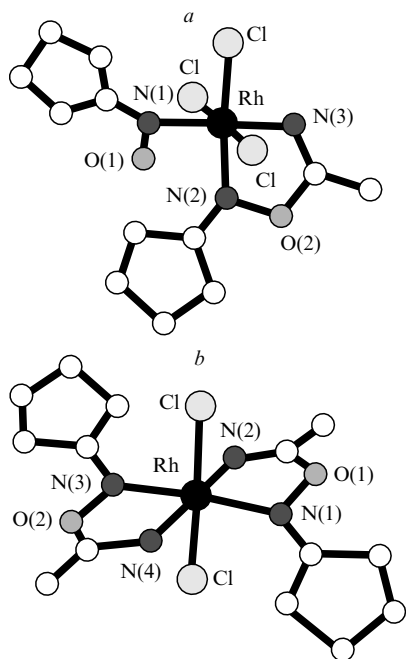
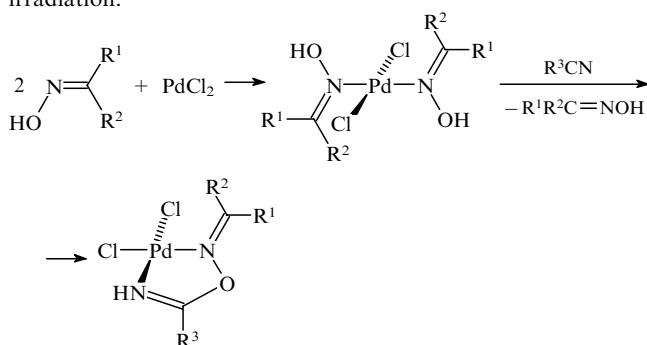


**Figure 2.** Molecular structures of complexes **8** (a) and **9** (b) [ $R_2^1 = (CH_2)_4$  and  $R^2 = Me$ ].

nucleophilic addition of oxime to nitrile. The molecular structures of complexes **8** and **9** are shown in Fig. 2.

Nickel(II) complexes promote the addition of sulfur-containing dioxime  $HON=C(Me)CH_2S(CH_2)_2SCH_2C(Me)=NOH$  to nitriles (see Section III.3).<sup>125, 126</sup> In the absence of metal the oxime does not react with nitriles.

It was found<sup>127</sup> that  $PdCl_2$  (which is consistent with the results of the study<sup>116</sup>) promotes nucleophilic addition of oximes  $R^1R^2C=NOH$  to nitriles  $R^3CN$  on heating in a solution of the corresponding nitrile to form the  $[PdCl_2\{NH=C(R^3)ONCR^1R^2\}]$  complex. The reaction proceeds through the formation of the oxime complex  $[PdCl_2\{HON=CR^1R^2\}_2]$ , whose heating in a solution of nitrile affords an imino complex. Garnovskii *et al.*<sup>127</sup> demonstrated that the reaction is accelerated under microwave irradiation.



$R^1 = R^2 = Me$ ;  $R^3 = Me, Et, Ph$ ;  $R^3 = Me$ ;  $R^1 = Me, R^2 = Me, Et$ ;  $R^1 - R^2 = (CH_2)_5$ .

The above data show that the nature of the imidoylation product of oxime (which can be coordinated to  $[M]$  in either monodentate or bidentate fashion), as well as the possibility of the independent synthesis of an imino compound by the reaction of an oxime complex with nitrile proceeding in the presence of labile metal complexes, depends on the nature of the central metal atom.

The oxidation state of the central atom has a substantial effect on nitrile activation, which is clearly demonstrated by comparing the reactivities of the related platinum(II and IV) nitrile complexes

$[PtCl_n(RCN)_2]$  ( $n = 2, 4$ ). Nitriles in the platinum(IV) complexes easily react with oximes at room temperature to give addition products. By contrast, for the platinum(II) complexes, the addition products were neither isolated nor detected in the reaction mixtures even in attempting to perform the reaction under much more drastic conditions (prolonged heating) or under microwave irradiation.<sup>117, 118</sup> The reaction of oximes with the dialkylcyanamide complex  $[Pt(PPh_3)_2(NCNR_2)_2](BF_4)_2$  is the only example of the addition of oximes to nitriles involved in a Pt(II) complex.<sup>128</sup> However, this reaction also proceeds due to additional activation of the ligand with yet another Lewis acid.

**The charge of a complex.** The effect of the charge of the complex on the addition of oximes to nitriles was examined in the study of the reactions of the neutral and anionic Pt(IV) complexes, *viz.*,  $[PtCl_4(MeCN)_2]$  and  $[Ph_3PCH_2Ph][PtCl_5(EtCN)]$ , respectively, with oximes  $R^1R^2C=NOH$  ( $R^1 = H$ ;  $R^2 = Ph$ ,  $o-HOC_6H_4$ ;  $R^1 = R^2 = Me$ ;  $R^1 - R^2 = (CH_2)_4, (CH_2)_5$ ). No substantial difference in the reaction rate for these compounds was revealed. Apparently, this provides evidence that activation of nitrile through coordination to Pt(IV) was sufficiently strong for the reaction to proceed in both cases.<sup>117–119</sup> For compounds of other metals, an analogous comparison was not performed, although it has been *a priori* assumed that the charge of a complex can also affect the rate of nucleophilic addition of oximes to coordinated nitriles.

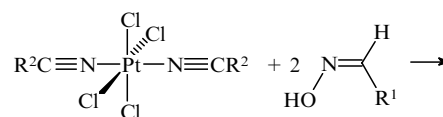
#### b. Electron-withdrawing properties of R in RCN

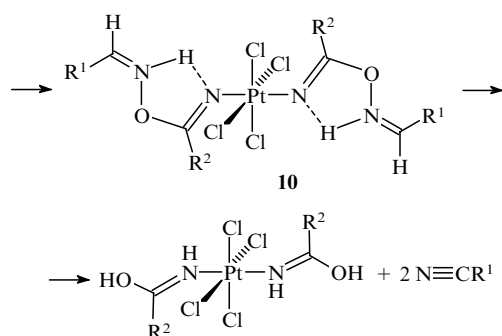
As mentioned above (see Section III.1), the rate of the reaction of oximes with free nitriles depends substantially on the nature of the R group in RCN. This phenomenon is also observed for coordinated nitriles. Nitriles containing electron-withdrawing groups R are more active in addition reactions with oximes. It was demonstrated<sup>122</sup> that compound **7** is more easily formed by the reaction with the use of PhCN than with the use of MeCN (the yield of the product was estimated after 48 h at 20–25 °C). By contrast, the reactivity of nitriles in the platinum(IV) complexes  $[PtCl_4(RCN)_2]$  depends only slightly on the character of the R group (electron-donating Me, Et, Bn or electron-withdrawing Ph).<sup>117, 118</sup> Apparently, this is associated with the fact that stronger activation by the central atom masks the less significant effect of the R group in RCN.

#### c. Nature of oxime

Variations in the nature of the R and X groups in the  $RXC=NOH$  molecule can change the rate of nucleophilic addition and determine both stability of the reaction product and the probability of occurrence of side reactions. For example, the reactions of imidoyl chlorides  $ArC(Cl)=NOH$  with nitriles in the  $[PtCl_4(MeCN)_2]$  complex are substantially more difficult to perform than the reactions of alkyl(aryl)- or dialkyl oximes,<sup>129</sup> whereas the reactivity of methyl *N*-hydroxyimidoate  $Me_3C_6H_2.C(OMe)=NOH$  in the addition reactions to coordinated nitrile is higher than the reactivities of ketoximes containing alkyl, aryl and electron-withdrawing groups.<sup>130</sup>

Aldoximes  $R^1(H)C=NOH$ , like ketoximes, readily react with coordinated nitriles in the platinum(IV) complexes  $[PtCl_4(R^2CN)_2]$ , but the resulting imino complexes **10** are unstable and undergo further transformations to give the carboximide complex  $[PtCl_4\{NH=C(OH)R^2\}_2]$  and nitrile  $R^1CN$ . The latter is formed as a result of dehydration of aldoxime.





$R^1 = \text{Me, Ph, PhC(O)}; R^2 = \text{Alk, Ar.}$

The molecular structure of the product obtained upon the addition of aldoxime  $\text{PhC(O)CH=NOH}$  to nitrile  $\text{EtC}\equiv\text{N}$  in the  $[\text{PtCl}_4(\text{NCEt})_2]$  complex is shown in Fig. 3.

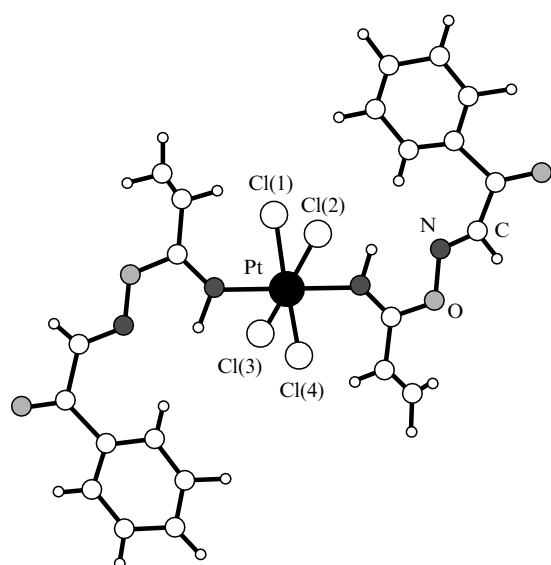
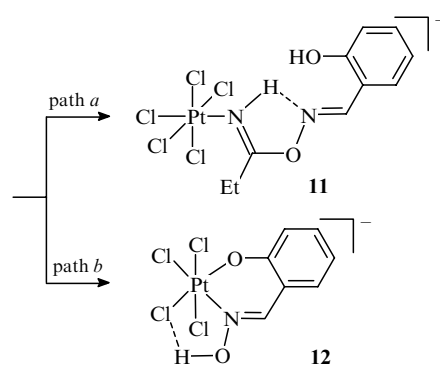
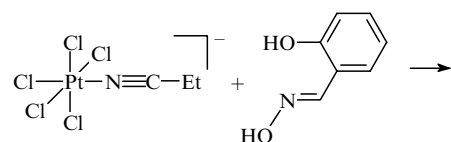


**Figure 3.** Molecular structure of complex **10** [ $R^1 = \text{PhC(O)}$ ,  $R^2 = \text{Et}$ ].

This transformation is the first example of dehydration of aldoximes with coordinated nitriles.<sup>131</sup> Derivatives of aliphatic aldoximes were found to be more reactive than derivatives of aromatic aldoximes, particularly if the aryl group contains bulky substituents.<sup>131</sup>

#### d. Concentration of reagents

In the study of the reaction of salicylaldoxime  $o\text{-HO}\cdot\text{C}_6\text{H}_4\text{C=NOH}$  with the anionic platinum(IV) complex  $[\text{Ph}_3\text{PCH}_2\text{Ph}][\text{PtCl}_5(\text{EtCN})]$ ,<sup>132</sup> the addition of oximes to coordinated nitriles was demonstrated to depend on the concentrations of the reagents. The addition of oxime to coordinated nitrile was found to compete with the replacement of nitrile with salicylaldoxime. In dilute solutions, one of these reactions becomes the major process. If the concentration of the  $[\text{Ph}_3\text{PCH}_2\text{Ph}][\text{PtCl}_5(\text{EtCN})]$  complex in  $\text{CH}_2\text{Cl}_2$  is  $0.36 \text{ mmol ml}^{-1}$ , the reaction follows the path *a* to form imino complex **11**.

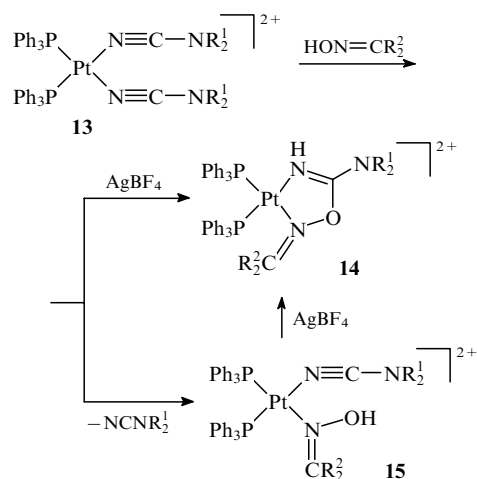


The reaction in a 50-fold diluted solution in wet  $\text{CH}_2\text{Cl}_2$  affords substitution product **12** (path *b*) and the  $[\text{Ph}_3\text{PCH}_2\text{Ph}]_2[\text{PtCl}_6]$  complex. The addition of a small amount of  $\text{EtCN}$  to a dilute reaction mixture suppresses the formation of product **12** and facilitates the formation of compound **11**. The 'switching' of the reaction from the addition (path *a*) to substitution (path *b*) by dilution of the reaction mixture was explained by an increase in dissociation of the  $\text{EtCN}$  ligand in a dilute solution and, correspondingly, by promotion of the replacement of nitrile.<sup>132</sup>

#### e. Activation of two donor centres in dialkylcyanamide

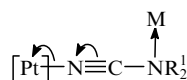
To understand the mechanism of the nucleophilic addition of oximes to nitriles, let us consider the reaction of oxime with dialkylcyanamide  $\text{NCNR}_2^1$  involved in platinum(II) complex **13** (Scheme 4).

Scheme 4



$R^1 = \text{Me, Et}; R^2 = \text{Me, } R_2^2 = (\text{CH}_2)_4.$

The dialkylcyanamide complexes  $[\text{Pt}(\text{NCNR}_2)_2](\text{PPh}_3)_2 \cdot (\text{BF}_4)_2$  (**13**) were found to react with oximes in the presence of a catalytic (10%) or stoichiometric amount of  $\text{AgBF}_4$  to form chelate **14**.<sup>128</sup> The reaction of the dialkylcyanamide complex with oxime in the absence of  $\text{Ag}^+$  affords complex **15**, in which the nitrile and oxime ligands do not interact with each other. Therefore, the presence of a silver salt is necessary for the reaction of coordinated dialkylcyanamide with oxime to proceed. A catalytic amount of  $\text{Cu}(\text{OAc})_2$  can be used instead of  $\text{AgBF}_4$ . It is believed that in this case metal additionally activates the nitrile group due to coordination of Lewis acid ( $\text{Ag}^+$  or  $\text{Cu}^{2+}$ ) to amide nitrogen resulting in an increase in electrophilicity of the carbon atom of the nitrile group.



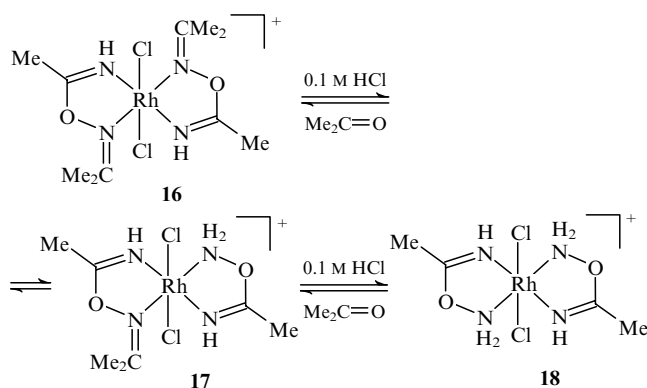
$M = \text{Ag}^+, \text{Cu}^{2+}.$

All attempts to perform the addition of oximes to nitriles in analogous platinum complexes with alkanonitrile

ligands instead of dialkylcyanamide  $\{[\text{Pt}(\text{RCN})_2(\text{PPh}_3)_2](\text{BF}_4)_2$ ;  $\text{R} = \text{Et}$ ,  $\text{C}_6\text{H}_4\text{OMe-}p$ \} and in complexes of another type  $\{[\text{PtCl}_2(\text{RCN})_2]$ ;  $\text{R} = \text{Me}$ ,  $\text{Ph}$ \} with nitrile ligands in the presence or absence of an  $\text{Ag}^+$  catalyst failed.<sup>117, 128</sup> This fact suggests that nitrile is insufficiently activated by platinum(II) for the nucleophilic addition of oxime to occur (addition at the  $\text{C}\equiv\text{N}$  bond becomes possible only for dialkylcyanamide complexes in the presence of Lewis acids, which additionally activate the nitrile group).

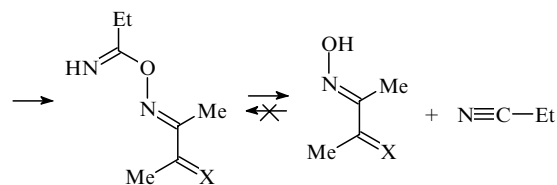
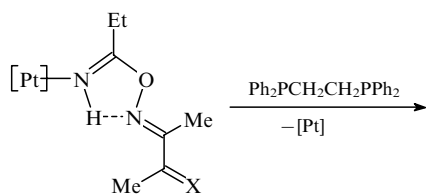
#### f. Role of the central atom in stabilisation of imino ligands

In most studies of nucleophilic addition of oximes to nitriles, it was noted that coordinated imines produced in these reactions are resistant to hydrolysis.<sup>117–120, 123, 124, 128</sup> For example, platinum(II) and rhodium(III) imino complexes,<sup>117–119, 123, 124</sup> which were prepared by the reactions in wet solvents, can be stored for a long period of time without changes. Storage of the rhodium imino complex  $[\text{RhCl}_2\{\text{NH}=\text{C}(\text{Me})\text{ON}=\text{CMe}_2\}_2]\text{Cl}$  (**16**) in 0.1 M HCl at 80 °C for several days was demonstrated to lead to hydrolysis of the  $\text{C}=\text{N}$  bond of oxime giving rise to products **17** and **18**, while the imine  $\text{C}=\text{N}$  bond remains intact.



It is also known that the  $\text{C}=\text{N}$  bond in oximes is rather stable, whereas the  $\text{C}=\text{N}$  bond in imines is readily hydrolysed. In this case, coordination to metal stabilises the imino group and destabilises the oxime group resulting in selective hydrolysis of the latter. This procedure was used to prepare the *O*-imidoylated hydroxylamine complex, whereas the reaction of free hydroxylamine with coordinated nitrile afforded a mixture of unidentified products.<sup>124</sup>

Stabilisation of a ligand through coordination is also evident from the fact that known free imidoxyated oximes are rather unstable (see Section III.1). Liberation of imines, which are generated through metal-mediated addition of oxime to nitrile, from metal complexes gave the decomposition products  $\text{HN}=\text{C}(\text{R}^3)\text{ON}=\text{CR}^1\text{R}^2$ .<sup>117, 118</sup> The imino ligand was liberated in the free state from the  $[\text{PtCl}_2\{\text{NH}=\text{C}(\text{Et})\text{ON}=\text{C}(\text{Me})-\text{C}(\text{Me})=\text{X}\}_2]$  complex ( $\text{X} = \text{O}$ ,  $\text{NNH}_2$ ) in the presence of 1,2-bis(diphenylphosphino)ethane in a  $\text{CDCl}_3$  solution.<sup>133, 134</sup> Although such imines can exist as ligands of platinum complexes during a long period of time even in wet solvents, free imines decompose in solution within a few hours to form the starting oxime and nitrile.<sup>133, 134</sup>

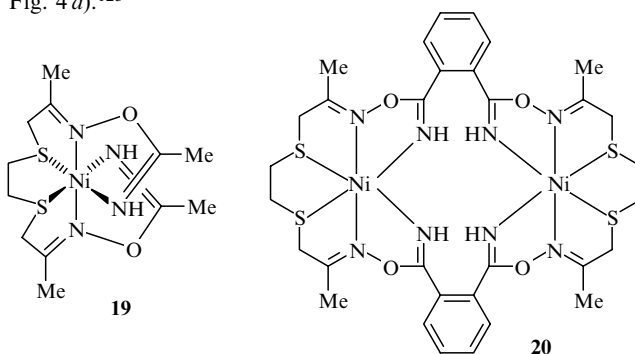


$\text{X} = \text{O}$ ,  $\text{NNH}_2$ .

Therefore, the central metal atom stabilises the resulting coordinated imine  $\text{HN}=\text{C}(\text{R}^3)\text{ON}=\text{CR}^1\text{R}^2$ , whereas the free imine is either unstable or does not exist at all. Coordination of nitriles favours  $\text{C}\equiv\text{N}$  triple bond activation in addition reactions of oximes, the reaction pathway and the character of the product being dependent on numerous factors, among which the nature of the metal and its oxidation state are of most importance. Coordination also provides stabilisation of the addition product of oxime.

#### 3. Reactions of functionalised oximes

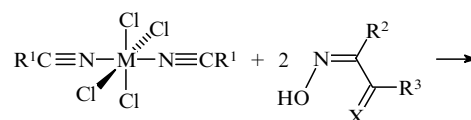
Functionalised oximes (with sulfide groups,<sup>125, 126</sup> *vic*-dioximes,<sup>118, 120</sup> ketoximes,<sup>133</sup> hydrazone oximes<sup>134</sup>), like 'simple' oximes, are involved in nucleophilic addition to metal-activated nitriles. For example, treatment of sulfur-containing dioxime  $\text{HON}=\text{C}(\text{Me})\text{CH}_2\text{S}(\text{CH}_2)_2\text{SCH}_2\text{C}(\text{Me})=\text{NOH}$  ( $\text{DtoxH}_2$ ) with nickel perchlorate in acetonitrile afforded two compounds, *viz.*, the trinuclear complex  $[\text{Ni}_3(\text{Dtox})(\text{DtoxH})_2](\text{ClO}_4)_2 \cdot \text{MeCN}$  and the imino complex  $[\text{Ni}\{\text{NH}=\text{C}(\text{Me})\text{ON}=\text{C}(\text{Me})\cdot\text{CH}_2\text{S}(\text{CH}_2)_2\text{SCH}_2\text{C}(\text{Me})=\text{NO}-\text{C}(\text{Me})=\text{NH}\}](\text{ClO}_4)_2$  (**19**, Fig. 4a).<sup>125</sup>



In the absence of a metal centre, dioxime  $\text{DtoxH}_2$  does not react with  $\text{MeCN}$ . Hence, it was suggested<sup>125</sup> that, on the one hand, the reaction is determined by activation of nitrile through coordination to  $\text{Ni}(\text{II})$  and, on the other hand, the reaction of oxime with nitrile is facilitated by the close arrangement of the reacting molecules upon coordination (the reaction product is stabilised through chelation).

More recently, unusual dinuclear complex **20** with a macrocyclic ligand (Fig. 4b) was prepared by the reaction of the dioxime complex  $[\text{Ni}(\text{DtoxH}_2)(\text{H}_2\text{O})_2](\text{ClO}_4)_2$  with *o*-phthalonitrile  $\text{C}_6\text{H}_4(\text{CN})_2$ .<sup>126</sup> The presence of additional functional (sulfide) groups in the oxime molecule is favourable for stabilisation of the macrocyclic ligand, which forms a stable complex with nickel.

The extremely reactive nitrile ligands in the rhenium(IV) and platinum(IV) complexes  $[\text{MCl}_4(\text{R}^1\text{CN})_2]$  react with *vic*-dioximes  $\text{HON}=\text{C}(\text{R}^2)\text{C}(\text{R}^3)=\text{NOH}$ ,<sup>118, 120</sup> ketoximes  $\text{HON}=\text{C}(\text{R}^2)\cdot\text{C}(\text{O})\text{R}^3$  (see Ref. 133) and hydrazone oximes  $\text{HON}=\text{C}(\text{R}^2)\cdot\text{C}(\text{R}^3)=\text{NNH}_2$  (see Ref. 134) to give imino complexes **21**.





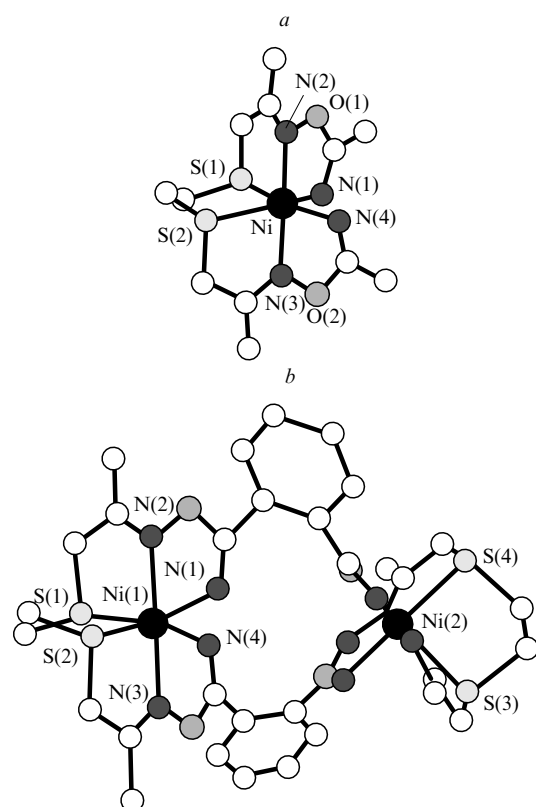
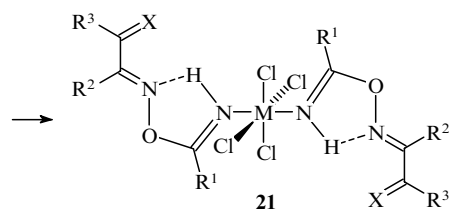


**Figure 4.** Structures of imino complex **19** (a) and dinuclear complex **20** with a macrocyclic ligand (b).



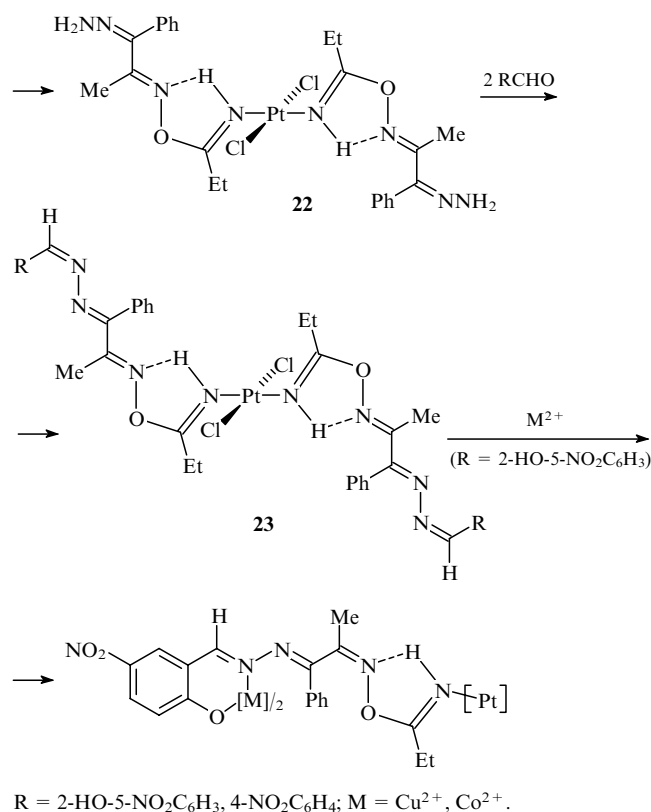
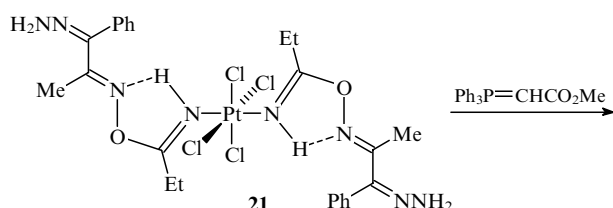
X = NOH; M = Re, Pt; R<sup>1</sup> = Me; R<sup>2</sup> = R<sup>3</sup> = Me,

R<sup>2</sup>–R<sup>3</sup> = (CH<sub>2</sub>)<sub>n</sub> (n = 4–6);

X = O; M = Pt; R<sup>1</sup> = Me, Et; R<sup>2</sup> = Me; R<sup>3</sup> = Me, Ph, C<sub>6</sub>H<sub>4</sub>F;

X = NNH<sub>2</sub>; M = Pt; R<sup>1</sup> = Me, Et; R<sup>2</sup> = Me; R<sup>3</sup> = Me, Ph.

Imino complexes **21** are of interest because the ligand formed upon nucleophilic addition of oxime to nitrile contains a remote free functional group, which can be involved in further reactions.<sup>134</sup> For example, reduction of imino complex **21** (M = Pt, X = NNH<sub>2</sub>, R<sup>1</sup> = Et, R<sup>2</sup> = Me, R<sup>3</sup> = Ph) with phosphorus ylide Ph<sub>3</sub>P=CHCO<sub>2</sub>Me afforded the corresponding platinum(II) complex **22** containing peripheral NH<sub>2</sub> groups, which undergo Schiff condensation with aromatic aldehydes RCHO (R = 2-HO-5-NO<sub>2</sub>C<sub>6</sub>H<sub>3</sub> and 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>) to give complexes **23** containing the newly formed free remote functionalised groups. Compound **23** with R = 2-HO-5-NO<sub>2</sub>C<sub>6</sub>H<sub>3</sub> was used as a metal-containing ligand for subsequent complexation with Cu<sup>2+</sup> and Co<sup>2+</sup>.<sup>134</sup>



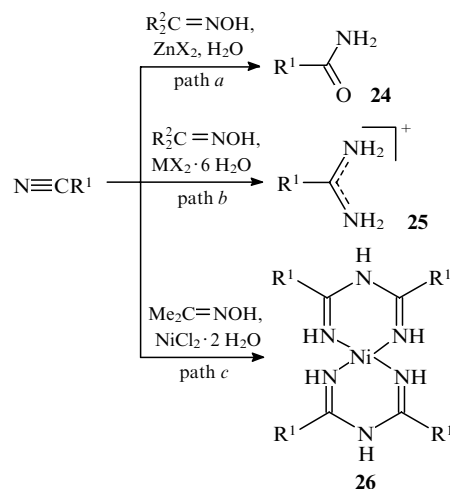
R = 2-HO-5-NO<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>; M = Cu<sup>2+</sup>, Co<sup>2+</sup>.

To summarise, a new type of reactivity of *vic*-dioximes, dione monooximes and hydrazone oximes with respect to nitriles was revealed in the studies of nucleophilic addition reactions.<sup>118, 120</sup>

#### 4. Transformations of nitriles promoted by 3d-metal–oxime systems

Reactions of nitriles with 'simple' oximes in the presence of complexes and salts of labile 3d metals afford products (free carboxamides **24**, amidinium salts **25** and coordinated imidoyl amidines **26**) different from those described in Sections III.2 and III.3. For example, catalytic hydrolysis of a series of nitriles R<sup>1</sup>CN in the presence of the ZnX<sub>2</sub>–R<sub>2</sub>C=NOH system produces the corresponding carboxamides R<sup>1</sup>C(O)NH<sub>2</sub> (Scheme 5, path a).<sup>74</sup>

Scheme 5

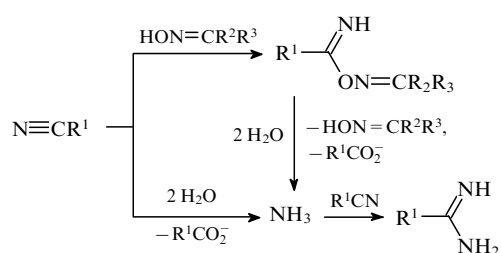


R<sup>1</sup> = Me, CH<sub>2</sub>Cl, Et, Pr<sup>n</sup>, Pr<sup>i</sup>, Bu<sup>n</sup>, Bu<sup>t</sup>, *p*-MeOC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>, Ph;  
R<sub>2</sub><sup>2</sup> = Me<sub>2</sub>, (CH<sub>2</sub>)<sub>4</sub>, (CH<sub>2</sub>)<sub>5</sub>; M = Co, Ni; X = Cl, NO<sub>3</sub>.

This system containing the zinc salt and oxime in a molar ratio of 1 : 4 (which is optimal for hydrolysis of RCN) allows one to transform nitriles into carboxamides under mild conditions with a

catalyst turnover number of about 100 for the majority of nitriles and up to 1000 for the conversion of *p*-MeOC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>CN into *p*-MeOC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>C(O)NH<sub>2</sub>. It should be noted that, taken separately, the zinc salt and oxime do not exhibit catalytic activity. The intermediate [ZnX<sub>2</sub>(R<sub>2</sub>C=NOH)<sub>2</sub>] was isolated and its catalytic activity in hydrolysis was experimentally confirmed, which provide evidence that this complex is directly involved in the catalytic cycle.<sup>74</sup> It is believed<sup>74</sup> that one step of the process involves the reaction of the [ZnX<sub>2</sub>(R<sub>2</sub>C=NOH)<sub>2</sub>] complex with R<sup>1</sup>CN, resulting in its electrophilic activation followed by the formation of the imino complex. The ZnX<sub>2</sub>–R<sub>2</sub>C=NOH reagent system is the most readily accessible and inexpensive catalytic system for the transformation of R<sup>1</sup>CN into the corresponding carboxamides R<sup>1</sup>C(O)NH<sub>2</sub>.<sup>135</sup>

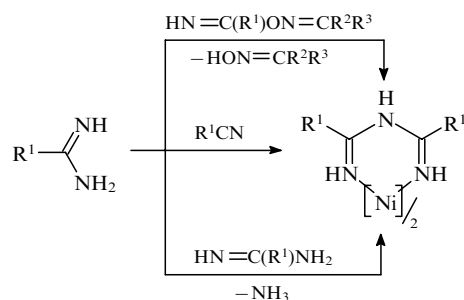
In the presence of salts MX<sub>2</sub>·6H<sub>2</sub>O (M = Co, Ni) and an excess of oxime R<sub>2</sub>C=NOH, sterically unhindered nitriles are quantitatively transformed into amidinium salts R<sup>1</sup>C(NH)NH<sub>2</sub>·HNO<sub>3</sub> (Scheme 5, path *b*).<sup>136, 137</sup> The optimal conditions for the formation of R<sup>1</sup>C(NH)NH<sub>2</sub>·HNO<sub>3</sub> are those where salt M(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O and oxime R<sub>2</sub>C=NOH are used in a molar ratio of 1:4. A change in the ratio to 1:2 leads to a substantial decrease in the yield of the target product and an increase in the reaction time. The results of investigation of the reaction products and intermediates suggested<sup>136, 137</sup> the following mechanism: initial metal-mediated hydrolysis of nitrile giving rise to R<sup>1</sup>CO<sub>2</sub>H and ammonia followed by the reaction of the latter with metal-activated nitrile to produce amidine (Scheme 6). It is believed that all steps of the process yielding amidines require the involvement of a metal centre, and some steps are additionally catalysed by oxime.



Scheme 6

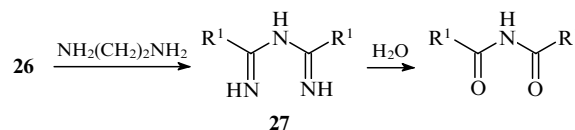
The reaction of nitriles with oximes in the presence of nickel salt NiCl<sub>2</sub>·2H<sub>2</sub>O, which is less hydrated than M(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O (M = Ni, Co), follows a different pathway.<sup>137</sup> For example, the reaction of R<sup>1</sup>CN with a NiCl<sub>2</sub>·2H<sub>2</sub>O–Me<sub>2</sub>C=NOH mixture affords the imidoamidinium complexes [Ni{N=CH(R<sup>1</sup>)}<sub>2</sub>]<sup>2+</sup> (Scheme 5, path *c*).

Although the mechanism of this process is not entirely understood, it was hypothesised<sup>137</sup> that the initial step affords coordinated amidines according to Scheme 6, which are then involved in transformations to give chelating imidoamidinium.



The resulting imidoamidinium ligand was isolated in the free state by the reaction with ethylenediamine or as a salt by the reaction of HBF<sub>4</sub>·Et<sub>2</sub>O with a solution of complex **26** in MeCN.<sup>137</sup> The reaction of ethylenediamine with complex **26** in an aqueous methanolic solution produced acylamides R<sup>1</sup>C(O)NHC(O)R<sup>1</sup> through hydrolysis of intermediate imidoamidinium

amidines **27**. This is a new procedure for the preparation of imidoamidinium **27**, which are used in the synthesis of triazines and triazine-containing polymers.

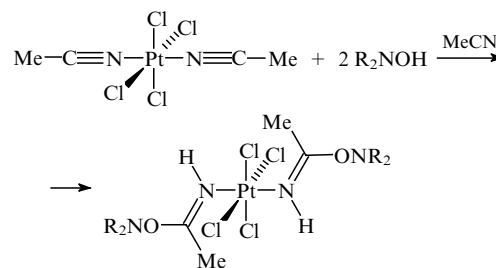


Therefore, 3d-metal salt–oxime systems can be employed to activate nitriles in the reactions giving rise to carboxamides, amidines, imidoamidinium and acylamides, which are of great commercial and/or preparative importance. It should be noted that variation of the metal salts in the activating system allows one to prepare selectively and in good yield different products from the same starting nitriles.

#### IV. Reactions of hydroxylamines and hydroxamic acids

Other HON-nucleophiles (along with oximes), such as substituted hydroxylamines and hydroxamic acids, can be used in addition reactions to coordinated nitriles. Although hydroxamic acids are formally hydroxylamine derivatives, the nitrogen atoms in these compounds are in different hybridisation states and, consequently, act as nucleophiles of different types.

Unsubstituted hydroxylamine, being an ambidentate N,O-nucleophile, can be involved in the addition to free nitriles at both centres. In most cases, the addition occurs at the nitrogen atom. These reactions produce amidoximes.<sup>11</sup> The addition of unsubstituted hydroxylamine NH<sub>2</sub>OH to complexed nitriles has not been documented. Several studies were devoted to reactions of alkylated hydroxylamines R<sub>2</sub>NOH with coordinated nitriles.<sup>138–140</sup> For instance, N-addition of alkylated hydroxylamines to Mo and W nitrile complexes was described.<sup>138, 139</sup> Only one example of addition of hydroxylamines R<sub>2</sub>NOH to coordinated nitrile in *trans*-[PtCl<sub>4</sub>(MeCN)<sub>2</sub>] involving the OH group is known.<sup>140</sup>



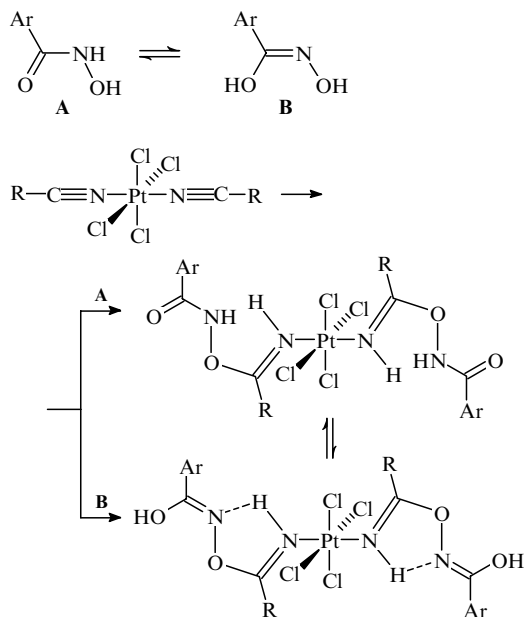
R = Me, Et, Bn.

Hydroxamic acids ArC(O)NHOH also show unusual reactivity with respect to the nitrile complex *trans*-[PtCl<sub>4</sub>(EtCN)<sub>2</sub>].<sup>141</sup> In this case, hydroxamic acids, which are known in chemistry primarily due to chelation reactions giving rise to stable five-membered metallacycles, act as nucleophiles and react with a coordinated nitrile.

Hydroxamic acids exist as two tautomeric forms **A** and **B**. Both forms can potentially act as HO-nucleophiles (Scheme 7).

Their contribution to the addition reactions was elucidated in the study of the reactions of *trans*-[PtCl<sub>4</sub>(EtCN)<sub>2</sub>] with hydroxamic acid PhC(O)N(Me)OH (corresponds to the form **A** in Scheme 7) and methyl *N*-hydroxyimidoate Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>.C(OMe)=NOH (corresponds to the form **B** in Scheme 7), which are 'frozen' through N- or O-alkylation.<sup>130</sup>

The reaction of the platinum(IV) nitrile complex with methyl *N*-hydroxyimidoate is completed at room temperature in a few minutes, whereas the reaction with hydroxamic acid requires more drastic conditions (heating to 50 °C) and longer reaction time (2–3 h), which is indicative of the difference in the reactivity of

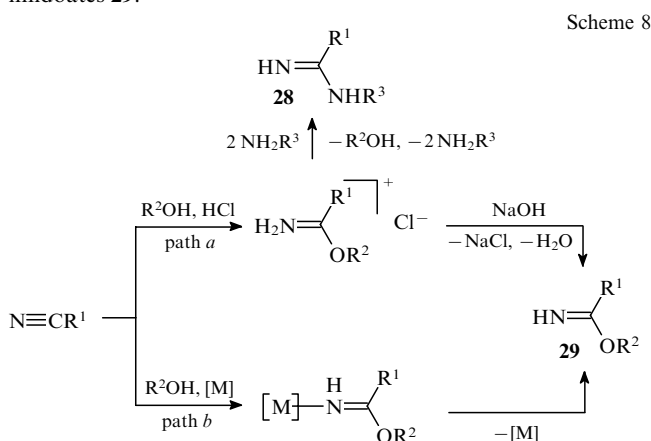


R = Alk, Ar; Ar = Ph, *o*-HOC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-MeC<sub>6</sub>H<sub>4</sub>, *p*-MeOC<sub>6</sub>H<sub>4</sub>.

these forms. This suggests that the form **B** makes a greater contribution to the nucleophilic addition of unsubstituted hydroxamic acids to coordinated nitriles.

## V. Reactions of alcohols with coordinated nitriles

The reaction of free nitriles with alcohols is involved in the two-step Pinner synthesis used for the preparation of amidines **28**. In the first step, the reaction of nitrile R<sup>1</sup>CN with alcohol R<sup>2</sup>OH in the presence of an excess of dry HCl (Scheme 8, path *a*) affords the salt [R<sup>1</sup>C(OR<sup>2</sup>)=NH<sub>2</sub>]<sup>+</sup>Cl<sup>−</sup>, which (in the second step) reacts with two moles of amines to form amidines **28** and with alkali to give imidoates **29**.

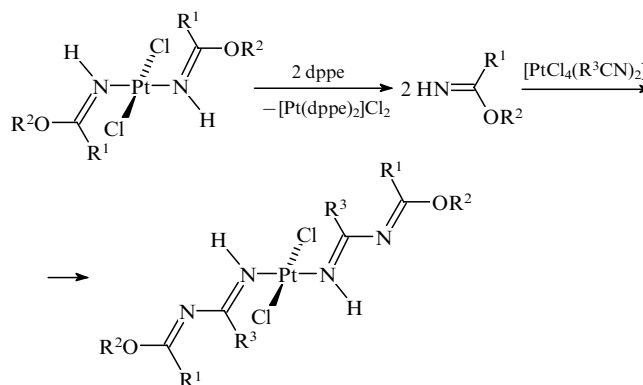


In this process, nitrile is activated through protonation. The main drawback of the Pinner synthesis of amidines is that it requires a large excess of HCl.

The reactions of alcohols with coordinated nitriles proceed analogously to the Pinner reaction with the difference that the metal centre serves as an activator (Scheme 8, path *b*). The nucleophilic addition of alcohols to nitriles affords imidoates, which are stabilised through coordination to the metal and, in the coordinated state, are resistant to hydrolysis. Since the nucleophilic addition of alcohols to nitriles has been surveyed in the reviews,<sup>17, 18</sup> we do not consider this reaction in detail. Table 1 gives examples of these reactions.<sup>93, 102, 142–188</sup>

In summary, it should be noted that the conditions of the reactions of alcohols with nitriles depend substantially on the oxidation state of the metal. The addition of R<sup>2</sup>OH to R<sup>1</sup>CN present in low-oxidation-state metal complexes [Pt(II),<sup>102, 143–146</sup> Pd(II),<sup>158</sup> Ni(II),<sup>165</sup> Ir(III),<sup>171</sup> Cu(II)<sup>177</sup>] requires that the nucleophilicity of R<sup>2</sup>OH be additionally increased by adding alkali or another base (for example, NR<sub>3</sub>; see Refs 158 and 165) in a catalytic or stoichiometric amount. Nitrile ligands in high-oxidation-state complexes [Pt(IV), Re(IV)]<sup>157, 174</sup> can react with alcohols in a neutral medium under rather mild conditions. The reaction is influenced by the nature of the R<sup>1</sup> group in the R<sup>1</sup>CN molecule, and the reactions with nitriles containing electron-withdrawing groups (for example, R<sup>1</sup> = Ph) proceed more readily.<sup>165, 167, 168</sup> The addition of alcohols to nitriles also depends substantially on the steric parameters of the R<sup>2</sup> group in the alcohol molecules. Alcohols containing unhindered groups (R<sup>2</sup> = Me, Et) react more readily, whereas sterically hindered alcohols or phenols (R<sup>2</sup> = Ph, Bu<sup>t</sup>) do not react at all.<sup>102, 142, 165, 167, 168</sup>

Imidoate complexes are of interest because they contain imine in the 'frozen' coordinated form, which provides stability of imidoates R<sup>1</sup>C(OR<sup>2</sup>)=NH. In the free state, the latter are generally easily subjected to hydrolysis. Imines can be isolated by decoordination under anhydrous conditions and used in subsequent reactions. An example of the use of this methodology was given in the study,<sup>189</sup> where imidoates were involved in subsequent reactions with nitriles included in platinum(IV) complexes in non-aqueous solutions.



Imidoates are better ligands than nitriles and they are more tightly held in the inner sphere of the metal, which, in most cases, excludes the possibility of a catalytic process. Nevertheless, several examples of catalytic alcoholysis of nitriles in the presence of Pd(II),<sup>93</sup> Re(III)<sup>175</sup> and Ir(III)<sup>171</sup> complexes have been documented. Unfortunately, the available data on the catalytic transformations of RCN into imidoates are insufficient for an understanding of the general features of this process.

## VI. Reactions of other HO-nucleophiles

Examples of the addition of HOP-nucleophiles to coordinated nitriles are scarce. For instance, heating of complex **30** with nitrile *p*-MeC<sub>6</sub>H<sub>4</sub>CN for two days afforded compound **31** containing a new five-membered ring formed through nucleophilic attack of the oxygen atom of the P–OH group on the coordinated nitrile.<sup>190</sup>

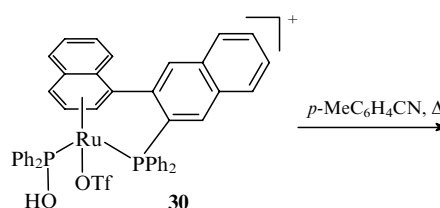


**Table 1.** Examples of nucleophilic addition of alcohols to coordinated nitriles.

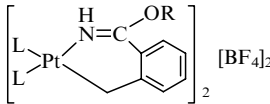
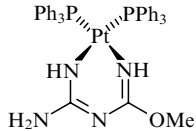
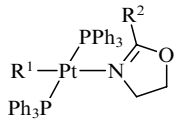
| Starting reagents                                                                                                                                                                                                                                                                                                                                                                                                     | Reaction conditions                                   | Reaction products                                                                                                                                                                                                                                                                                                                                    | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Ref.     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| $[\text{PtR}^1\text{XL}_2] + \text{C}_6\text{F}_4(\text{CN})_{2-p} + \text{R}^2\text{OH}$<br>$\text{R}^1 = \text{Me}; \text{X} = \text{Cl}, \text{L} = \text{PMe}_2\text{Ph}, \text{AsMe}_3;$<br>$\text{R}^1 = \text{CF}_3; \text{X} = \text{I}, \text{L} = \text{PMe}_2\text{Ph};$<br>$\text{R}^2 = \text{Me}, \text{Et}, \text{Pr}^n, \text{Pr}^i, \text{CH}_2\text{CH}_2\text{OMe},$<br>$(\text{CF}_3)_2\text{CH}$ | in the presence of $\text{Ag}^+$ salts                | $[\text{L}_2\text{MePt}\{\underline{\text{NH}} = \text{C}(\text{OMe})\text{C}_6\text{F}_4\text{C}(\text{OMe}) = \underline{\text{NH}}\}\text{PtL}_2\text{Me}]$ ,<br>$[\text{L}_2\text{MePt}\{\underline{\text{N}} \equiv \text{CC}_6\text{F}_4\text{C}(\text{OR}^2) = \underline{\text{NH}}\}\text{PtL}_2\text{Me}]$<br>for $\text{R}^1 = \text{Me}$ | a complex with bis-imidoate is formed only by the reaction with MeOH, whereas the reaction with $\text{R}^2\text{OH}$ ( $\text{R}^2 = \text{Et}, \text{Pr}^n, \text{CH}_2\text{CH}_2\text{OMe}$ ) affords monoaddition products; $\text{Pr}^i\text{OH}$ and $(\text{CF}_3)_2\text{CHOH}$ are not involved in addition reactions. If $\text{R}^1 = \text{CF}_3$ , the reaction proceeds more rapidly than that involving compounds with $\text{R}^1 = \text{Me}$ | 142      |
| $[\text{PtCl}_2(\text{MeCN})_2] + \text{ROH}$<br>$\text{R} = \text{Me}, \text{Et}, \text{Pr}^i$                                                                                                                                                                                                                                                                                                                       | 1 equiv. of KOH or 3 equiv. of KOPh, room temperature | $[\text{PtCl}_2\{\underline{\text{NH}} = \text{C}(\text{OR})\text{Me}\}_2]$                                                                                                                                                                                                                                                                          | yield of the product is 50% – 70%                                                                                                                                                                                                                                                                                                                                                                                                                               | 143      |
| $\text{K}[\text{PtCl}_3(\text{R}^1\text{CN})] + \text{R}^2\text{OH}$<br>$\text{R}^1 = \text{Me}, \text{Et}, \text{Ph}, \text{Bu}^t; \text{R}^2 = \text{Me}, \text{Et}, \text{Ph}$                                                                                                                                                                                                                                     | catalytic amount of KOH                               | $\text{K}[\text{PtCl}_3\{\underline{\text{NH}} = \text{C}(\text{OR}^2)\text{R}^1\}]$                                                                                                                                                                                                                                                                 | the reaction was demonstrated to produce initially the $[\text{PtCl}_3\{(Z)\text{-NH} = \text{C}(\text{OR}^2)\text{R}^1\}]^-$ complex followed by either complete isomerisation to $[\text{PtCl}_3\{(E)\text{-NH} = \text{C}(\text{OR}^2)\text{R}^1\}]^-$ , if $\text{R}^2 = \text{Me}$ or Et, or the formation of an equilibrium mixture of <i>E</i> and <i>Z</i> isomers, if $\text{R}^2 = \text{Ph}$                                                         | 144, 145 |
| $\text{cis}(\text{trans})\text{-}[\text{PtCl}_2(\text{R}^1\text{CN})_2] + \text{R}^2\text{OH}$<br>$\text{R}^1 = \text{Me}, \text{Et}, \text{Ph}, \text{Bu}^t; \text{R}^2 = \text{Me}, \text{Et}, \text{Ph}$                                                                                                                                                                                                           | the same                                              | $[\text{PtCl}_2\{\text{NH} = \text{C}(\text{OR}^2)\text{R}^1\}_2]$                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 144, 145 |
| $[\text{Pt}(\text{EtCN})_4][\text{CF}_3\text{SO}_3]_2 + \text{EtOH}$                                                                                                                                                                                                                                                                                                                                                  | 2 equiv. of KOH                                       | $[\text{Pt}\{(E)\text{-NH} = \text{C}(\text{OEt})\text{Et}\}_4][\text{CF}_3\text{SO}_3]_2$                                                                                                                                                                                                                                                           | the <i>E</i> configuration of the ligand was confirmed by X-ray diffraction                                                                                                                                                                                                                                                                                                                                                                                     | 146      |
| $[\text{Pt}(\mu_2\text{-C}, N\text{-CH}_2\text{C}_6\text{H}_4\text{C} \equiv \text{N})\text{L}_2]_2[\text{BF}_4]_2 + \text{ROH}$<br>$\text{L} = \text{Ph}_3\text{P}, \text{L}_2 = \text{Ph}_2\text{P}(\text{CH}_2)_2\text{PPh}_2$ (dppe);<br>$\text{R} = \text{Me}, \text{Et}, \text{Pr}^i, \text{Bn}, \text{Bu}^t, \text{Ph}$                                                                                        | —                                                     |                                                                                                                                                                                                                                                                    | the effect of steric hindrance of the R group of alcohol on the reaction rate was studied: the reaction does not occur for compounds with $\text{R} = \text{Bu}^t$                                                                                                                                                                                                                                                                                              | 102      |
| $\text{cis-}[\text{Pt}\{\text{NCN} = \text{C}(\text{NH}_2)_2\}_2(\text{PPh}_3)_2][\text{BPh}_4]_2 + \text{MeOH}$                                                                                                                                                                                                                                                                                                      | —                                                     |                                                                                                                                                                                                                                                                   | addition of a methanol molecule at the triple bond of one of the ligands, decoordination of another ligand and the metallacycle formation                                                                                                                                                                                                                                                                                                                       | 147, 148 |
| $[\text{PtCl}_2(\text{RCN})_2] + \text{HO}(\text{CH}_2)_2\text{Cl}$<br>$\text{R} = \text{Alk}, \text{Ar}$                                                                                                                                                                                                                                                                                                             | BuLi or NEt <sub>3</sub>                              | $[\text{PtCl}_2\{\text{N} = \text{C}(\text{R})\text{OCH}_2\text{CH}_2\}_2]$                                                                                                                                                                                                                                                                          | in the reaction in the presence of NEt <sub>3</sub> , the formation of $[\text{PtCl}_2\{\text{NH} = \text{C}(\text{R})\text{OCH}_2\text{CH}_2\text{Cl}\}_2]$ as an intermediate was detected. The reaction of dppe with complexes afforded $\Delta^2$ -oxazolines                                                                                                                                                                                               | 149, 150 |
| $[\text{Pt}(\text{R}^1)(\text{NCR}^2)(\text{PPh}_3)_2]^+ + \text{HO}(\text{CH}_2)_2\text{Cl}$<br>$\text{R}^1 = \text{H}, \text{Me}, \text{CF}_3; \text{R}^2 = \text{Alk}, \text{Ar}$                                                                                                                                                                                                                                  | Bu <sup>n</sup> Li                                    |                                                                                                                                                                                                                                                                  | the reaction of an excess of $\text{Cl}^-$ with the $[\text{Pt}(\text{CF}_3)\{\text{N} = \text{C}(\text{R})\text{OCH}_2\text{CH}_2\}_2(\text{PPh}_3)_2]^+$ complex produced free $\Delta^2$ -oxazoline                                                                                                                                                                                                                                                          | 151, 152 |
| $[\text{PtCl}_2(\text{NCR})_2] + \text{HOCH}_2\text{C}^*(\text{H})(\text{Cl})\text{Me}$<br>$\text{R} = \text{Alk}, \text{Ar}$                                                                                                                                                                                                                                                                                         | Bu <sup>n</sup> Li                                    | $[\text{PtCl}_2\{\text{N} = \text{C}(\text{R})\text{OCH}_2\text{CH}(\text{Me})\}_2]$                                                                                                                                                                                                                                                                 | the absolute configuration of the chiral carbon atom in the $\Delta^2$ -oxazoline ligand is retained                                                                                                                                                                                                                                                                                                                                                            | 153      |

**Table 1** (continued).

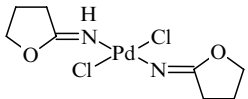
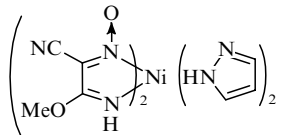
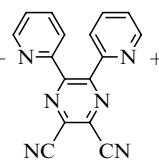
| Starting reagents                                                                                                                                                                                                                                        | Reaction conditions                | Reaction products                                                                                                                                                                                                                                                                                                                                                                                                                                           | Comments                                                                                                                                                                                                                                                                                                                                                                                   | Ref.     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| $[\text{PtCl}_2(\text{NCR})_2] + \text{HO}(\text{CH}_2)_3\text{Cl}$<br>$\text{R} = \text{Alk, Ar}$                                                                                                                                                       | $\text{Bu}^n\text{Li}$             | $[\text{PtCl}_2\{\text{N}=\text{C}(\text{R})\text{OCH}_2\text{CH}_2\text{CH}_2\}_2]$                                                                                                                                                                                                                                                                                                                                                                        | the reaction of dppe with the complex afforded 1,3-oxazine                                                                                                                                                                                                                                                                                                                                 | 154      |
| $[\text{Pt}(\text{CF}_3)(\text{NCR})(\text{PPh}_3)_2]^+ + \text{HO}(\text{CH}_2)_3\text{Cl}$<br>$\text{R} = \text{Alk, Ar}$                                                                                                                              | $\text{Bu}^n\text{Li}$             | $[\text{Pt}(\text{CF}_3)\{\text{N}=\text{C}(\text{R})\text{OCH}_2\text{CH}_2\text{CH}_2\}(\text{PPh}_3)_2]^+$                                                                                                                                                                                                                                                                                                                                               | the reaction of $[(\text{PPh}_3)_2\text{N}]\text{Cl}$ with the complex produced 1,3-oxazine                                                                                                                                                                                                                                                                                                | 154      |
| $[\text{PtMe}_2\text{I}_2(\text{PMe}_2\text{Ph})_2] + \text{C}_6\text{F}_5\text{CN} + \text{MeOH}$                                                                                                                                                       | $\text{AgPF}_6$                    | $[\text{PtMe}_2\{\text{NH}=\text{C}(\text{OMe})\text{C}_6\text{F}_5\}_2(\text{PMe}_2\text{Ph})_2]$                                                                                                                                                                                                                                                                                                                                                          | it was suggested that the reaction proceeds through the formation of the solvated complex $[\text{PtMe}_2(\text{MeOH})_2(\text{PMe}_2\text{Ph})_2]^{2+}$ , which then reacts with nitrile                                                                                                                                                                                                  | 155, 156 |
| $[\text{PtCl}_4(\text{NCR}^1)_2] + \text{R}^2\text{OH}$<br>$\text{R}^1 = \text{Me, Et, Bn, Ph};$<br>$\text{R}^2 = \text{Me, Et, Pr}^n, \text{Pr}^i, \text{Bu}^n$                                                                                         | 40 °C in the absence of a base     | $[\text{PtCl}_4\{\text{NH}=\text{C}(\text{OR}^2)\text{R}^1\}_2]$                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                            | 157      |
| <i>cis</i> - $[\text{Pd}(\mu_2\text{-C, N-CH}_2\text{C}_6\text{H}_4\text{CN})\text{L}_2]_2[\text{BF}_4]_2 + \text{MeOH}$<br>$\text{L} = \text{PPh}_3, \text{L}_2 = \text{Ph}_2\text{P}(\text{CH}_2)_2\text{PPh}_2$                                       | $\text{NEt}_3$                     | $[\text{Pd}\{\mu_2\text{-C, N-CH}_2\text{C}_6\text{H}_4\text{C}(\text{OMe})=\text{NH}\}\text{L}_2]^+$                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                            | 158      |
| $\text{Na}_2[\text{PdCl}_4] + \text{HO}(\text{CH}_2)_3\text{CN}$                                                                                                                                                                                         | —                                  |                                                                                                                                                                                                                                                                                                                                                                           | in the absence of the palladium complex, nitrile $\text{HO}(\text{CH}_2)_3\text{CN}$ is not subjected to intramolecular cyclisation                                                                                                                                                                                                                                                        | 159      |
| $[\text{Pd}_2(\text{C}_6\text{F}_5)_4(\mu\text{-OH})_2]^{2-} + \text{R}^1\text{CN} + \text{R}^2\text{OH}$<br>$\text{R}^1 = \text{Me, Ph, NC}(\text{CH}_2)_n \ (n = 1, 2),$<br>$2\text{-NC}_5\text{H}_4; \text{R}^2 = \text{Me, Et}$                      | —                                  | $[\text{Pd}(\text{C}_6\text{F}_5)_2\{\text{NH}=\text{C}(\text{OR}^2)\text{R}^1\}_2]$ (for $\text{R}^1 = \text{Me, Ph}$ ),<br>$[\text{Pd}(\text{C}_6\text{F}_5)_2\{\text{NH}=\text{C}(\text{OR}^2)(\text{CH}_2)_n\text{C}(\text{OR}^2)=\text{NH}\}]$<br>(for $\text{R}^1 = \text{NC}(\text{CH}_2)_n$ ) and<br>$[\text{Pd}(\text{C}_5\text{F}_5)_2\{\text{NC}_5\text{H}_4\text{C}(\text{OR}^2)=\text{NH}\}_2]$<br>(for $\text{R}^1 = \text{NC}_5\text{H}_4$ ) | in solution, imidoate complexes exist as equilibrium mixtures of <i>E,E</i> , <i>E,Z</i> and <i>Z,Z</i> isomers                                                                                                                                                                                                                                                                            | 160–164  |
| $[\text{Pd}(\text{solv})_2\{\text{HO}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{OH}\}]^{2+} +$<br>$+ \text{MeOH} + \text{Cl}_2\text{CHCN}$<br>$\text{solv} = \text{D}_2\text{O}, (\text{CD}_3)_2\text{CO}, \text{CD}_3\text{OD}$ | —                                  | $\text{Cl}_2\text{CHC}(\text{OMe})=\text{NH}$                                                                                                                                                                                                                                                                                                                                                                                                               | the $[\text{Pd}(\text{solv})_2\{\text{HO}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{OH}\}]^{2+}$ complex catalyses methanolysis of nitrile $\text{Cl}_2\text{CHCN}$ . The reaction is accelerated by a factor of $10^6$ compared to the uncatalysed reaction. An intermolecular mechanism of the reaction of coordinated nitrile with free alcohol was established | 93       |
| $[\text{Ni}(\text{C}_6\text{Cl}_5)(\text{NCR}^1)\text{L}_2][\text{ClO}_4] + \text{R}^2\text{OH}$<br>$\text{R}^1 = \text{Me, Ph}; \text{L} = \text{PPh}_2\text{Me, PPhMe}_2;$<br>$\text{R}^2 = \text{Me, Et}$                                             | catalytic amount of $\text{NEt}_3$ | $[\text{Ni}(\text{C}_6\text{Cl}_5)\{\text{NH}=\text{C}(\text{OR}^2)\text{R}^1\}\text{L}_2][\text{ClO}_4]$                                                                                                                                                                                                                                                                                                                                                   | the formation of the product is determined by steric hindrance of phosphine and/or $\text{R}^2\text{OH}$ and the electron-withdrawing properties of the $\text{R}^1$ group in $\text{R}^1\text{CN}$                                                                                                                                                                                        | 165      |
| $\text{Ni}(\text{NO}_3)_2 +$  $+ \text{NaON}=\text{C}(\text{CN})_2 +$<br>$+ \text{MeOH}$                                                                              | —                                  |                                                                                                                                                                                                                                                                                                                                                                         | the complex was characterised by X-ray diffraction                                                                                                                                                                                                                                                                                                                                         | 160, 166 |
| $\text{Ni}^{2+} +$  $+ \text{ROH} \ (\text{R} = \text{Me, Et})$                                                                                                       | —                                  | the complex with the imidoate ligand                                                                                                                                                                                                                                                                                                                                                                                                                        | the complex was characterised by X-ray diffraction                                                                                                                                                                                                                                                                                                                                         | 161, 162 |

**Table 1** (continued).

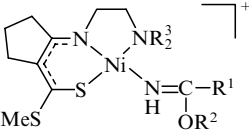
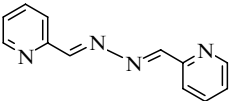
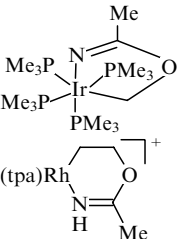
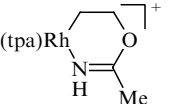
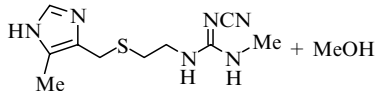
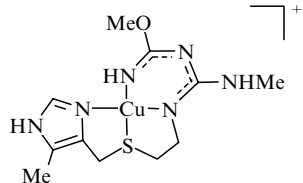
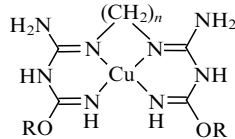
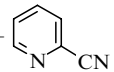
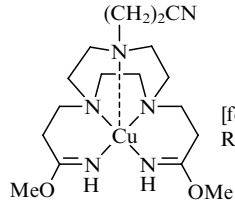
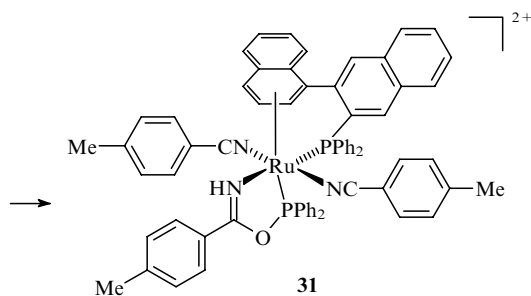
| Starting reagents                                                                                                                                                                                                       | Reaction conditions                                          | Reaction products                                                                                                                                                                                                 | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Ref.     |
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| $[\text{NiL}(\text{NCR}^1)][\text{ClO}_4] + \text{R}^2\text{OH}$<br>L is an <i>S,N,N</i> -tridentate ligand;<br>$\text{R}^1 = \text{Me, Et, Ph}; \text{R}^2 = \text{Me, Et, Pr}^n$                                      | reflux in the presence of an excess of $\text{R}^1\text{CN}$ |                                                                                                                                 | the reaction rate is determined by the steric properties of the $\text{R}^1$ and $\text{R}^2$ groups and can be increased by four orders of magnitude with the use of catalytic amounts of $\text{NaOR}^2$ . The reaction in wet alcohol produces $[\text{NiL}\{\text{NH}_2\text{COR}^1\}][\text{ClO}_4]$ due to hydrolysis of the imidoate ligand                                                                                                                                                     | 167, 168 |
| $[\text{IrL}(\text{NO})(\text{PPh}_3)_2][\text{PF}_6]_2 + \text{RCN} + \text{EtOH}$<br><br>$\text{R} = \text{Me, Ph Bn}; \text{L} = $  | $\text{CH}_2\text{Cl}_2$ , room temperature, 30–40 days      | $[\text{Ir}\{(2\text{-C}_5\text{H}_4\text{N})\text{CH}=\text{N}-\text{N}=\text{C}(\text{NOH})(\text{NC}_5\text{H}_4\text{-2})\} \cdot \{\text{NH}=\text{C}(\text{OEt})\text{R}\}(\text{PPh}_3)_2][\text{PF}_6]_2$ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 169      |
| $[\text{IrMeCl}(\text{CO})\text{L}_2] + \text{NCC}_6\text{F}_5 + \text{MeOH}$<br>$\text{L} = \text{PMe}_2\text{Ph, PMePh}_2$                                                                                            | $\text{AgPF}_6$                                              | $[\text{IrMeCl}(\text{CO})\{\text{NH}=\text{C}(\text{OMe})\text{C}_6\text{F}_5\}\text{L}_2]^+$                                                                                                                    | $\text{Ag}^+$ is used for binding iodide to form $\text{AgI}$ , the reaction proceeds through the formation of the $[\text{IrMeCl}(\text{MeOH})(\text{CO})\text{L}_2]^+$ intermediate, which reacts with nitrile                                                                                                                                                                                                                                                                                       | 170      |
| $[\text{Cp}^*\text{Ir}(\eta^3\text{-CH}_2\text{CHCHPh})(\text{NCMe})]^+ + \text{ROH}$<br>$\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5, \text{R} = \text{Me, Et, Pr}^i$                                                   | —                                                            | $[\text{Cp}^*\text{Ir}(\eta^3\text{-CH}_2\text{CHCHPh})\{\text{NH}=\text{C}(\text{OR})\text{Me}\}]^+$                                                                                                             | the initially formed mixture of <i>E</i> and <i>Z</i> isomers of the imidoate ligand ( $\text{R} = \text{Me, Et}$ ) is transformed into the <i>Z</i> isomer in the presence of the corresponding alcohol. For $\text{Pr}^i\text{OH}$ , only the <i>Z</i> isomer was isolated. Imidoate $\text{NH}=\text{C}(\text{OR})\text{Me}$ was isolated from the $[\text{Cp}^*\text{Ir}(\eta^3\text{-CH}_2\text{CHCHPh})\{\text{NH}=\text{C}(\text{OR})\text{Me}\}]^+$ complex by replacement with $\text{PPh}_3$ | 171      |
| $[\text{Cp}^*\text{Ir}(\eta^3\text{-CH}_2\text{CHCHPh})(\text{NCPh})][\text{SO}_3\text{CF}_3] + \text{PhCN} + \text{MeOH}$                                                                                              | catalysis, $\text{Na}_2\text{CO}_3$ , 70 °C                  | free $\text{NH}=\text{C}(\text{OMe})\text{Ph}$                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 171      |
| $[\text{Ir}(\text{CH}_2\text{OH})(\text{MeCN})(\text{PMe}_3)_4]^{2+}$                                                                                                                                                   | catalysis by Py or $\text{PMe}_3$                            |                                                                                                                                | in the absence of a catalyst, the reaction proceeds more slowly and is suppressed upon the addition of $\text{HBF}_4 \cdot \text{Et}_2\text{O}$                                                                                                                                                                                                                                                                                                                                                        | 172      |
| $[\text{Rh}(\text{tpa})\{\text{CH}_2\text{CH}_2\text{O}\}]^+ + \text{MeCN}$<br>tpa is <i>N,N,N</i> -tris(2-pyridylmethyl)amine                                                                                          | $\text{NH}_4\text{PF}_6$                                     |                                                                                                                               | the reaction proceeds through the formation of the $[\text{Rh}(\text{tpa})(\text{CH}_2\text{CH}_2\text{OH})(\text{MeCN})]^{2+}$ intermediate                                                                                                                                                                                                                                                                                                                                                           | 173      |
| $[\text{ReCl}_4(\text{MeCN})_2] + \text{ROH}$<br>$\text{R} = \text{Me, Et}$                                                                                                                                             | —                                                            | $[\text{ReCl}_4\{\text{NH}=\text{C}(\text{OR})\text{Me}\}_2]$                                                                                                                                                     | free imidoate was isolated from the complex upon the addition of $\text{PPh}_3$                                                                                                                                                                                                                                                                                                                                                                                                                        | 174      |
| $[\text{Re}_6(\mu_3\text{-Se})_8]^{2+} + \text{MeCN} + \text{ROH}$<br>$\text{R} = \text{Me, Et}$                                                                                                                        | UV irradiation, catalysis by a Re cluster                    | $\text{NH}=\text{C}(\text{OR})\text{Me}$                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 175      |
| $\text{AuCl}_3 + \text{R}^1\text{CN} + \text{R}^2\text{OH}$<br>$\text{R}^1 = \text{Me, Et}; \text{R}^2 = \text{Me, Et}$                                                                                                 | —                                                            | $[\text{R}^1\text{C}(\text{OR}^2)\text{NH}_2][\text{AuCl}_4]$                                                                                                                                                     | the $[\text{EtC}(\text{OEt})\text{NH}_2][\text{AuCl}_4]$ complex was characterised by X-ray diffraction                                                                                                                                                                                                                                                                                                                                                                                                | 176      |

**Table 1** (continued).

| Starting reagents                                                                                                                                                                                                                                                                                                         | Reaction conditions         | Reaction products                                                                                                                                                                                                                  | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Ref.     |
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| $\text{Cu}(\text{ClO}_4)_2 + $  $+ \text{MeOH}$                                                                                                                                                                                          | KOH, 60 °C                  |                                                                                                                                                 | the complex was characterised by X-ray diffraction                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 177      |
| $\text{CuSO}_4 + \text{NCNC}(\text{NH}_2)\text{NH}(\text{CH}_2)_n\text{NHC}(\text{NH}_2)\text{NCN} + $<br>$+ \text{ROH}$<br>$\text{R} = \text{Me, Et; } n = 2, 3$                                                                                                                                                         | reflux, 8–12 h              |                                                                                                                                                 | —                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 178      |
| $\text{Cu}(\text{NO}_3)_2 + \text{KN}(\text{CN})_2 + \text{MeOH}$                                                                                                                                                                                                                                                         | Py                          | $[\text{Cu}\{\text{NH}=\text{C}(\text{OMe})\text{NC}(\text{OMe})=\text{NH}\}_2]$                                                                                                                                                   | the reaction affords a product isoelectronic to the $\beta$ -diketonate complexes $[\text{M}(\text{acac})_2]$                                                                                                                                                                                                                                                                                                                                                                                                                                              | 179, 180 |
| $[\text{Cu}(\text{bipy})]^{2+} + [\text{ONC}(\text{CN})_2]^- + \text{MeOH}$                                                                                                                                                                                                                                               | —                           | the complex with the chelate ligand $\text{N}(\text{O})\text{C}(\text{C}\equiv\text{N})\text{C}(\text{OMe})=\text{NH}$                                                                                                             | the compound was characterised by X-ray diffraction                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 181, 182 |
| $\text{CuX}_2 + $  $+ \text{ROH}$<br>$\text{X} = \text{Cl, Br, NCS, ClO}_4; \text{R} = \text{Me, Et, Bu}^n$                                                                                                                              | —                           | complexes with chelated pyridinecarboximidoate $\text{NH}=\text{C}(\text{OMe})\text{C}_5\text{H}_4\text{N}$                                                                                                                        | the reactions of $\text{Na}_2(\text{EDTA})$ with the $[\text{CuCl}_2(\text{H}_2\text{O})_2\{\text{NH}=\text{C}(\text{OR})\text{C}_5\text{H}_4\text{N}\}_2]$ and $[\text{CuCl}_2\{\text{NH}=\text{C}(\text{OR})\text{C}_5\text{H}_4\text{N}\}]$ complexes gave imidoate, which underwent rapid hydrolysis to form $\text{O}=\text{C}(\text{OR})\text{C}_5\text{H}_4\text{N}$ . In the absence of a metal salt, 2-cyanopyridine does not react with methanol. Analogous complexes with imidoates were prepared starting from Co(II), Ni(II) and Fe(II) salts | 183–185  |
| $\text{CuX}_2 + \text{ArCH}=\text{NNHC}(\text{O})\text{CH}_2\text{CN} + \text{EtOH}$<br>$\text{X} = \text{Cl, Br, } 0.5 \text{ SO}_4$                                                                                                                                                                                     | —                           | the complex with the imidoate ligand $\text{ArCH}=\text{NNHC}(\text{O})\text{CH}_2\text{C}(\text{OEt})=\text{NH}$                                                                                                                  | the ligand is coordinated in a tridentate fashion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 186      |
| $[\text{CuCl}(\text{NHR}^1\text{R}^2)\{\text{NH}=\text{C}(\text{OMe})\text{C}_5\text{H}_4\text{N}\}]\text{Cl} + $<br>$+ \text{NC}_5\text{H}_3\text{R}^3\text{R}^4 + \text{MeOH}$<br>$\text{R}^1 = \text{H, R}^2 = \text{Bn; R}^1-\text{R}^2 = (\text{CH}_2)_5;$<br>$\text{R}^3 = 2\text{-CN; R}^4 = \text{H, 4-CN, 6-CN}$ | in the presence of Cu salts | free $\text{NH}=\text{C}(\text{OMe})\text{C}_5\text{H}_4\text{N}$ ,<br>2- $\{\text{NH}=\text{C}(\text{OMe})\}$ -4- $\text{NCC}_5\text{H}_3\text{N}$ and<br>2,6- $\{\text{NH}=\text{C}(\text{OMe})\}_2\text{C}_5\text{H}_3\text{N}$ | copper salt catalysed the formation of imidoates, the reactivity of alcohols decreases with increasing steric hindrance of amine                                                                                                                                                                                                                                                                                                                                                                                                                           | 187      |
| $\text{CuX}_2 + 1,4,7\text{-tris}(\text{R})\text{-triazacyclononane} + \text{MeOH}$<br>$\text{X} = \text{Cl, BF}_4; 1,4,7\text{-tris}(\text{R})\text{-}$ is 1,4,7-tris(cyanomethyl)-,<br>1,4,7-tris(2-cyanoethyl)-, 1,4-bis(2-cyanoethyl)-7-methyl                                                                        | reflux                      | <br>[for $\text{X} = \text{BF}_4$ and $\text{R} = (\text{CH}_2)_2\text{CN}$ ]                                                                 | only copper-coordinated nitrile groups of the macrocycle are subjected to methanolysis. If $\text{X} = \text{Cl}$ , only one nitrile group is involved in the reaction with methanol                                                                                                                                                                                                                                                                                                                                                                       | 188      |

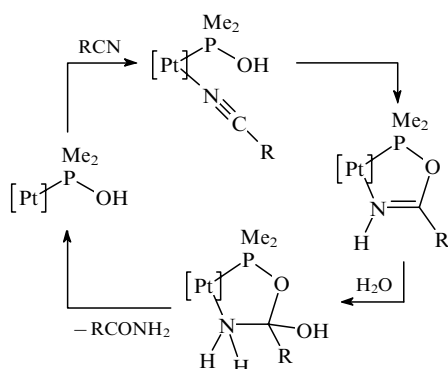




Otf =  $\text{O}_3\text{SCF}_3$ .

The structure of compound **31** was confirmed by elemental analysis,  $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{31}\text{P}$ ,  $^{19}\text{F}$  and  $^{15}\text{N}$ – $^1\text{H}$  COSY NMR spectroscopy and FAB mass spectrometry.<sup>190</sup>

Several of the most efficient systems for catalytic hydrolysis of nitriles giving rise to amides are based on the platinum phosphinite complexes  $[\text{PtX}(\text{R}_2\text{PO}\cdots\text{H}\cdots\text{OPR}_2)(\text{PR}_2\text{OH})]$  ( $\text{X} = \text{H}, \text{Hal}$ ;  $\text{R} = \text{Alk}, \text{Ar}$ ).<sup>32</sup> It was hypothesised that the initial step involves dissociation of the complex to form the  $[\text{Pt}(\text{R}_2\text{PO}\cdots\text{H}\cdots\text{OPR}_2)(\text{PR}_2\text{OH})]^+$  cation followed by coordination of nitrile.<sup>32</sup> Hydrolysis of coordinated nitrile involves the intramolecular attack of the oxygen atom of hydroxy phosphine on RCN to give an intermediate analogous to that described in the study.<sup>190</sup>



Systems based on the  $[\text{PtX}(\text{R}_2\text{PO}\cdots\text{H}\cdots\text{OPR}_2)(\text{PR}_2\text{OH})]$  complexes allow one to perform efficient transformations of various nitriles into amides, including the synthesis of acrylamide, which is of great commercial importance.<sup>32, 73</sup>

The platinum phosphinite complexes  $[\text{PtH}(\text{R}_2\text{PO}\cdots\text{H}\cdots\text{OPR}_2)(\text{PR}_2\text{OH})]$  catalyse the formation of *N*-substituted amidines from nitriles and primary (or secondary) amines. Presumably,<sup>191</sup> the mechanism of this reaction is analogous to the mechanism of hydrolysis of nitriles involving these complexes.

## VII. Conclusion

The present review surveys recent data on the addition of HO-nucleophiles to nitriles. In most cases, additional electrophilic activation of the  $\text{C}\equiv\text{N}$  group is required for these reactions to occur. Analysis of the published data shows that coordination to a metal centre is one of the most efficient ways of activating nitriles. Since the nucleophilic addition to nitriles provides the basis for the synthesis of a series of compounds of commercial value, the determination of optimal conditions for these reactions is an important problem in preparative chemistry.

Coordination of nitriles leads to a substantial increase in electrophilicity of the  $\text{C}\equiv\text{N}$  group, which substantially influences their reactivity. A comparative evaluation of the rates of hydrolysis of free and coordinated nitriles shows that the reaction constant increases by 6–8 orders of magnitude in metal-mediated processes. Nitrile ligands in high-oxidation-state metal complexes can bind nucleophiles. These reactions with free nitriles do not occur even under drastic conditions. In some cases, the resulting imino ligands can be isolated.

Metals not only increase the reactivity of the  $\text{C}\equiv\text{N}$  group but also influence the course of the reaction of nitriles with HO-nucleophiles. For instance, metal-mediated hydrolysis of nitriles, unlike hydrolysis of free RCN, generally stops at the formation of carboxamides, which do not undergo transformations into carboxylic acids. The latter fact is associated with a change in the ratio of the rate constants of the first and second steps of hydrolysis and stabilisation of the product formed in the first step (carboxamide) through coordination. In the presence of metal complexes, the reactions of nitriles with HO-nucleophiles proceed by mechanisms distinct from those observed in the absence of metal complexes (for example, nitriles are hydrolysed in the presence of nickel and cobalt salts to amidinium salts and imidoil imidates).

In the addition of HO-nucleophiles to nitriles, metal often serves as a stabiliser of the reaction product. In most cases, metal-mediated reactions of HO-nucleophiles with nitriles produce coordinated imino compounds, which are generally unstable in the free state or do not exist at all (for example, the addition products of oximes and hydroxamic acids at the  $\text{C}\equiv\text{N}$  bond). Coordination to the metal centre stabilises these compounds and allows one to isolate such imino complexes in individual form. Coordination can also lead to stabilisation of the reaction products in a tautomeric form different from that in which the free compounds exist.

Due to the possibility of varying the nature of the metal, its oxidation state and ligand environment over wide ranges, a large number of nucleophiles of different strength can be used in addition reactions to coordinated nitriles and a broad spectrum of products can be synthesised. For example, complexes with imino and imidoilamidate ligands, as well as amidinium salts and free carboxamides, can be prepared by metal-mediated reactions of nitriles with oximes by varying the nature of the metal atom. In addition, the nature of the metal atom is responsible for the stoichiometric or catalytic character of the process. It should be noted that most known metal-mediated transformations of nitriles and HO-nucleophiles afford coordinated imines and require a stoichiometric amount of metal. The transformation products can be isolated in the free state as an additional step of the synthesis.

Examples of catalytic transformations of nitriles (hydrolysis and alcoholysis) are described in the literature. These reactions are of interest for the synthesis of compounds of commercial and/or pharmaceutical importance. Intermediates in catalytic systems are often too labile for preparative isolation and investigation. Model systems are used to understand the mechanisms of these reactions. Nitrile complexes of kinetically inert metals (for example, platinum) can serve as such models. The reactions of these complexes with nucleophiles give stable analogues of intermediates of catalytic processes. Studies of systems involving kinetically inert complexes would contribute to the design of new catalytic systems.

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# Iminium ylides from carbenes and carbenoids: generation and synthetic applications

A F Khlebnikov, M S Novikov, R R Kostikov

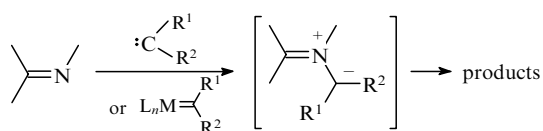
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**Abstract.** The carbene method for the synthesis of iminium ylides based on reactions of carbenes and metallocarbenoids with compounds containing a C=N bond is considered. Special attention is given to the use of iminium ylides in the synthesis of various classes of nitrogen-containing compounds. The bibliography includes 163 references.

## I. Introduction

In recent years, iminium ylides have found wide application in organic synthesis. This is associated with the discovery of new transformations of these compounds, on the one hand, and the perfection of methods for their generation, on the other hand. About ten different procedures for the preparation of iminium ylides are known. To date, the so-called carbene method based on reactions of electrophilic carbenes or metallocarbenoids with compounds containing a C=N bond (an attack at an unshared electron pair of the nitrogen atom) is the most dynamically developing procedure.



This approach allows the introduction of synthetically useful functional groups (e.g., halogen atoms, alkoxy-carbonyl groups) into ylides and their use in domino reactions. Recent reviews<sup>1–6</sup> that touch upon, to a certain degree, the problems of generation of ylides from carbenes and carbenoids cover the literature published more than ten years ago. The present review is a generalisation of the data from the last 15 years devoted to the carbene methods for the generation of iminium ylides and their successful synthetic applications.

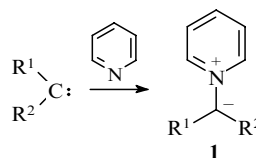
A F Khlebnikov, M S Novikov, R R Kostikov Department of Chemistry, St Petersburg State University, Universitetsky prosp. 26, Petrodvorets, 198504 St Petersburg, Russian Federation. Fax (7-812) 428 69 39, tel. (7-812) 428 40 21, e-mail: Alexander.Khlebnikov@pobox.spbu.ru (A F Khlebnikov), Mikhail.Novikov@pobox.spbu.ru (M S Novikov), rkost@PK1198.spb.ru (R R Kostikov)

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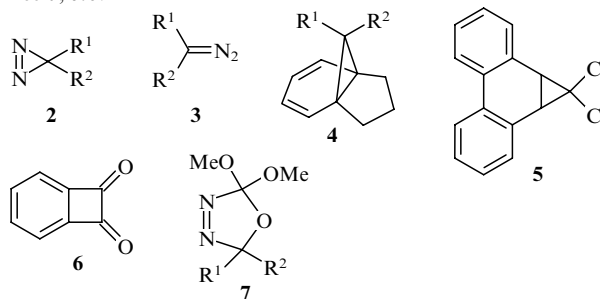
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## II. Spectroscopic methods for identification of iminium ylides

With rare exception, nitrogen ylides represent unstable intermediates that can nevertheless be identified by spectroscopic methods. Thus ylide species were detected by spectroscopy upon reactions of carbenes with various nitrogen-containing compounds<sup>7</sup> such as amines,<sup>8–10</sup> nitriles<sup>8, 11–13</sup> and pyridine.<sup>14, 15</sup> Carbenes react with pyridine at the maximum rate; therefore, this reaction is considered to be ideal for measuring absolute rates of carbene reactions and was used as a basis for the so-called 'pyridine probe technique'.<sup>16, 17</sup> A vast array of ylides **1** have been prepared from pyridine and diverse carbenes in the past 15 years.



Ylides **1** are prepared in solutions or on matrices using flash vacuum thermolysis (FVT) or laser flash photolysis (LFP) of various compounds such as diazirines **2**, aliphatic diazo compounds **3**, tricyclo[4.3.1.0<sup>1,6</sup>]deca-2,4-diene derivatives **4**, the adduct of dichlorocarbene with phenanthrene (**5**), bicyclo[4.2.0]octa-1,3,5-triene-7,8-dione (**6**), substituted 1,3,4-oxadiazolines **7**, etc.



The ylides **1** formed manifest a characteristic absorption in the UV or the visible region of the spectrum related to the  $\pi \rightarrow \pi^*$ -transition similar to the *B*-band in benzene derivatives. The wavelength of the absorption band depends on the type of the substituents R<sup>1</sup> and R<sup>2</sup> in the ylide **1**:  $\lambda_{\max} = 340–380$  nm for dialkyl- or monochloro-substituted ylides,  $\lambda_{\max} = 390–450$  nm for dihalogeno ylides and  $\lambda_{\max} = 430–480$  nm for phenyl- or carbonyl-substituted ylides. The absorption maxima of pyridi-

nium ylides in the UV region and the absolute rate constants for the formation are listed in Table 1 (for comparison, the rate constants for the reactions of carbenes with tetramethylethylene are given). These data suggest that carbenes react with pyridine several times (from 2 to 30) faster than with tetramethylethylene. The majority of carbenes react with pyridine with the rate constants ranging from  $10^8$  to  $10^{10}$  litre mol $^{-1}$  s $^{-1}$ . Lower activities are characteristic of methoxy carbenes (presumably, by virtue of their nucleophilic nature) as well as of adamantylidene and chloro(2,2-dimethylcyclopropyl)carbene, which can be attributed to steric factors.

The activation parameters of the addition reaction of the singlet carbenes RCIC: to pyridine have been determined:

| R          | $E_a$ /kJ mol $^{-1}$ | log $A$       | Ref. |
|------------|-----------------------|---------------|------|
| Ph         | $5.4 \pm 2.0$         | $9.7 \pm 0.2$ | 66   |
| PhOCH $_2$ | $5.8 \pm 0.8$         | 10.9          | 67   |
| MeOC(O)    | $11.1 \pm 0.8$        | $9.1 \pm 0.2$ | 40   |

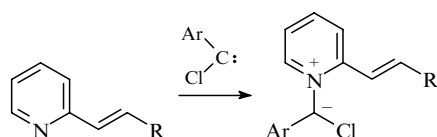
The rates of formation of ylides ( $\lambda_{\max} = 540$  nm) in the reactions of phenyl- and (4-chlorophenyl)chlorocarbenes with some substituted pyridines have been determined.<sup>68</sup>

**Table 1.** The rate constants for the reactions of singlet carbenes R<sup>1</sup>R<sup>2</sup>C: with tetramethylethylene (TME) and pyridine (Py) and the absorption bands of ylides **1** in the UV region at room temperature.

| Carbene source | R <sup>1</sup>           | R <sup>2</sup>                                                                    | $k_{\text{TME}}$ /litre mol $^{-1}$ s $^{-1}$ | $k_{\text{Py}}$ /litre mol $^{-1}$ s $^{-1}$ | $\lambda_{\max}$ /nm | Ref.   |
|----------------|--------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------|----------------------|--------|
| 4              | F                        | Cl                                                                                | $(1.1 - 2.9) \times 10^8$                     | $8 \times 10^9$                              | 450                  | 18     |
| 5              | Cl                       | Cl                                                                                | $(3.8 \pm 0.2) \times 10^9$                   | $(7.9 \pm 0.2) \times 10^9$                  | 390                  | 19     |
| 4              | Cl                       | Br                                                                                | $6 \times 10^9$                               | —                                            | 407                  | 20     |
| 4              | Br                       | Br                                                                                | $2.8 \times 10^9$                             | $5 \times 10^9$                              | 436                  | 20     |
| 2              | Cl                       | Me                                                                                | $(1.32 \pm 0.06) \times 10^9$                 | $(8.9 \pm 0.1) \times 10^9$                  | 360                  | 21, 22 |
| 2              | Cl                       | Pr <sup>i</sup>                                                                   | —                                             | $(1.1 \pm 0.3) \times 10^{10}$               | —                    | 22     |
| 2              | Cl                       | cyclo-Pr                                                                          | $(1.2 \pm 0.1) \times 10^7$                   | $7.4 \times 10^8$                            | 370                  | 23     |
| 2              | Cl                       | cyclo-Pr                                                                          | —                                             | $(4.7 \pm 0.3) \times 10^8$                  | —                    | 22, 24 |
| 2              | Cl                       |  | —                                             | $(4.7 \pm 0.2) \times 10^7$                  | 275                  | 25     |
| 2              | Cl                       | cyclo-Bu                                                                          | —                                             | $(2.0 \pm 0.2) \times 10^8$                  | 375                  | 26     |
| 2              | Cl                       | Bu <sup>t</sup>                                                                   | —                                             | $(2.4 \pm 0.2) \times 10^9$                  | 376                  | 16, 22 |
| 2              | Cl                       | Bu <sup>t</sup>                                                                   | —                                             | $(4.2 \pm 0.2) \times 10^9$                  | —                    | 27     |
| 2              | Cl                       | PhCH $_2$                                                                         | $(1.2 \pm 0.1) \times 10^8$                   | $(4.2 \pm 0.2) \times 10^9$                  | 379                  | 28     |
| 2              | Cl                       | PhCH $_2$                                                                         | —                                             | $(7.5 \pm 0.5) \times 10^9$                  | —                    | 22, 29 |
| 2              | Cl                       | PhCH $_2$                                                                         | $1.31 \times 10^8$                            | —                                            | —                    | 30     |
| 2              | Cl                       | 4-CF $_3$ C $_6$ H $_4$ CH $_2$                                                   | $(5.7 \pm 0.3) \times 10^8$                   | $(1.4 \pm 0.2) \times 10^{10}$               | 380                  | 31     |
| 2              | Cl                       | 4-ClC $_6$ H $_4$ CH $_2$                                                         | $(5.5 \pm 0.5) \times 10^8$                   | $(1.8 \pm 0.4) \times 10^{10}$               | 380                  | 31     |
| 2              | F                        | PhOCH $_2$                                                                        | —                                             | $(1.4 \pm 0.1) \times 10^{10}$               | 380                  | 32     |
| 2              | Cl                       | PhOCH $_2$                                                                        | —                                             | $(1.2 \pm 0.1) \times 10^{10}$               | 380                  | 32     |
| 2              | F                        | Ph                                                                                | $(1.6 \pm 0.2) \times 10^8$                   | $(1.5 \pm 0.2) \times 10^9$                  | 460                  | 32     |
| 2              | Cl                       | Ph                                                                                | $(1.2 \pm 0.1) \times 10^8$                   | $(3.4 \pm 0.3) \times 10^8$                  | 475                  | 16, 33 |
| 2              | Cl                       | Ph                                                                                | $(2.8 \pm 0.2) \times 10^8$                   | $(7.6 \pm 0.9) \times 10^8$                  | —                    | 26, 34 |
| 2              | Cl                       | Ph                                                                                | —                                             | $(1.5 \pm 0.2) \times 10^9$                  | 480                  | 32     |
| 2              | Cl                       | Ph                                                                                | $1.3 \times 10^8$                             | —                                            | —                    | 35     |
| 2              | Cl                       | Ph                                                                                | —                                             | $(3.7 \pm 0.4) \times 10^8$                  | —                    | 36     |
| 2              | Cl                       | 4-MeC $_6$ H $_4$                                                                 | $1.2 \times 10^8$                             | $(2.9 \pm 0.3) \times 10^8$                  | 430                  | 37     |
| 2              | Cl                       | 4-MeOC $_6$ H $_4$                                                                | $1.4 \times 10^7$                             | —                                            | —                    | 26     |
| 2              | Cl                       | 4-MeOC $_6$ H $_4$                                                                | —                                             | $(2.9 \pm 0.4) \times 10^7$                  | 460                  | 36     |
| 2              | Cl                       | 4-MeOC $_6$ H $_4$                                                                | —                                             | $(1.58 \pm 0.05) \times 10^8$                | 460                  | 37     |
| 2              | Cl                       | 4-NO $_2$ C $_6$ H $_4$                                                           | —                                             | $(2.3 \pm 0.4) \times 10^9$                  | 665                  | 36     |
| 2              | Cl                       | 4-NO $_2$ C $_6$ H $_4$                                                           | —                                             | $(7.5 \pm 0.1) \times 10^9$                  | 605                  | 37     |
| 2              | Cl                       | 4-NO $_2$ C $_6$ H $_4$                                                           | $1.2 \times 10^9$                             | —                                            | —                    | 38     |
| 2              | Br                       | Ph                                                                                | —                                             | $(1.2 \pm 0.1) \times 10^9$                  | 480                  | 32     |
| 2              | Br                       | Ph                                                                                | $(3.8 \pm 0.3) \times 10^8$                   | —                                            | —                    | 36     |
| 4              | Cl                       | CN                                                                                | —                                             | $5 \times 10^9$                              | 450                  | 39     |
| 4              | Cl                       | CO $_2$ Me                                                                        | $4.1 \times 10^8$                             | $2 \times 10^9$                              | 440                  | 40     |
| 2              | tetraphenylglucosylidene | —                                                                                 | —                                             | $8.9 \times 10^8$                            | 500                  | 41     |
| 2              | OMe                      | Me                                                                                | —                                             | $(6.6 \pm 0.7) \times 10^5$                  | 380                  | 32     |
| 2              | OMe                      | CF $_3$                                                                           | $(4.5 \pm 0.2) \times 10^6$                   | $(4.3 \pm 0.1) \times 10^9$                  | 375                  | 42     |
| 2              | OCH $_2$ CF $_3$         | Me                                                                                | —                                             | $(1.6 \pm 0.2) \times 10^7$                  | 380                  | 32     |
| 2              | OCH $_2$ CF $_3$         | cyclo-Pr                                                                          | —                                             | $(1.0 \pm 0.1) \times 10^6$                  | 385                  | 32     |
| 2              | OMe                      | Ph                                                                                | —                                             | $(1.2 \pm 0.1) \times 10^5$                  | 480                  | 32     |
| 2              | OMe                      | Ph                                                                                | —                                             | $6.9 \times 10^4$                            | —                    | 43     |
| 2              | OCH $_2$ CF $_3$         | Ph                                                                                | —                                             | $(1.8 \pm 0.2) \times 10^6$                  | 465                  | 32     |
| 2              | OAc                      | Ph                                                                                | $1 \times 10^6$                               | $(3.5 \pm 0.3) \times 10^7$                  | 480                  | 43, 44 |
| 2              | OCOPh                    | Ph                                                                                | —                                             | $(2.1 \pm 0.1) \times 10^8$                  | 470                  | 43     |
| 2              | OCOBu <sup>t</sup>       | Ph                                                                                | —                                             | $(7.4 \pm 0.1) \times 10^7$                  | 470                  | 43     |
| 2              | OSiMe $_3$               | Ph                                                                                | —                                             | —                                            | —                    | 45     |
| 2              | Cl                       | MeO                                                                               | —                                             | —                                            | 472                  | 32     |
| 2              | Cl                       | OCH $_2$ CF $_3$                                                                  | —                                             | —                                            | 400                  | 32     |

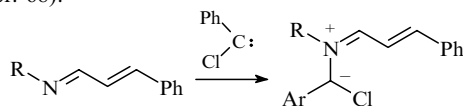
Table 1 (continued).

| Carbene source | R <sup>1</sup>                                              | R <sup>2</sup>                    | $k_{\text{TME}}/\text{litre mol}^{-1} \text{ s}^{-1}$ | $k_{\text{Py}}/\text{litre mol}^{-1} \text{ s}^{-1}$ | $\lambda_{\text{max}}/\text{nm}$ | Ref.   |
|----------------|-------------------------------------------------------------|-----------------------------------|-------------------------------------------------------|------------------------------------------------------|----------------------------------|--------|
| 2              | OCH <sub>2</sub> CF <sub>3</sub>                            | PhOCH <sub>2</sub>                | —                                                     | $(8.6 \pm 0.9) \times 10^8$                          | 390                              | 32     |
| 2              | OAc                                                         | PhOCH <sub>2</sub>                | —                                                     | $(1.03 \pm 0.06) \times 10^9$                        | 390                              | 32, 44 |
| 6              | — <i>o</i> -C <sub>6</sub> H <sub>4</sub> C(O)O—            | —                                 | —                                                     | $(7.7 \pm 0.4) \times 10^8$                          | 575                              | 46     |
| 3              | —C(O)O—CMe <sub>2</sub> —OC(O)—                             | —                                 | —                                                     | $(1-5) \times 10^9$ (see <sup>a</sup> )              | 530                              | 47     |
| 2              | H                                                           | Cl                                | $8.1 \times 10^9$                                     | $8 \times 10^9$                                      | 374                              | 48     |
| 3              | H                                                           | CHO                               | —                                                     | $(1-5) \times 10^9$ (see <sup>a</sup> )              | 460                              | 49     |
| 3              | H                                                           | CO <sub>2</sub> Et                | —                                                     | $(1-5) \times 10^9$ (see <sup>a</sup> )              | 430                              | 50     |
| 2              | H                                                           | cyclo-Pr                          | —                                                     | $(1-5) \times 10^9$ (see <sup>a</sup> )              | 379                              | 51     |
| 3              | H                                                           | Ph                                | —                                                     | $1 \times 10^9$ (see <sup>a</sup> )                  | 460                              | 52     |
| 3              | H                                                           | C <sub>6</sub> F <sub>5</sub>     | —                                                     | $1 \times 10^9$ (see <sup>a</sup> )                  | 450                              | 53     |
| 2              | H                                                           | 1-adamantyl                       | —                                                     | $1 \times 10^9$ (see <sup>a</sup> )                  | 370                              | 54     |
| 2              | Me                                                          | Me                                | —                                                     | —                                                    | 364                              | 55, 56 |
| 2              | Me                                                          | Me                                | —                                                     | $3 \times 10^9$                                      | —                                | 57     |
| 7              | Pr                                                          | Pr                                | —                                                     | $3 \times 10^9$ (see <sup>a</sup> )                  | 360                              | 58     |
| 2              | adamantylidene                                              | —                                 | —                                                     | $(1.5 \pm 0.2) \times 10^6$                          | 337                              | 59     |
| 2              | homocuban-9-ylidene                                         | —                                 | $(0.7-1.2) \times 10^8$                               | $3.4 \times 10^8$                                    | 400                              | 60, 61 |
| 3              | Me                                                          | Ph                                | —                                                     | $1 \times 10^9$                                      | 450                              | 62     |
| 2              | CF <sub>3</sub>                                             | 4-MeC <sub>6</sub> H <sub>4</sub> | —                                                     | $4 \times 10^8$                                      | 420                              | 63     |
| 3              | — <i>o</i> -C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> — | —                                 | $1.9 \times 10^8$                                     | $3.7 \times 10^8$                                    | 455–460                          | 64, 65 |
| 3              | CO <sub>2</sub> Me                                          | CO <sub>2</sub> Me                | —                                                     | $(1-5) \times 10^9$ (see <sup>a</sup> )              | 450                              | 47     |

<sup>a</sup> The tentative value is presented.

| Ar                                | R                                 | $k \times 10^{-8}/\text{litre mol}^{-1} \text{ s}^{-1}$ |
|-----------------------------------|-----------------------------------|---------------------------------------------------------|
| 4-ClC <sub>6</sub> H <sub>4</sub> | H                                 | 2.0                                                     |
|                                   | Ph                                | $3.6 \pm 0.2$                                           |
|                                   | 4-ClC <sub>6</sub> H <sub>4</sub> | $4.0 \pm 0.2$                                           |
|                                   | 4-MeC <sub>6</sub> H <sub>4</sub> | $2.6 \pm 0.2$                                           |
| Ph                                | Ph                                | 2.3                                                     |
|                                   | 2-Py                              | 3.7                                                     |
|                                   | 4-Py                              | $13 \pm 1$                                              |

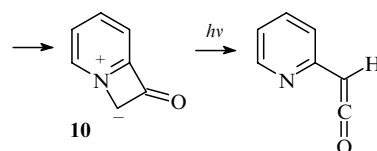
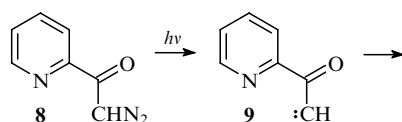
In the reaction of chloro(phenyl)carbene with *trans*-1-phenyl- and 1,5-diphenyl-4-azapenta-1,3-diene, the corresponding ylides ( $\lambda_{\text{max}} = 550 \text{ nm}$ ) are formed with the rate constants of  $(1.0 \pm 0.1) \times 10^9$  and  $(3.6 \pm 0.2) \times 10^8 \text{ litre mol}^{-1} \text{ s}^{-1}$  (see Ref. 68).



R = Me, Bn.

In all these cases, the C=C bond is inactive with respect to carbene.

Studies on matrix photolysis of 2-(diazooacetyl)pyridine (**8**) ( $\nu_{\text{C=O}} = 1652 \text{ cm}^{-1}$ ) using time-resolved infrared spectroscopy (TRIR) have shown that compound **8** yields carbene **9**, which undergoes intramolecular cyclisation into ylide **10** with a characteristic band  $\nu_{\text{C=O}}$  at  $1759 \text{ cm}^{-1}$ . Upon subsequent photolysis at  $\lambda_{\text{max}} > 320 \text{ nm}$ , the ylide **10** is converted into (2-pyridyl)ketene ( $\nu_{\text{C=C=O}} = 2123-2132 \text{ cm}^{-1}$ ).<sup>69</sup>



Studies of reactions of triplet carbenes with pyridine revealed that in this case ylide intermediates are also formed, but the rate constants for their formation are significantly lower (by more than an order of magnitude) than the rate constants for ylide formation from singlet carbenes (Table 2). This is especially noticeable in the case of sterically hindered carbenes (e.g., with a trypticyl substituent).<sup>71</sup> Since the ylide formed exists in the singlet state, it was assumed that the triplet carbene first passes into the singlet state and then reacts with pyridine. Hence, the rate constant for the reaction of a triplet carbene with pyridine comprises the equilibrium constant between the triplet and the singlet carbenes. These considerations were employed for the calculation of the energies of the triplet–singlet conversions of aryl carbenes.<sup>52, 53</sup>

It is known that the triplet diphenylcarbene is 12–16 kJ mol<sup>−1</sup> more stable than the singlet one. Studies of the reaction of diphenylcarbene with pyridine have shown that the activation barrier for the formation of ylides from the triplet diphenylcarbene is equal to 8–12 kJ mol<sup>−1</sup>, which is smaller than the aforementioned difference in the stabilities of states. Thus, it was suggested<sup>69</sup> that the mechanism of the reaction of diphenylcarbene with pyridine does not include preliminary conversion of the triplet carbene into the singlet carbene. Presumably, the triplet and singlet potential reaction surfaces are crossed in this case.<sup>69</sup>

### III. Ylides from metallocarbenoids

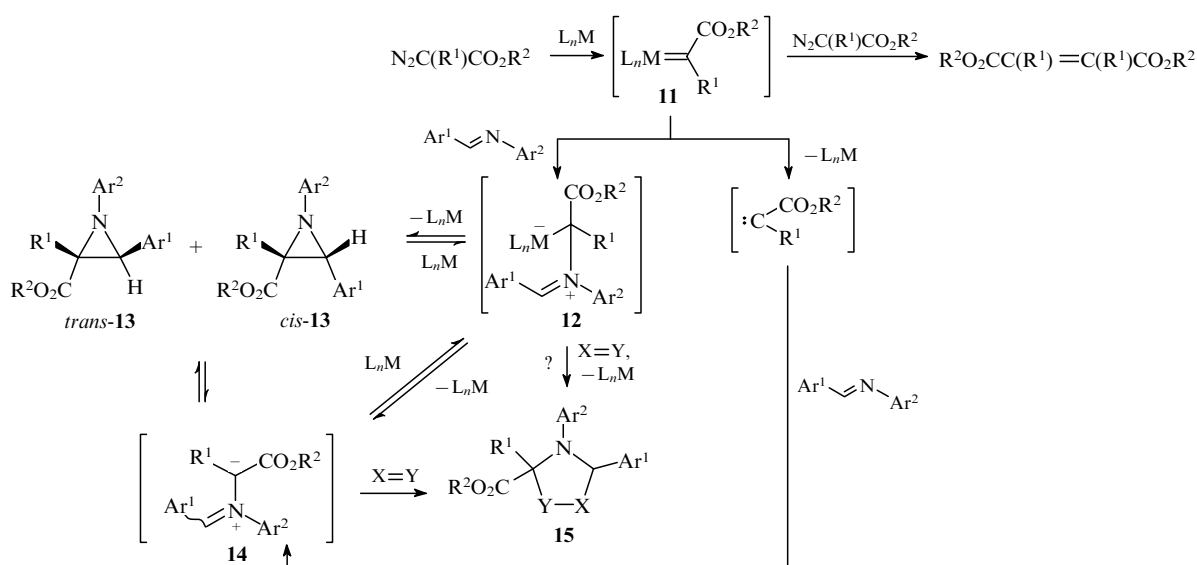
Reactions of diazo compounds with imines form the basis of an important procedure for the preparation of aziridines and aziridine-2-carboxylic acid derivatives in particular. Let us consider two main types of catalytic reactions of diazo compounds with imines leading to aziridines. The first, so-called ‘carbene’ type reaction (Scheme 1) consists of the reaction of a diazo compound with a metallocarbenoid catalyst that gives an unstable metallocarbenoid **11**. The reaction of the latter with the unshared electron pair of an imine results in the complex **12**, which either undergoes cyclisation into aziridine **13** or is converted into



**Table 2.** Rate constants for reactions of the triplet carbenes  $R^1R^2C:$  with pyridine, and absorption bands of ylides **1** in the UV region at room temperature.

| Carbene source | $R^1$      | $R^2$                                           | $k_{Py}$ /litre mol <sup>-1</sup> s <sup>-1</sup> | $\lambda_{max}$ /nm | Ref. |
|----------------|------------|-------------------------------------------------|---------------------------------------------------|---------------------|------|
| <b>3</b>       | H          | 1-naphthyl                                      | —                                                 | 535                 | 8    |
| <b>3</b>       | H          | Ph                                              | $9.3 \times 10^6$                                 | 450                 | 52   |
| <b>3</b>       | H          | Ph                                              | $(1.9 \pm 0.3) \times 10^7$                       | —                   | 53   |
| <b>3</b>       | H          | mesityl                                         | $1.35 \times 10^7$                                | 430                 | 52   |
| <b>3</b>       | H          | C <sub>6</sub> F <sub>5</sub>                   | $5.1 \times 10^7$                                 | 450                 | 53   |
| <b>3</b>       | Me         | Ph                                              | $(2.00 \pm 0.01) \times 10^7$                     | 450                 | 62   |
| <b>3</b>       | Me         | 4-MeOC <sub>6</sub> H <sub>4</sub>              | $(1.01 \pm 0.03) \times 10^8$                     | 427                 | 62   |
| <b>3</b>       | Me         | 4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> | $(2.56 \pm 0.09) \times 10^7$                     | 520                 | 62   |
| <b>3</b>       | Ph         | Ph                                              | $(2.8 - 4.2) \times 10^5$                         | 500                 | 70   |
| <b>2</b>       | Ph         | trypticen-1-yl                                  | $1 \times 10^4$                                   | 380                 | 71   |
| <b>2</b>       | 1-naphthyl | trypticen-1-yl                                  | $1.2 \times 10^2$                                 | 380                 | 71   |
| <b>2</b>       | 2-naphthyl | trypticen-1-yl                                  | $6 \times 10^3$                                   | 380                 | 71   |

Scheme 1

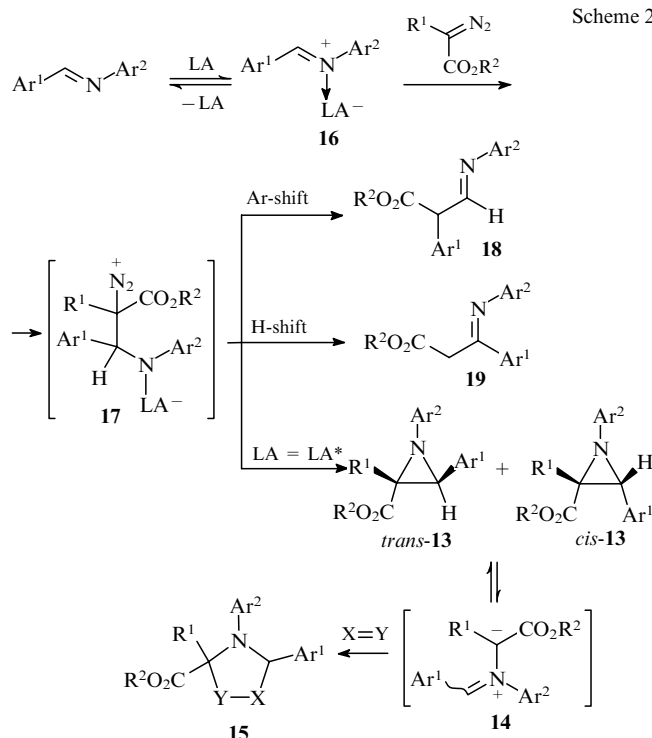


azomethine ylide **14** the cyclisation of which also yields aziridine **13**. If the formation of aziridines occurs *via* the complex **12**, the use of a catalyst with chiral ligands yields optically active products. In contrast, the formation of aziridines *via* free azomethine ylide **14** would result in a racemate. In the presence of dipolarophiles  $X=Y$ , azomethine ylide **14** yields the [3 + 2]-cycloaddition products **15** which can probably be formed *via* the intermediate **12**.

The second, 'non-carbene' type reaction (Scheme 2) includes the reaction of the unshared electron pair of an imine with a Lewis acid (LA) to give a complex **16**; in certain cases, this is stable. Increased electrophilicity of the latter in comparison with the free imine favours the addition of a nucleophilic diazo compound (e.g., diazoacetates) to give the intermediate **17**, which eliminates the nitrogen molecule to give aziridines **13** (the use of chiral Lewis acids  $LA^*$  affords optically active products). Compounds **18** and **19** are obtained as side products in this reaction.

Many papers were devoted to the search for efficient catalysts for the reactions of diazoacetates ( $N_2CHCO_2R$ ) with imines resulting in aziridines, especially optically active aziridines. It was shown<sup>72</sup> that it is upon Cu-catalysed thermolysis of ethyl diazoacetate that ethoxycarbonylcarbene formed reacted with  $Bu^tCH=NMe$ ,  $PhCH=NBu^t$  and  $PhCH=NPh$  to give the corresponding 2-ethoxycarbonylaziridines (yields 15%–30%). It was found that diazoacetates reacted *cis*-diastereoselectively to give predominantly *cis*-**13**, if Lewis acids [e.g.,  $BF_3$ ,<sup>73–77</sup>  $AlCl_3$ ,<sup>73,76</sup>  $TiCl_4$ ,<sup>73,76</sup>  $SnCl_4$ ,<sup>74,76,78,79</sup>  $TiCl_2(OPr^i)_2$ ,<sup>77</sup>], salts  $[Cu(OTf)_2]$ ,<sup>77,80</sup> 1-butyl-3-methylimidazolium tetrafluoroborate,<sup>81</sup>  $Ln(OTf)_3$ ,<sup>82,83</sup>  $Yb(OTf)_3$ ,<sup>75,77,82</sup>  $Zn(OTf)_2$ ,<sup>77</sup>] and the metal complexes  $\{[Cu(PF_6)(MeCN)_4]$ ,<sup>84</sup>  $[(\eta^5-C_5H_5)Fe(CO)_2]$ .

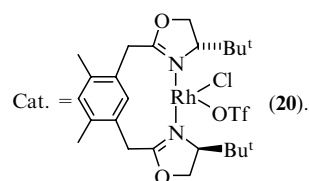
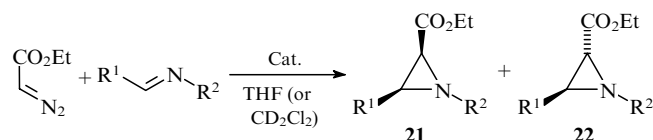
Scheme 2



$\cdot(\text{THF})]^+[\text{BF}_4]^-$  (Ref. 85) and  $\text{W(II)}^{86}$  were used as catalysts. Cu(II) salts that represent catalysts for carbene reactions of diazo compounds, on the one hand, and Lewis acids, on the other hand, direct the reactions with imines along the non-carbene pathway. Chiral catalysts<sup>84, 87, 88</sup> and reaction conditions have been found that allow preparation of the corresponding aziridines with a high enantiomeric excess.<sup>87, 88</sup>

At the same time, one cannot assert, with a full degree of confidence, that in the presence of rhodium<sup>89–92</sup> and rhenium<sup>93–95</sup> derivatives as efficient catalysts for carbene reactions of diazoesters, those resulting in aziridinecarboxylates proceed through the carbene pathway. In some cases, where the carbene pathway was suggested, the reaction was *trans*-diastereoselective<sup>90, 93–95</sup> and was accompanied by the formation of fumarates and maleates as side products. This is considered as indirect evidence for the involvement of carbene (carbenoid) intermediates. Dirhodium acetate is especially popular,<sup>89, 92</sup> while other derivatives, *e.g.*,  $[\text{Rh(III)-K10-alumina}, \text{Rh/C}]$ , are used less frequently.<sup>90</sup>

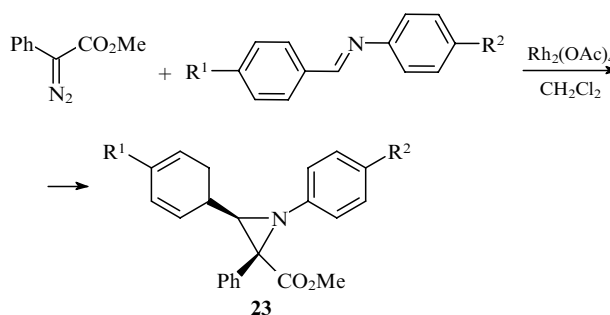
The reaction of ethyl diazoacetate with imines catalysed by the mononuclear rhodium catalyst **20**,<sup>91</sup> results in aziridines **21** and **22**.



| R <sup>1</sup>                            | R <sup>2</sup>                            | Solvent                         | Yield<br>( <b>21</b> + <b>22</b> ) (%) | Ratio <b>21</b> : <b>22</b> |
|-------------------------------------------|-------------------------------------------|---------------------------------|----------------------------------------|-----------------------------|
| Ph                                        | Ph                                        | THF                             | 46                                     | 75 : 25                     |
| <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> | Ph                                        | THF                             | 43                                     | 58 : 42                     |
| Ph                                        | <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> | THF                             | 47                                     | 73 : 27                     |
| Bu <sup>t</sup>                           | Ph                                        | THF                             | 40                                     | 70 : 30                     |
| Ph                                        | Bn                                        | THF                             | 12                                     | 86 : 14                     |
| <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> | <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> | THF                             | 43                                     | 71 : 29                     |
| <i>p</i> -HOC <sub>6</sub> H <sub>4</sub> | Ph                                        | THF                             | 29                                     | 90 : 10                     |
| Ph                                        | Ph                                        | CD <sub>2</sub> Cl <sub>2</sub> | 36                                     | 69 : 31                     |
| <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> | Ph                                        | CD <sub>2</sub> Cl <sub>2</sub> | 18                                     | 75 : 25                     |
| Ph                                        | <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> | CD <sub>2</sub> Cl <sub>2</sub> | 10                                     | 87 : 13                     |

The reaction with *N*-benzylideneaniline ( $\text{R}^1 = \text{R}^2 = \text{Ph}$ ) proceeds stereoselectively with the predominant formation of the *cis*-isomer **21** (3 : 1). The diastereoselectivity and the product yields are comparable with those achieved<sup>84</sup> with the copper complex  $[\text{Cu}(\text{PF}_6)(\text{MeCN})_4]$  as a catalyst with addition of a chiral ligand (*S,S*)-2,2-bis(4-phenyl-2-oxazolin-2-yl)propane. As to the enantioselectivity, this is significantly lower (*ee* ≤ 11%) than that reported<sup>84</sup> (*ee* = 35%–44%). The substitution of other ligands in the chiral Rh-catalyst results in the disappearance of the catalytic activity. The yields of products for the reaction carried out in THF are higher than those in dichloromethane.

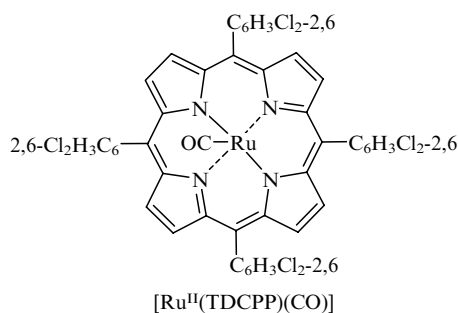
Aziridine **23** containing *cis*-aryl groups in positions 2 and 3 (see Ref. 92) is the reaction product of methyl diazophenylacetate with *N*-benzylideneanilines catalysed by  $\text{Rh}_2(\text{OAc})_4$ . This reaction occurs stereoselectively. It is believed that aziridine is formed as a result of cyclisation of the intermediate azomethine ylide.



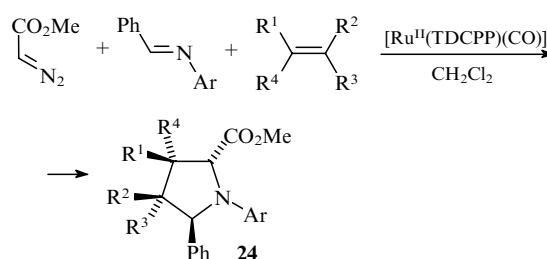
$\text{R}^1 = \text{R}^2 = \text{H}$  (79%);  $\text{R}^1 = \text{NO}_2$ ,  $\text{R}^2 = \text{H}$  (64%);  
 $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{NO}_2$  (89%).

Unfortunately, in the majority of studies aimed at the synthesis of aziridine-2-carboxylates, the possibility of interconversion of aziridines of the type **13** and ylides of the type **14** under reaction conditions (especially upon heating), which might influence significantly the stereoselectivity, was not analysed. The same is true of studies devoted to the synthesis of [3 + 2]-cycloaddition products of azomethine ylides of the type **14** generated in catalytic reactions of diazo compounds with imines in the presence of dipolarophiles.

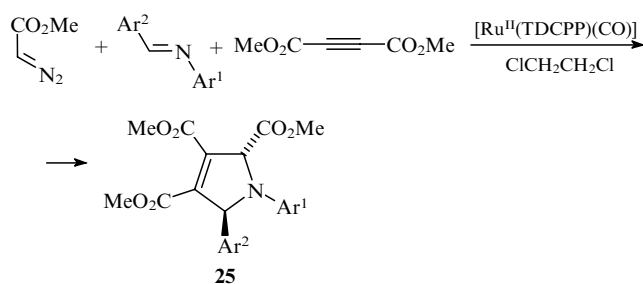
The porphyrin ruthenium complexes  $[\text{Ru}^{\text{II}}(\text{TDCPP})(\text{CO})]$



(0.1 mol.%) catalyse a three-component coupling of  $\alpha$ -diazo esters with *N*-benzylideneanilines and activated alkenes (or alkynes) resulting in the stereoselective formation of 2,5-*trans*-disubstituted pyrrolidines (**24**) or dihydropyrroles (**25**).<sup>96</sup>



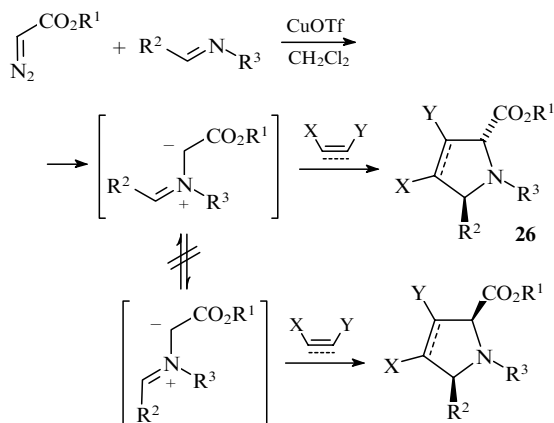
| Ar                                 | R <sup>1</sup> | R <sup>2</sup>     | R <sup>3</sup> | R <sup>4</sup> | Yield<br>of <b>24</b> (%) |
|------------------------------------|----------------|--------------------|----------------|----------------|---------------------------|
| Ph                                 | H              | CO <sub>2</sub> Me | H              | H              | 91                        |
| 4-MeOC <sub>6</sub> H <sub>4</sub> | H              | CO <sub>2</sub> Me | H              | H              | 63                        |
| 4-MeOC <sub>6</sub> H <sub>4</sub> | H              | C(O)Me             | H              | H              | 57                        |
| 4-MeOC <sub>6</sub> H <sub>4</sub> | H              |                    | H              | H              | 61                        |
| 4-MeOC <sub>6</sub> H <sub>4</sub> | H              | CO <sub>2</sub> Me | Me             | H              | 45                        |
| 4-MeOC <sub>6</sub> H <sub>4</sub> | H              | C(O)Ph             | H              | Ph             | 51                        |
| 4-MeOC <sub>6</sub> H <sub>4</sub> | H              | –C(O)N(Ph)C(O)–    | H              | H              | 52                        |



Ar<sup>2</sup> = Ph: Ar<sup>1</sup> = Ph (90%), 4-MeOC<sub>6</sub>H<sub>4</sub> (84%), 4-ClC<sub>6</sub>H<sub>4</sub> (85%),  
3-ClC<sub>6</sub>H<sub>4</sub> (69%), 2-ClC<sub>6</sub>H<sub>4</sub> (0%);  
Ar<sup>1</sup> = Ph: Ar<sup>2</sup> = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> (59%), 4-ClC<sub>6</sub>H<sub>4</sub> (92%),  
4-MeOC<sub>6</sub>H<sub>4</sub> (87%), 4-MeC<sub>6</sub>H<sub>4</sub> (98%),  
3-MeOC<sub>6</sub>H<sub>4</sub> (90%).

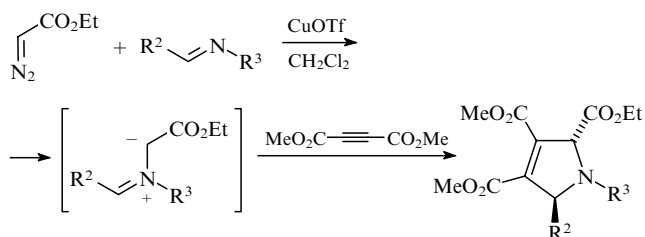
Considering the fact that porphyrin ruthenium(II) complexes form ruthenium–carbene complexes with diazo compounds, Li *et al.* suggested<sup>96</sup> that this reaction occurs *via* azomethine ylides, which undergo 1,3-dipolar cycloaddition with activated alkenes. In the case of non-symmetrical activated alkenes as dipolarophiles, one of two possible regioisomers was isolated. An increase in the steric crowding at the nitrogen atom of the imine hinders the reaction: *e.g.*, *N*-benzylidene-3-chloroaniline yields the cycloadduct with a lower yield than *N*-benzylidene-4-chloroaniline, whereas *N*-benzylidene-2-chloroaniline does not react at all.

Copper(I) triflate catalyses the reactions of various α-diazo esters with imines and alkenes (or alkynes) in dichloromethane to yield polysubstituted pyrrolidines (or dihydropyrroles) **26** (see Ref. 97). This reaction is stereo- and regioselective. It is suggested that the reaction of copper(I) with a diazo compound yields a metalcarbenoid, which forms an azomethine ylide with the imine, the ‘carbenoid’ carbon being in the *cis*-position relative to the substituent R<sup>2</sup>. It is noteworthy that no isomerisation of the ylide takes place, since only 2,5-*trans*-adducts are formed.



Dirhodium acetate Rh<sub>2</sub>(OAc)<sub>4</sub> also catalyses this reaction, but the yield of the adduct of ethyl diazoacetate with dimethyl acetylenedicarboxylate (DMAD) and *N*-benzylideneaniline is lower than in the case of copper(I) triflate. Dichloromethane appeared to be the solvent of choice; in other solvents, the yields were lower and no reaction occurred in THF or DME. The effects of the substituents in *N*-benzylideneanilines on the yields of the corresponding adducts were studied in reactions of ethyl diazoacetate with dimethyl acetylenedicarboxylate and various *N*-benzylideneanilines. It was found that nitrophenyl-substituted imines do not react. It was assumed that THF or DME as the solvent and

the nitro group in the imine decrease the activity of the catalyst due to complex formation.



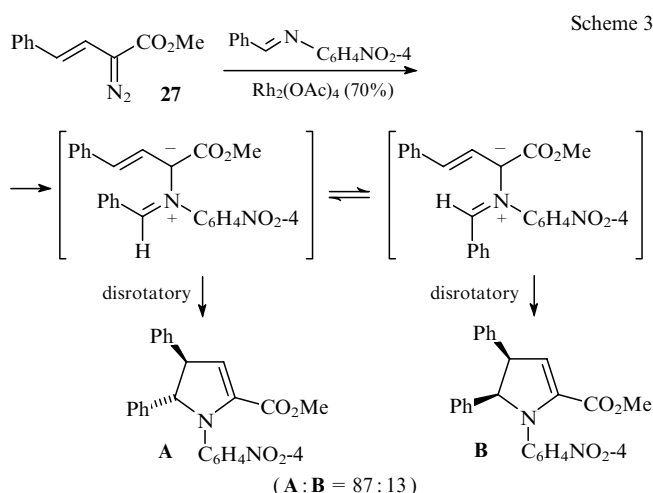
R<sup>2</sup> = Ph: R<sup>3</sup> = Ph (91%), 4-ClC<sub>6</sub>H<sub>4</sub> (75%), 4-MeOC<sub>6</sub>H<sub>4</sub> (43%),  
4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> (0%), Bn (43%);  
R<sup>3</sup> = Ph: R<sup>2</sup> = 4-ClC<sub>6</sub>H<sub>4</sub> (77%), 2-ClC<sub>6</sub>H<sub>4</sub> (74%), 4-BrC<sub>6</sub>H<sub>4</sub> (79%),  
4-MeC<sub>6</sub>H<sub>4</sub> (86%), 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> (0%), 4-MeOC<sub>6</sub>H<sub>4</sub> (54%),  
3-MeOC<sub>6</sub>H<sub>4</sub> (51%), 2-furyl (94%), cyclo-C<sub>6</sub>H<sub>11</sub> (35%).

| R <sup>1</sup>     | R <sup>2</sup>     | Yield (%) | A : B ratio |
|--------------------|--------------------|-----------|-------------|
| CO <sub>2</sub> Me | CO <sub>2</sub> Me | 77        | 2 : 1       |
| –C(O)N(Me)C(O)–    |                    | 70        | 2 : 1       |
| –C(O)OC(O)–        |                    | 55        | 5 : 1       |

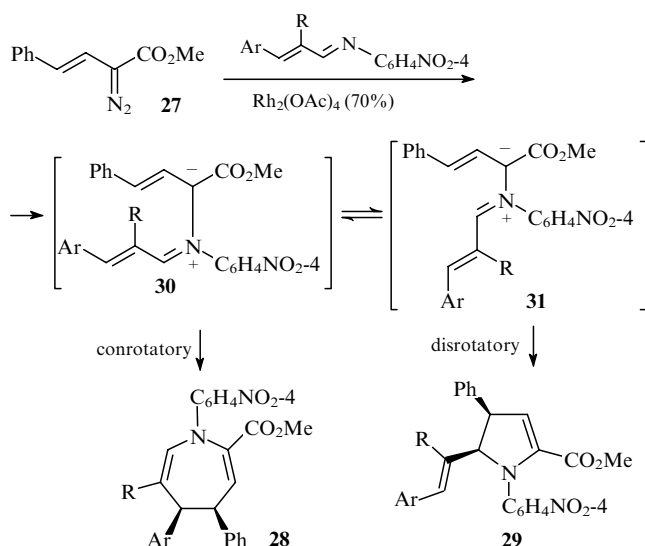
| R <sup>1</sup>     | R <sup>2</sup>     | Yield (%) | A : B ratio |
|--------------------|--------------------|-----------|-------------|
| CO <sub>2</sub> Et | CO <sub>2</sub> Et | 77        | 2 : 1       |
| CN                 |                    | 70        | 2 : 1       |
| Ph                 | PhC(O)             | 43        | 5 : 1       |
| H                  | CO <sub>2</sub> Et | 47        | 2 : 1       |

Diazostrylacetate (**27**) is an efficient reagent for the generation of azomethine ylides containing unsaturated fragments; their cyclisation affords dihydropyrroles or dihydroazepines with a high degree of stereocontrol and in high yields.<sup>98</sup> The reaction of diazostrylacetate with *N*-benzylidene-4-nitroaniline catalysed by Rh<sub>2</sub>(OAc)<sub>4</sub> yields dihydropyrrole derivatives predominantly as the *trans*-isomer, which can be attributed to the relative configurational stability of the ylides leading to particular stereoisomers (Scheme 3).

The catalytic reaction of the ester **27** with azadienes yields a mixture of dihydroazepine **28** and dihydropyrrole **29**. The presence of a methyl group in position 3 of the azadiene strongly affects the dihydroazepine : dihydropyrrole ratio. It is assumed that the introduction of a methyl group decreases the stability of



ylide **30** in comparison with ylide **31** resulting in the exclusive formation of dihydroazepine.

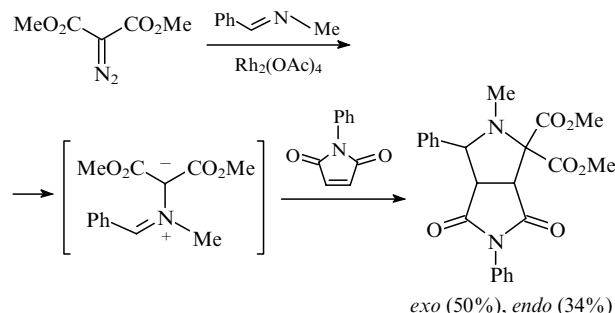


| R  | Ar                                               | Yield of <b>28</b> + <b>29</b> (%) | Ratio of <b>28</b> : <b>29</b> |
|----|--------------------------------------------------|------------------------------------|--------------------------------|
| H  | Ph                                               | 78                                 | 50 : 50                        |
| H  | C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> -4 | 78                                 | 68 : 32                        |
| Me | C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> -4 | 73                                 | 100 : 0                        |

The reactions of alkenyl-substituted diazo compounds **32** with imines **33** (Scheme 4) in the presence of various catalysts including Rh<sub>2</sub>(OAc)<sub>4</sub>, CuPF<sub>6</sub>, CuOTf and Cu(OTf)<sub>2</sub> have been studied.<sup>99</sup> It was found that the reaction of diazostyrylacetate (**32**, R = Ph)

with *N*-cinnamylidene-4-nitroaniline (**33a**, Ar = Ph) catalysed by dirhodium(II) acetate yields the corresponding dihydropyrrole **34**, whereas a similar reaction catalysed by copper salts with copper(II) triflate as the catalyst of choice affords dihydropyrrole **35**. This dependence of the reaction route on the catalyst was demonstrated for a broad range of compounds (Table 3). The results obtained prompted a conclusion that dihydropyrrole **34** is formed from ylide **A** derived upon addition of the imine **33** to the metallocarbenoid, whereas dihydropyrrole **35** is formed from the intermediate **B** resulting from electrophilic addition of the activated imine **33** to the diazo compound **32**.

The reaction of *N*-methylbenzylideneamine with dimethyl diazomalonate catalysed by Rh<sub>2</sub>(OAc)<sub>4</sub> in the presence of *N*-phenylmaleimide yielded 1,3-dipolar cycloaddition products.<sup>100</sup>



Metallocarbenoids obtained from diazo compounds reacted with heterocyclic compounds containing C=N bonds to give iminium ylides; the 1,3-dipolar cycloaddition of the latter to fumarates or DMAD is a convenient approach to the synthesis of fused heterocyclic compounds. Some examples of these reactions are given below.<sup>101, 102</sup>

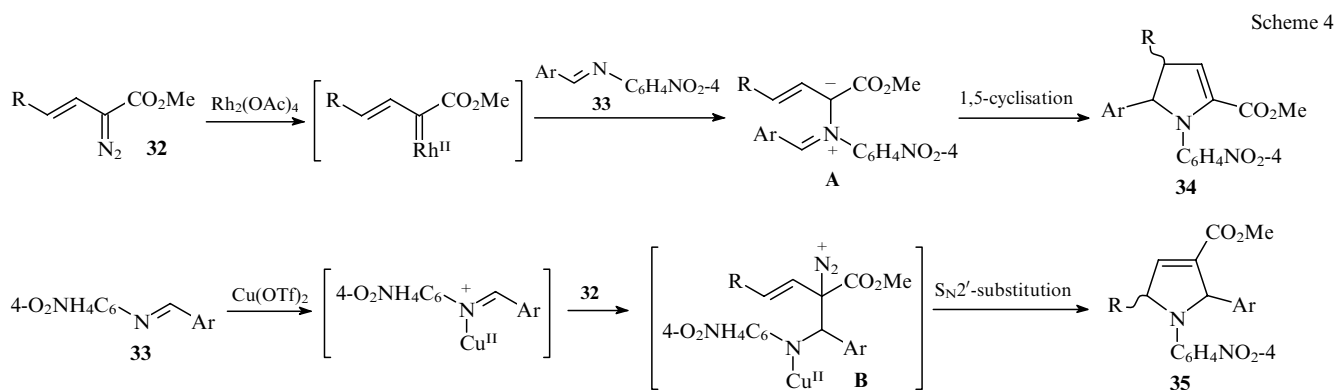
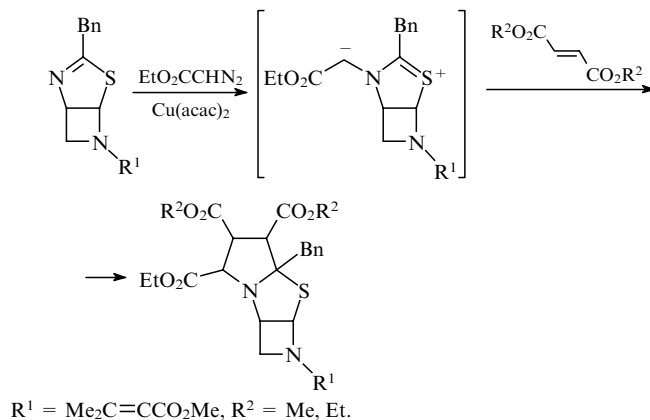
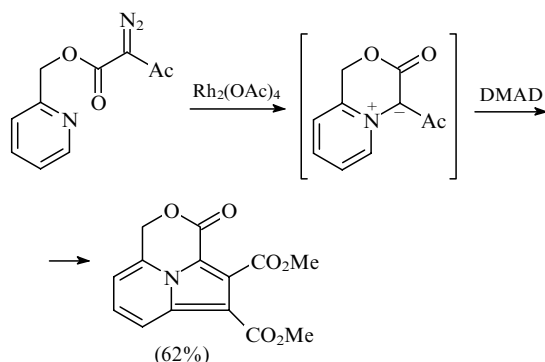
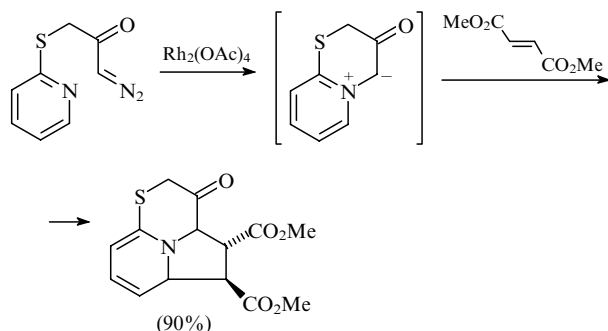
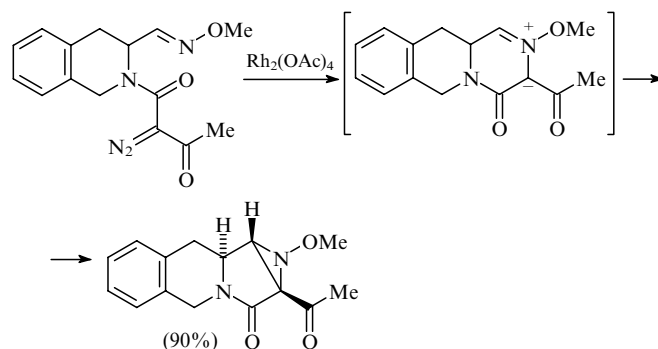
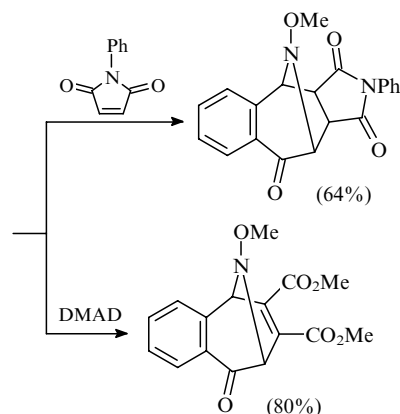
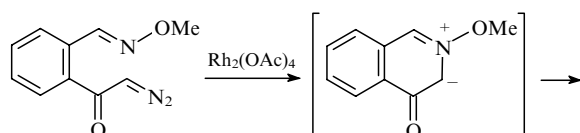
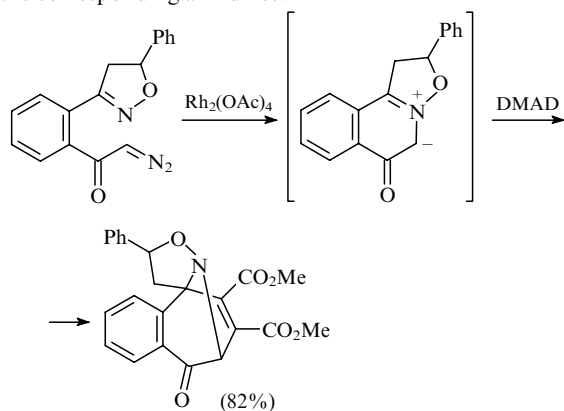


**Table 3.** Ratios and yields of catalytic reaction products of diazo compounds **32** with imines **33**.

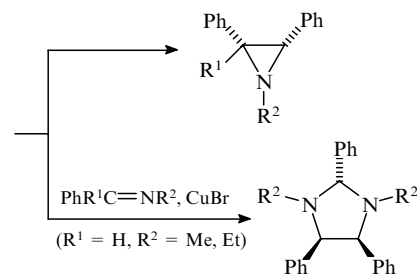
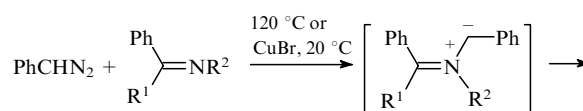
| R                  | Ar                                              | Reaction catalysed by Rh <sub>2</sub> (OAc) <sub>4</sub> |                                             | Reaction catalysed by Cu(OTf) <sub>2</sub> |                                             |
|--------------------|-------------------------------------------------|----------------------------------------------------------|---------------------------------------------|--------------------------------------------|---------------------------------------------|
|                    |                                                 | yield of product <b>34</b>                               | ratio of <i>trans</i> : <i>cis</i> -isomers | yield of product <b>35</b>                 | ratio of <i>trans</i> : <i>cis</i> -isomers |
| Ph                 | Ph                                              | 66                                                       | < 98 : 2                                    | 67                                         | 91 : 9                                      |
| Ph                 | 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> | 12                                                       | 100 : 0                                     | 40                                         | 98 : 2                                      |
| Ph                 | 4-ClC <sub>6</sub> H <sub>4</sub>               | 47                                                       | 100 : 0                                     | 66                                         | 96 : 4                                      |
| Ph                 | 4-MeC <sub>6</sub> H <sub>4</sub>               | 56                                                       | 100 : 0                                     | 63                                         | 88 : 12                                     |
| Ph                 | 4-MeOC <sub>6</sub> H <sub>4</sub>              | 62                                                       | 100 : 0                                     | 74                                         | 83 : 17                                     |
| Me                 | Ph                                              | 42                                                       | 90 : 10                                     | 0                                          |                                             |
| CO <sub>2</sub> Me | Ph                                              | 51                                                       | 93 : 7                                      | 0                                          |                                             |



*N*-Ylides generated as a result of an intramolecular attack of a metalcarbenoid on the unshared electron pair of the nitrogen atom of the *N*-alkoxyimino group either yield 1,3-dipolar cycloaddition products with dipolarophiles<sup>103</sup> or undergo cyclisation to the corresponding aziridines.<sup>104</sup>



The decomposition of phenyldiazomethane in the presence of imines results in azomethine ylides which undergo conrotatory cyclisation to give *cis*-aziridines in low yields. This cyclisation competes with the 1,3-cycloaddition of the ylide ( $R^1 = H$ ,  $R^2 = Me, Et$ ; CuBr as the catalyst) to the imine, which results in the corresponding imidazolidine.<sup>105</sup>



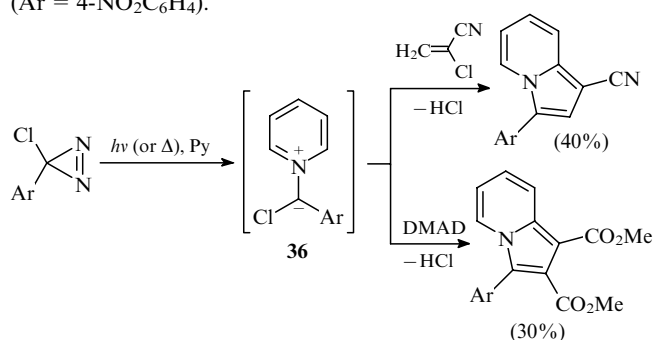
$R^1 = H, Me$ ;  $R^2 = Me, Et, Pr^i, Bu^t$ .

## IV. Ylides from halogeno carbenes

### 1. Ylides from alkyl- and aryl(chloro)carbenes

#### a. 1,3-Dipolar cycloaddition

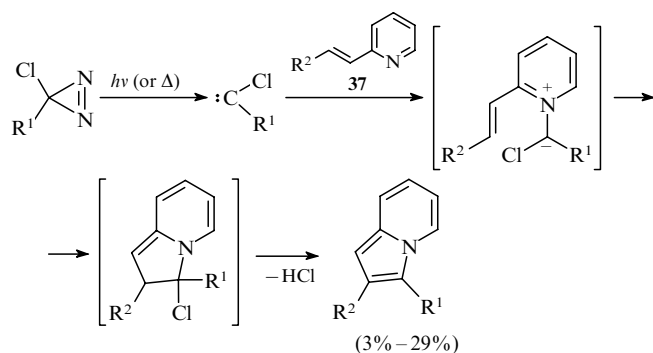
Photolysis or thermolysis of aryl chlorodiazirines in the presence of pyridine is a method for the generation of chloro-substituted pyridinium ylides **36**. Earlier studies have demonstrated the possibility of using these non-stabilised intermediates in the synthesis of indolizines by 1,3-dipolar cycloaddition to dimethyl acetylenedicarboxylate<sup>16</sup> and  $\alpha$ -chloroacrylonitrile.<sup>37</sup> The absolute rate constants for these reactions have recently been determined. Thus the rate constant for the reaction of dimethyl acetylenedicarboxylate with the ylide **36** (Ar = Ph) is equal to  $(1.57 \pm 0.06) \times 10^6$  litre mol<sup>-1</sup> s<sup>-1</sup> (see Refs 16 and 66).  $\alpha$ -Chloroacrylonitrile reacts with ylides **36** regioselectively; the absolute rate constants for various Ar are equal to  $(1.88 \pm 0.03) \times 10^7$  (Ar = 4-MeOC<sub>6</sub>H<sub>4</sub>),  $(1.46 \pm 0.04) \times 10^7$  (Ar = 4-MeC<sub>6</sub>H<sub>4</sub>),  $(7.7 \pm 0.4) \times 10^6$  (Ar = Ph) and  $(2.3 \pm 0.1) \times 10^5$  litre mol<sup>-1</sup> s<sup>-1</sup> (Ar = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>).



These results suggest that ylides behave as nucleophiles in the 1,3-dipolar addition.<sup>37</sup> The ylide prepared from 1-naphthylcarbene and pyridine undergoes cycloaddition to dimethyl fumarate [the rate constant for this reaction is equal to  $(5.3 \pm 1.0) \times 10^5$  litre mol<sup>-1</sup> s<sup>-1</sup>].<sup>8</sup> The rate constants for the ylide formed from chloro (methyl)carbene and pyridine with acrylonitrile or  $\alpha$ -chloroacrylonitrile are equal to  $(2.06 \pm 0.02) \times 10^7$  and  $(1.60 \pm 0.15) \times 10^8$  litre mol<sup>-1</sup> s<sup>-1</sup>, respectively.<sup>21</sup>

#### b. 1,5-Cyclisation

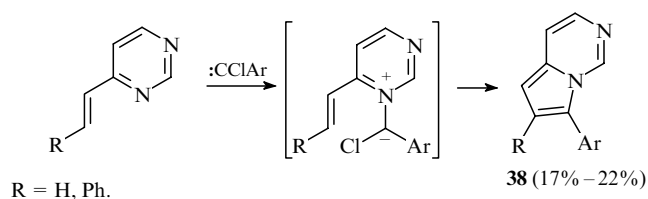
A multistep reaction of aryl(chloro)carbenes with 2-alkenylpyridines **37** and diazines, which involves ylide formation, 1,5-cyclisation and dehydrochlorination, is an alternative approach to the synthesis of indolizines and their hetero analogues.<sup>68,106</sup> Kinetic studies have shown that 1,5-cyclisation under conditions of vacuum flash photolysis of aryl(chloro)diazirines in isooctane in the presence of 2-vinylpyridine (**37**, R<sup>2</sup> = H) is characterised by



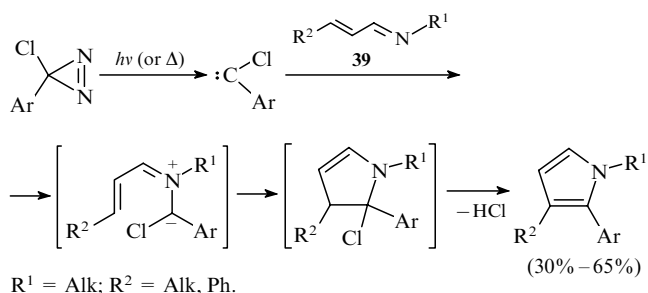
R<sup>1</sup> = Ar, Bn; R<sup>2</sup> = H, Ar, 2-pyridyl.

a noticeable activation barrier ( $E_a \approx 50$  kcal mol<sup>-1</sup>), which suggests that the transition state is somewhat compressed.<sup>107</sup> A phenyl substituent on the double bond favours the cyclisation by lowering this barrier to 33–37 kcal mol<sup>-1</sup>. Presumably, the dehydrochlorination step is fast, since in none of the cases studied were the primary cyclisation products (*viz.*, the corresponding dihydro-indolizines) detected even in trace amounts.

It was shown that the addition of chloro(phenyl)carbene derived upon photolysis of 3-chloro-3-phenyldiazirine to 1-(2-pyridyl)-2-(4-pyridyl)ethylene (**37**, R<sup>2</sup> = 4-pyridyl) is directed to the nitrogen atom of the *para*-, rather than the *ortho*-substituted pyridine ring.<sup>68</sup> No target indolizine could be obtained from this substrate. However, ylides generated from 4-vinyl- and 4-styrylpyrimidines where both reactive nitrogen atoms are localised in the same ring, do undergo 1,5-cyclisation resulting in pyrrolo[1,2-*c*]pyrimidines **38**.<sup>108</sup>

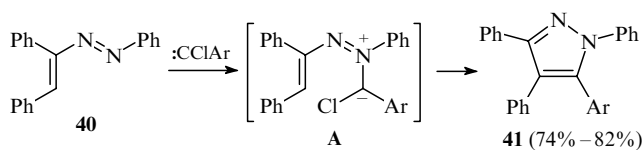


Ylides generated from azadienes **39** and aryl(chloro)carbenes represent acyclic analogues of 2-alkenylpyridinium ylides. These intermediates undergo cyclisation to give 1,2,3-trisubstituted pyrroles in yields exceeding those of the corresponding indolizines in an analogous reaction of pyridines.<sup>68,109</sup> The activation parameters of the 1,5-cyclisation of the 'azadiene' ylides are as follows:  $E_a = 47.0$ – $51.5$  kJ mol<sup>-1</sup>,  $\log A = 12.1$ – $12.9$ .



This reaction occurs smoothly both upon thermolysis in boiling benzene and in the photolysis in hexane and affords pyrroles in comparable yields. This method can also be used for the preparation of 2-heteryl-substituted pyrroles starting from (chloro)-2-pyridyl- and -2-thienylcarbenes, but in this case the yields of the reaction products do not exceed 15%.<sup>110</sup>

The azo compound **40** contains two sites reactive with respect to aryl(chloro)carbene, however, only one of the two ylides formed affords pyrazole as a result of 1,5-cyclisation. Indeed, thermolysis of some aryl(chloro)diazirines in the presence of the azo compound **40** yields the ylide intermediate **A**; cyclisation of the latter and subsequent elimination of HCl afford the tetraaryl-substituted pyrazoles **41** in high yields.<sup>108</sup>

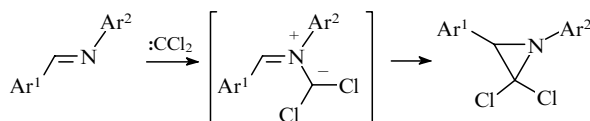


## 2. Ylides from dichlorocarbene

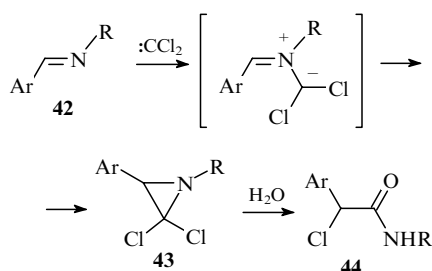
### a. Azomethine ylides from dichlorocarbene

Dichloro-substituted azomethine ylides formed upon reaction of azomethines with dichlorocarbene undergo three types of conversions: (1) 1,3-cyclisation, (2) 1,3-dipolar cycloaddition to dipolarophiles and (3) 1,4-H-shift. Which particular 'stabilisation' pathway occurs depends on the structure of the ylide which, in turn, depends on the structure of the starting imine.

**1,3-Cyclisation.** The analysis of the dependence of the chemical behaviour of *gem*-dichloro-substituted ylides on their geometry calculated by the MNDO method has demonstrated that cyclisation to *gem*-dichloroaziridines is more typical of ylides in which the dichloromethylene fragment is turned appreciably relative to the C=N=C plane (the angle  $\theta_1$  is equal to 34–50°). This type of ylide comprises intermediates generated upon reactions of dichlorocarbene with benzophenone *N*-alkylimines and benzaldehyde *N*-aryl- and *N*-alkylimines (the latter should contain secondary or tertiary alkyl substituents at the nitrogen atom). Reactions of *N*-arylbenzylideneamines with dichlorocarbene have long been known as a convenient method for the synthesis of aziridines;<sup>2, 111, 112</sup> however, experimental evidence in favour of the ylide mechanism of this conversion was obtained as late as 1993.<sup>113</sup>

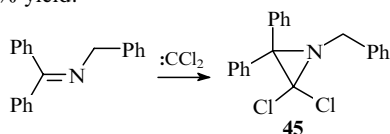


Substitution of the primary alkyl substituent at the nitrogen atom for an aryl substituent results in resinification of reaction mixtures (no aziridines could be obtained from such imines).<sup>114</sup> Sterically more crowded imines **42** containing an isopropyl, a cyclohexyl or a *tert*-butyl group on the nitrogen atom yield the desired aziridines **43** with dichlorocarbene generated upon treatment of chloroform with an alkali.<sup>114</sup> These are easily hydrolysed to the corresponding amides **44** (16%–95%) during column chromatography on silica gel. Nevertheless, some aziridines can be isolated in an analytically pure state in up to 80% yields.



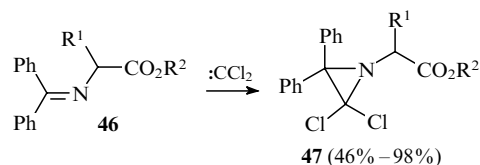
R = Pr<sup>i</sup>, Bu<sup>t</sup>, cyclo-C<sub>6</sub>H<sub>11</sub>.

Much more stable aziridines were prepared from benzophenone *N*-alkylimines. Thus *N*-benzhydrylidene-*N*-benzylamine reacts with dichlorocarbene to give *gem*-dichloroaziridine **45** in 72% yield.<sup>115</sup>



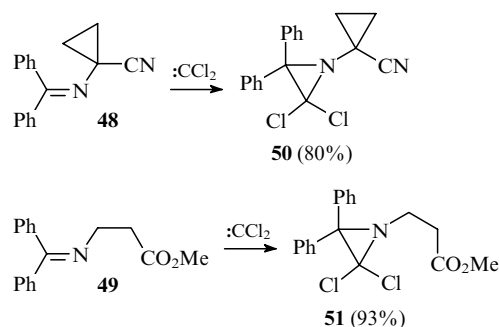
Aziridination of *N*-benzhydrylideneamino acid derivatives<sup>114, 115</sup> yields functionalised aziridines, which represent valuable building blocks for the synthesis of multifunctional amino acids, certain heteropolycyclic systems<sup>116</sup> and functionalised ketene imines, and is preparatively the most efficient among other reactions of benzophenone imines.<sup>117</sup> It has been found<sup>115</sup> that the nature of the transformation products of benzhydrylidene derivatives of glycine esters, alanine esters and related systems

depends significantly on the method used for the generation of dichlorocarbene. The reaction of dichlorocarbene generated in a KOH–CHCl<sub>3</sub>–Et<sub>3</sub>N<sup>+</sup>CH<sub>2</sub>Ph Cl<sup>–</sup> (TEBA) system with imines **46** was used for the preparation of *gem*-dichloroaziridines **47**.

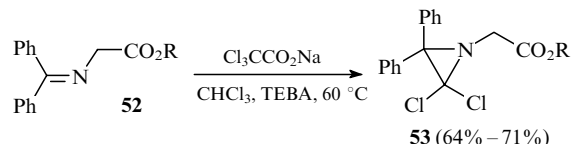


R<sup>1</sup> = Me, Et, Bn, CH<sub>2</sub>=CHCH<sub>2</sub>; R<sup>2</sup> = Me, Et.

Benzophenone imines **48** and **49** yield the corresponding aziridines **50** and **51** under identical conditions.

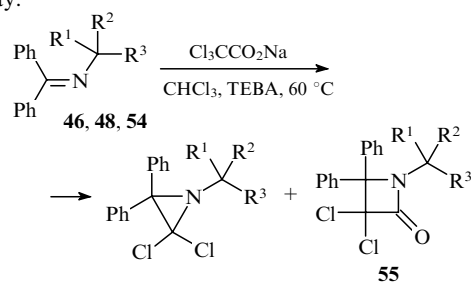


In contrast to the alanine derivatives **46**, **48** and **49**, the glycine derivatives **52** do not yield *gem*-dichloroaziridines with dichlorocarbene generated from chloroform upon alkaline treatment. Presumably, compounds **52** manifesting higher CH-acidity undergo deprotonation under the action of KOH, which changes the direction of the reaction. However, the use of a 'neutral' method of decomposition of sodium trichloroacetate for the thermocatalytic generation of dichlorocarbenes affords the desired *gem*-dichloroaziridines **53**.



R = Me, Et.

This method is also suitable for the synthesis of aziridines from sterically more crowded imines **54**; however, azetidinone **55** is formed as a side product; the relative yield of azetidinone increases with an increase in the steric volume of the substituents at the C=N bond. Studies using labelled compounds have shown that azetidine derivatives are formed through a non-carbene pathway.<sup>118</sup>

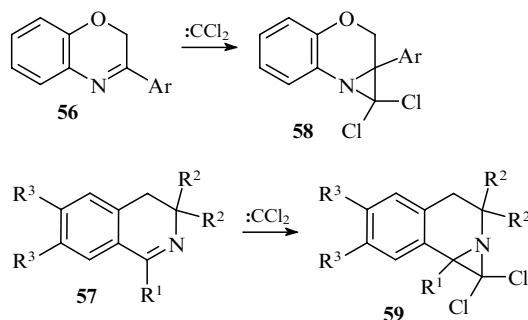


R<sup>1</sup> = H, R<sup>2</sup> = Alk, R<sup>3</sup> = CO<sub>2</sub>Me; R<sup>1</sup>–R<sup>2</sup> = CH<sub>2</sub>CH<sub>2</sub>, R<sup>3</sup> = CN.

Reactions of dichlorocarbene with substrates containing an endocyclic C=N bond have found applications in the synthesis of fused aziridine compounds. Thus benzoxazines **56** and substituted 3,4-dihydroisoquinolines **57** yield aziridinobenzoxazines **58**.<sup>119</sup>

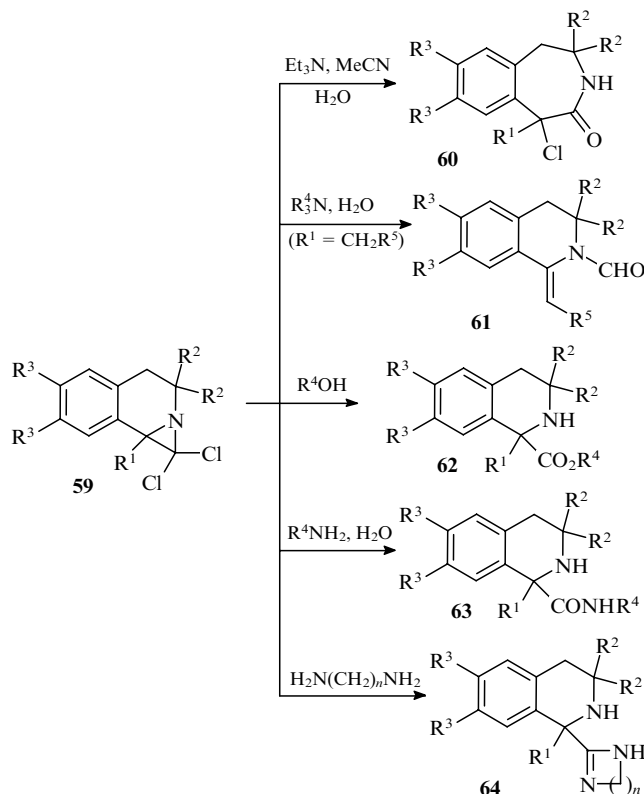


and aziridinoisoquinolines **59**, respectively, upon reaction with dichlorocarbene.<sup>114</sup>



$\text{R}^1 = \text{H, Alk, Ar}$ ;  $\text{R}^2 = \text{H, Alk}$ ;  $\text{R}_2^2 = (\text{CH}_2)_n$  ( $n = 4, 5$ );  $\text{R}^3 = \text{H, OMe}$ .

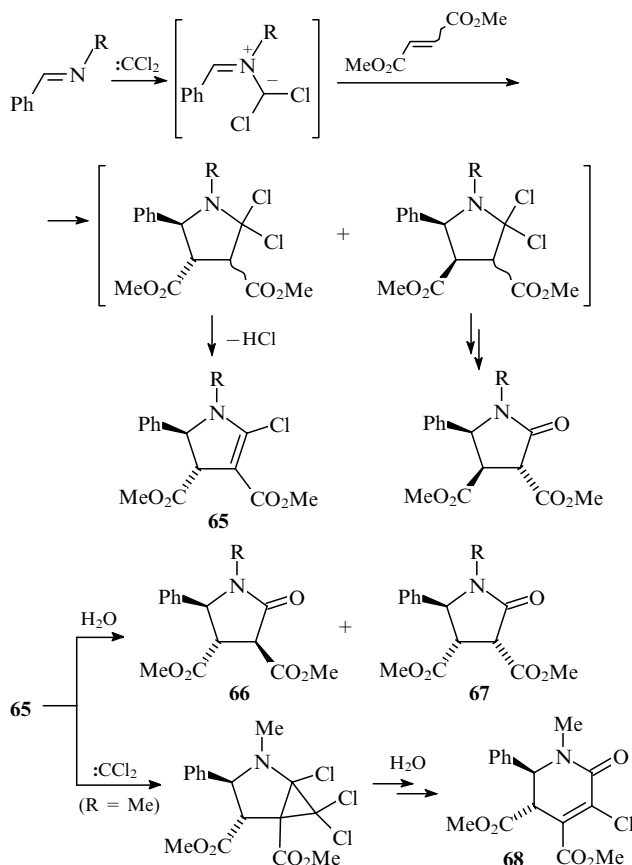
Approaches to the cleavage of either of the non-equivalent bonds in the aziridine ring in 1,1-dichloro-1,3,4,8b-tetrahydroazirino[2,1-*a*]isoquinolines (**59**) have been developed.<sup>120</sup> This opens a convenient way to the synthesis of substituted 3-benzazepin-2-ones (**60**), *N*-formyltetrahydroisoquinolines **61** as well as isoquinoline-1-carboxylic acid derivatives, *viz.*, esters **62**, amides **63** and cyclic amidines **64** of the imidazole and pyrimidine series.



It should be noted that 1,3-cyclisation of the aforementioned chlorinated azomethine ylides occurs at a rather fast rate, since the addition of dipolarophilic reagents containing activated double bonds to the reaction mixtures does not change the direction of the reaction with the carbene.

**Cycloaddition.** *gem*-Dichloro-substituted azomethine ylides with the dichloromethylene fragment slightly deviated from the  $\text{Cl}_2\text{C}-\text{N}=\text{C}$  plane [the dihedral angle ( $\theta$ ) between the  $\text{Cl}_2\text{C}-\text{N}=\text{C}$  and  $\text{Cl}_2\text{C}$  planes is equal to  $0-30^\circ$ ] are not prone to yield 1,3-cyclisation products. Intermediates having such geometry are formed in reactions of dichlorocarbene with benzaldehyde *N*-alkylimines only if  $\text{R} = \text{n-Alk}$ . The cycloaddition to the electron-deficient  $\text{C}=\text{C}$  bond is the most characteristic reaction of these azomethine ylides; this can be used as a convenient method for the synthesis of some pyrrolidine and pyridine derivatives.

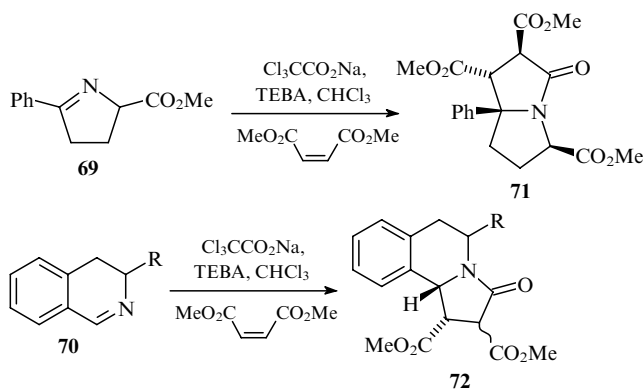
Thus *N*-alkylimines yield the corresponding 2-chlorodihydropyrroles **65** in reactions with dichlorocarbene generated from trichloroacetate or under alkaline phase-transfer conditions and maleates or fumarates.<sup>114</sup> These compounds are hydrolysed to lactams **66** and **67** upon isolation by column chromatography on silica gel (the yields of the isomers vary from 27% to 66%).



$\text{R} = \text{Me, Et, Bn}$ .

Pyridone **68** was prepared in 32% yield from *N*-benzylidene-*N*-methylamine using an excess of the source of dichlorocarbene.

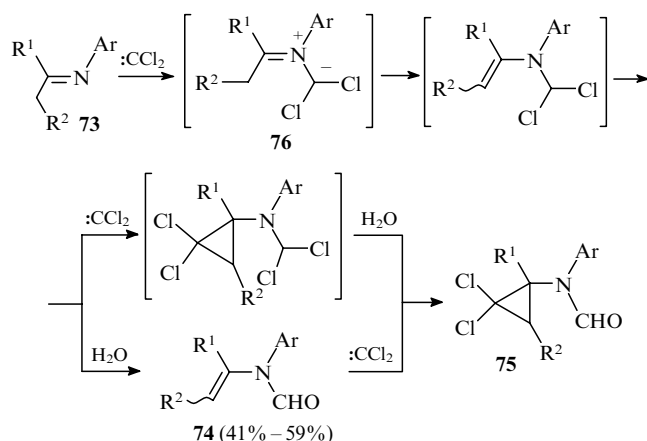
Fused cyclic compounds **71** and **72** containing a tetrahydropyrrole fragment can be prepared in this way from cyclic analogues of benzaldehyde *N*-alkylimines, *viz.*, dihydropyrrole **69** and 3,4-dihydroisoquinolines **70**.<sup>114</sup>



$\text{R} = \text{H, Me}$ .

**1,4-H-Shift.** Chlorinated ylides generated from imines of aliphatic ketones manifest specific chemical behaviour. It has been found<sup>121</sup> that the reaction of dichlorocarbene generated by decomposition of sodium trichloroacetate with ketone anils **73** yields predominantly enamides **74**, while the corresponding *gem*-dichlorocyclopropanes **75** (35%–42%) are formed when an

excess of the source of the carbene is used. Cyclopropanes **75** are prepared in good yields by a reaction of dichlorocarbene with isolated enamides **74** (56%–83%).<sup>121</sup>

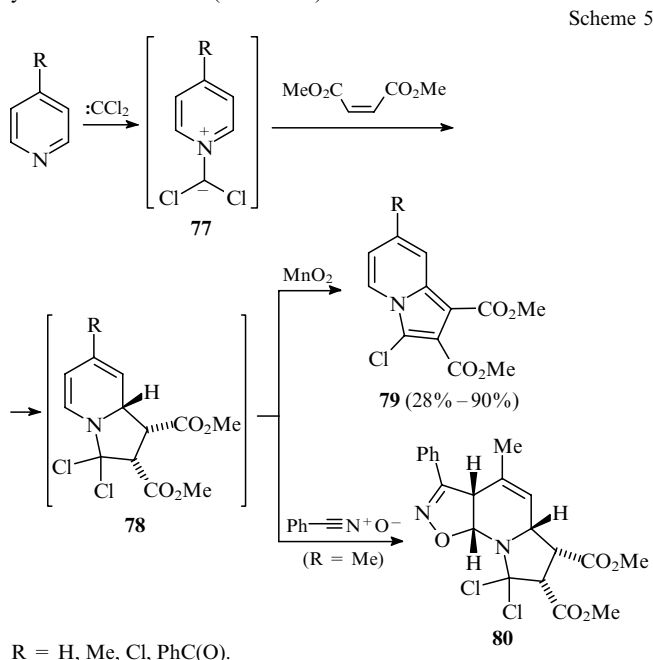


$R^1 = \text{Me, Et, cyclo-C}_3\text{H}_5$ ;  $R^2 = \text{H, Me}$ .

Studies of reactions with deuterated compounds corroborated the formation of enamides **74** *via* ylides **76** with a subsequent intramolecular 1,4-H-shift with a six-electron transition state rather than by a reaction of carbene with an enamine tautomer of imine.

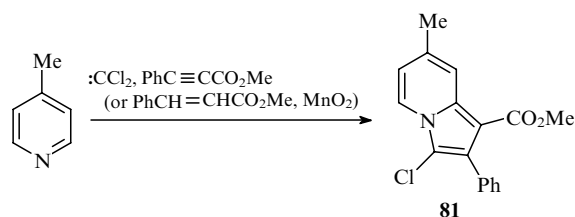
#### b. Azinium and diazinium ylides from dichlorocarbene

Ylides generated by a reaction of dichlorocarbene with azines, diazines and their benzoannulated derivatives are convenient synthons for the chloro-substituted indolizines and their heteroatomic and benzoannulated analogues. Two different approaches to the formation of the indolizine system on the basis of azinium ylides **77** are known (Scheme 5).

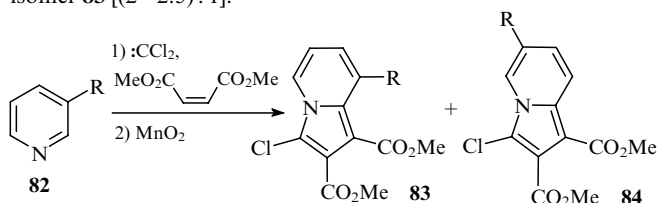


One of them represents a domino reaction that includes intermolecular cycloaddition of dichloroylide to an alkene-type or an alkyne-type dipolarophile. For example, the generation of dichlorocarbene using the alkaline or the trichloroacetate method in the presence of pyridines and dimethyl maleate results in unstable tetrahydroindolizines **78**, which are converted into substituted indolizines **79** (28%–90%) upon treatment with mild oxidants (see Scheme 5).<sup>122</sup> The intermediate tetrahydroindolizine **78** could be identified by its adduct with benzonitrile oxide (the adduct **80**).<sup>123</sup>

A series of substituted indolizines have been synthesised by the reaction of 4-picoline with dichlorocarbene in the presence of various electron-deficient unsaturated compounds.<sup>123</sup> Indolizine **81** can be prepared from 4-picoline using methyl phenylpropiolate or methyl cinnamate (in the latter case, the product yields are significantly lower).

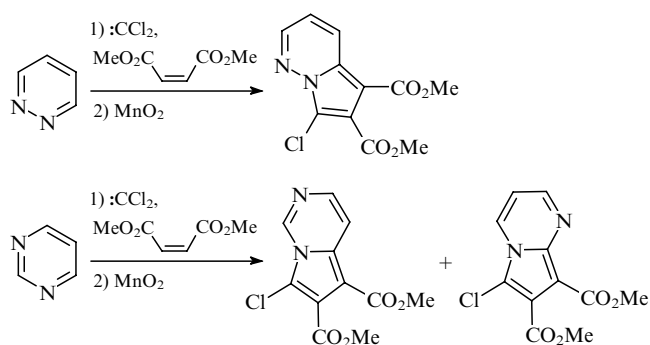


As a rule, the reactions of 3-substituted pyridines **82** yield both regioisomeric indolizines **83** and **84** with the predominance of the isomer **83** [(2–2.5):1].

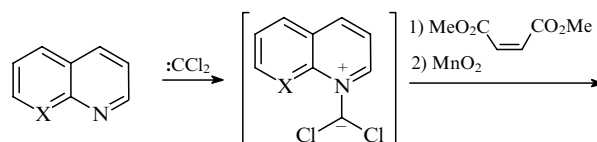


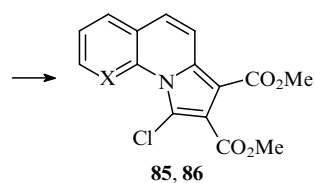
No indolizines are obtained in the reactions of 2-substituted pyridines with dichlorocarbene in the presence of dimethyl maleate.<sup>123</sup>

The above-described approach can be used in the synthesis of chlorinated aza-analogues of indolizines, *e.g.*, pyrrolo[1,2-*b*]pyridazines, pyrrolo[1,2-*c*]- and pyrrolo[1,2-*a*]pyrimidines.<sup>124</sup>

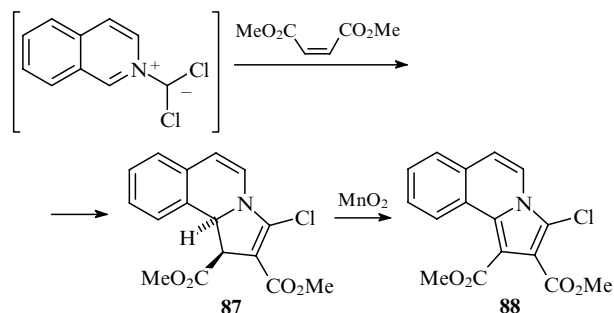


The chemical behaviour of benzoannulated analogues of azines and diazines in the above reaction has a number of specific features. Quinoline reacts slowly with dichlorocarbene in the presence of dimethyl maleate to give substituted pyrrolo[1,2-*a*]quinoline **85** in very low yield (~5%); 8-methylquinoline reacts even more slowly. The reaction of 1,8-naphthyridine with dichlorocarbene and dimethyl maleate gave pyrrolo[1,2-*a*]naphthyridine **86** (11%). Isoquinoline is more reactive than quinoline with respect to dichlorocarbene. Besides, it produces only one of two possible structural isomers. Interestingly, in this case the use of dimethyl maleate as a dipolarophile has made it possible to isolate the intermediate chlorodihydropyrrole derivative **87** (30%), the dehydrohalogenation product of the primary cycloadduct, compound **87**, was converted into pyrroloisoquinoline **88** (80%) under the action of oxidants.





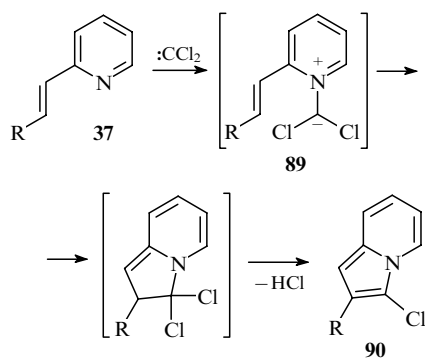
X = CH (85), N (86).



The syntheses of chloro-substituted pyrrolo[2,1-*a*]phthalazine, pyrrolo[1,2-*c*]quinazoline, pyrrolo[1,2-*a*]quinoxaline and pyrrolonaphthridine systems based on analogous reactions of phthalazines, quinoxalines, quinoxalines<sup>124, 125</sup> and benzo[*h*]naphthridines with dichlorocarbene have been described.<sup>126</sup>

On the whole, intermolecular cycloaddition reactions of dichloro-substituted azinium and diazinium ylides occur regioselectively with respect to both the non-symmetrical ylide and the non-symmetrical dipolarophile. The calculation of ylides formed in reactions of pyridine, 3- and 4-substituted pyridines and isoquinoline with dichlorocarbene by the MNDO method revealed that these molecules are planar. At the same time, the plane of CCl<sub>2</sub> in ylides based on 2-substituted pyridines and quinoline is turned relative to the plane of the pyridine ring (26–34°). The data obtained suggest that non-planar ylides are less stable and their formation is energetically less favourable. Considering that concerted processes are sensitive to the spatial characteristics of the reactants, it can be assumed that the inertness of 2-substituted pyridines and low degree of conversion of quinolines in this reaction are due to the fact that the presence of *ortho*- and *peri*-substituents in the azine makes the corresponding ylide non-planar.

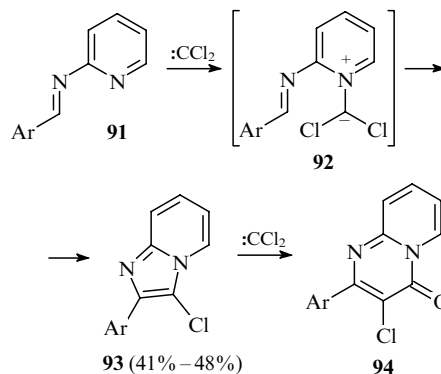
An alternative approach to the synthesis of chloro-substituted indolizine and related systems is based on the 1,5-cyclisation of the azinium dichloroylide **89** containing an unsaturated substituent in the *ortho*-position. 3-Chloro-substituted indolizines **90** can be prepared from compound **37** under conditions of generation of dichlorocarbene.<sup>127, 128</sup>



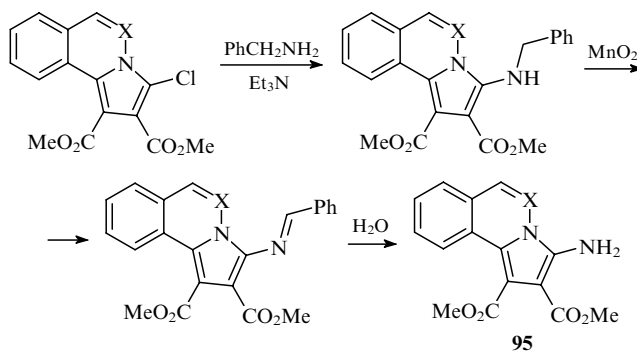
R = H, Ar, CO<sub>2</sub>Et.

The reaction of dichlorocarbene with 2-(arylideneamino)pyridines **91** does not affect the azomethine bond C=N, but includes an attack of carbene at the nitrogen atom of pyridine, which yields pyridinium ylide **92** and makes this reaction suitable for the

synthesis of 3-chloroimidazo[1,2-*a*]pyridines **93**.<sup>129</sup> If the aryl group in compound **91** contains no electron-withdrawing substituents, the synthetic chain can be elongated owing to the addition of carbene to the C=C bond of the imidazole ring of compound **93** with the subsequent ring expansion and the formation of chloro-substituted pyridopyrimidones **94**.



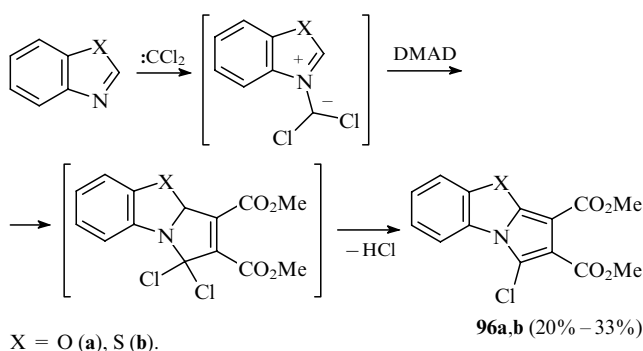
Chloro-substituted heterocycles formed as a result of above-described conversions of azinium ylides are valuable intermediates for organic synthesis. Their synthetic potential has increased considerably after the discovery of a simple and efficient method for the amination of the chloropyrrole fragment,<sup>124</sup> which opens an access to 3-aminopyrrolo[1,2-*a*]azine-1,2-dicarboxylates **95**, which represent convenient building blocks for the synthesis of miscellaneous fused heterocyclic systems.



X = CH, N.

### c. Azolium ylides from dichlorocarbene

Benzazoles afford 2,2'-bis(benzazoly)ls under conditions of generation of dichlorocarbene from CHCl<sub>3</sub> and NaOH in the presence of TEBA.<sup>130</sup> Although the reaction products do not contain fragments that might be generated from carbene, it was assumed that the putative mechanism involves the intermediate formation of benzazolium ylides. This mechanism was later confirmed by performing a reaction of dichlorocarbene with benzoxazole or benzothiazole in the presence of dimethyl acetylenedicarboxylate.<sup>131</sup> This reaction occurs through cycloaddition



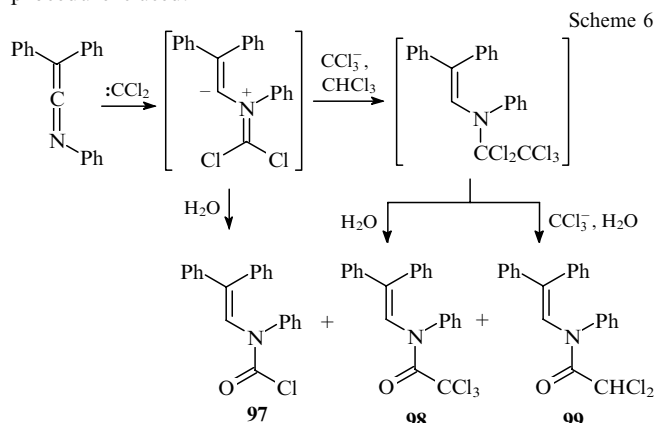
X = O (a), S (b).

of benzazolium ylide to the triple bond of the dipolarophile with subsequent elimination of HCl, and can be employed for the preparation of pyrrolo[2,1-*b*]benzoxazoles (**96a**) and pyrrolo[2,1-*b*]benzothiazoles (**96b**).

#### d. Ketene imine ylides from dichlorocarbene

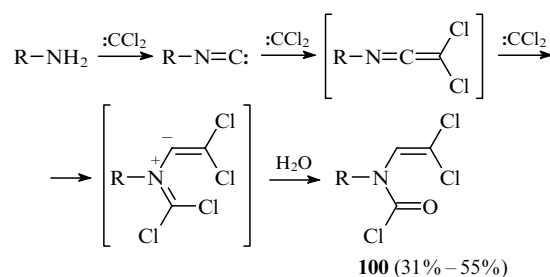
Calculations suggest that ketene imine ylides (alkylidene azomethine ylides) formed upon reaction of dichlorocarbene with ketene imines represent azomethine ylides with reversed polarity.<sup>4</sup> This difference in the electronic structure is manifested in different chemical behaviour of ketene imine ylides and ylides generated from azomethines, azines and azoles and, as a consequence, in significant changes in the array of products that might be synthesised therefrom.

The result of the reaction of ketene imines with dihalocarbenes depends on the method used for the generation of the carbene, since its choice determines the presence or the absence of other reagents in the reaction mixture (*e.g.*, water, trichloromethyl anion, *etc.*). For example, the reaction of triphenylketene imine with dichlorocarbene generated upon thermocatalytic degradation of sodium trichloroacetate in the presence of TEBA yields three main products, *viz.*, compounds **97–99** (Scheme 6). Rational choice of reaction conditions (method for the generation of carbene, phase-transfer catalysts, *etc.*) allows direction of the reaction towards the formation of one of these products.<sup>132</sup> Thus trichloroacetamide **98** is predominantly formed upon addition of an equimolar amount of sodium trichloroacetate, while the use of an excess of trichloroacetate yields dichloroacetamide **99**. Carbamoyl chlorides **97** are the main products if dichlorocarbene is generated from  $\text{CHCl}_3$  and  $\text{Bu}^t\text{OK}$  or if the phase-transfer procedure is used.<sup>133, 134</sup>

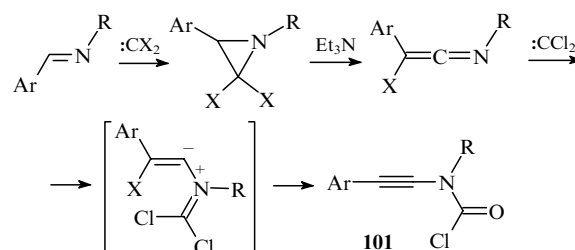


| Conditions                                     | Product yield (%) |    |    |
|------------------------------------------------|-------------------|----|----|
|                                                | 97                | 98 | 99 |
| $\text{Cl}_3\text{CCO}_2\text{Na}$ , TEBA      | 8                 | 57 | 9  |
| $\text{Cl}_3\text{CCO}_2\text{Na}$ (excess)    | —                 | 4  | 43 |
| $\text{CHCl}_3$ , KOH, TEBA                    | 58                | —  | 10 |
| $\text{CHCl}_3$ , $\text{Bu}^t\text{OK}$       | 45                | —  | —  |
| $\text{CHCl}_3$ , KOH, $\text{Me}_4\text{NBr}$ | 78                | —  | 2  |

A convenient one-step procedure for the synthesis of *N*-(2,2-dichlorovinyl)carbamoyl chlorides **100** from the simplest compounds, *viz.*, primary amines and chloroform, has been developed.<sup>135</sup> The conversion of an amine into a carbamoyl chloride is an example of an unusual iterative tandem reaction successively occurring *via* isocyanide, ketene imine and ketene imine ylide, it is noteworthy that three molecules of dichlorocarbene take part in the construction of dichlorovinylcarbamoyl chloride **100**. Thus, this reaction demonstrates the feasibility of ‘one-pot’ assembly of the carbon skeleton from dihalogeno carbene.

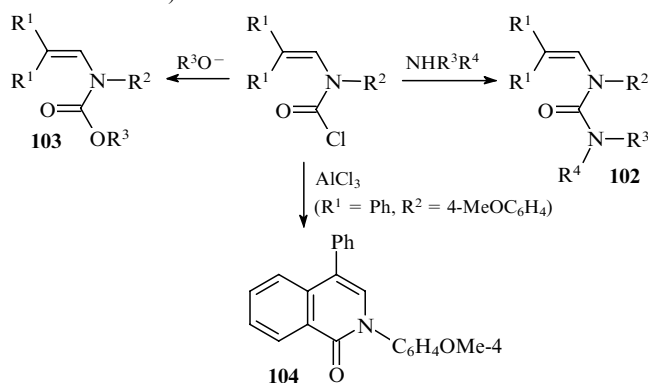


A three-step synthesis of *N*-alkynylcarbamoyl chlorides **101** from benzyldeneamines is yet another example of the successful application of dihalogeno carbene as a building block for the elongation of the carbon skeleton.<sup>136</sup> The reaction of *C*-halogeno ketene imine with dichlorocarbene generated upon thermolysis of sodium trichloroacetate in the presence of TEBA yields a trihalogeno-substituted ketene imine ylide and is the final step of this synthetic sequence. The unusual stabilisation of the latter and the formation of a triple carbon–carbon bond result in terminal *N*-alkynylcarbamoyl chlorides **101** as the final products.



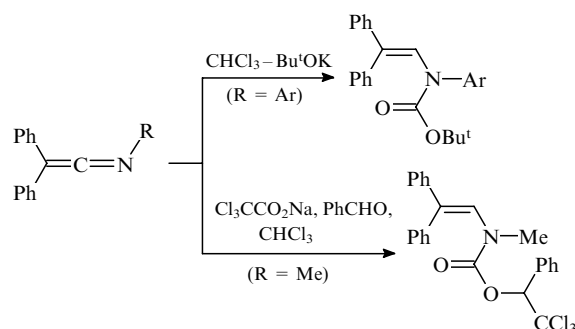
$\text{R} = \text{Ar}, \text{Bu}^t; \text{X} = \text{Cl}, \text{Br}.$

The carbamoyl chlorides with unsaturated substituents on the nitrogen atom thus prepared are valuable intermediates in the synthesis of various derivatives of carbamic acid (*e.g.*, ureas **102**,<sup>133</sup> carbamates **103**<sup>132, 133, 137</sup>) and heterocycles (*e.g.*, isoquinolinone **104**<sup>134</sup>).

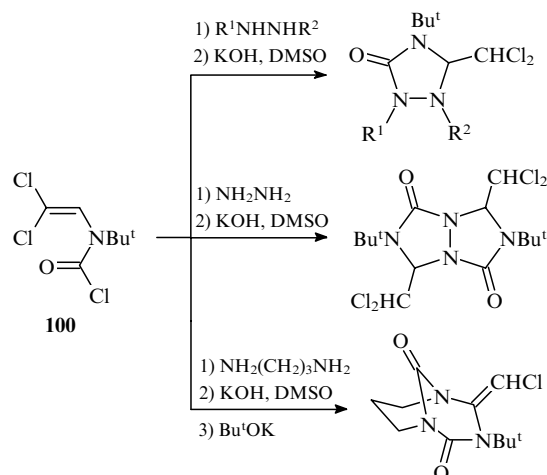


$\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4 = \text{Alk}, \text{Ar}.$

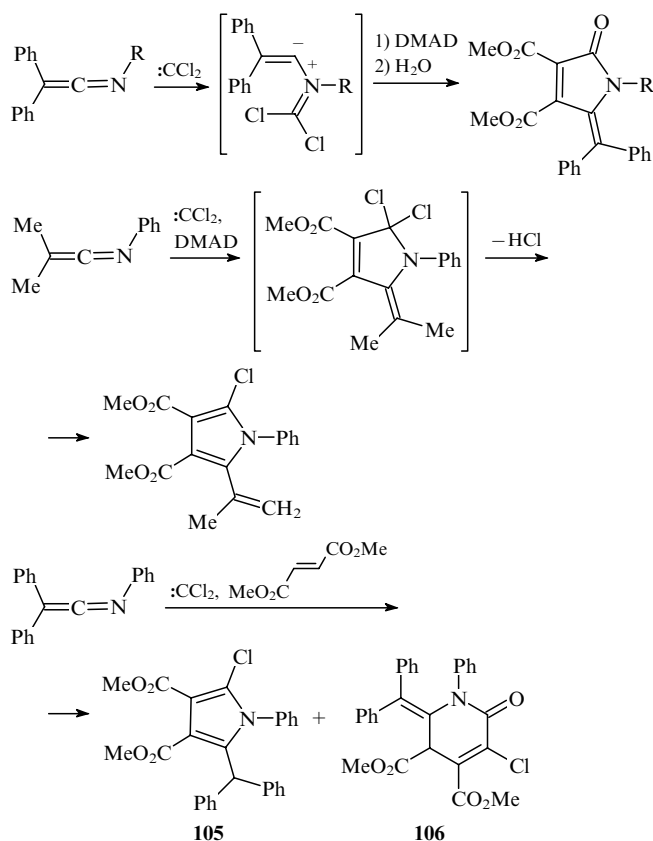
Carbamates can be prepared from the corresponding ketene imines without isolation of carbamoyl chloride.<sup>132, 133, 137</sup>



Dichlorovinyl-substituted carbamoyl chloride **100** was used for the preparation of various heterocyclic systems.<sup>138</sup> In these syntheses, compounds **100** can be regarded as synthetic equivalents of the bielectrophilic synthons  $O=C^+N(R)C^+(H)CHCl_2$ .



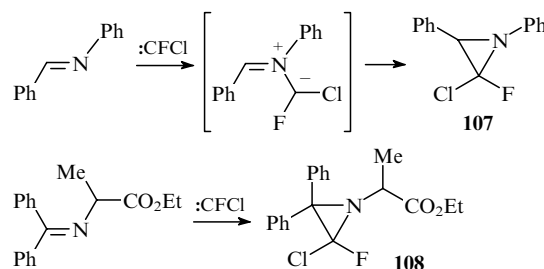
Cycloaddition of ketene imine ylides to electron-deficient alkenes<sup>131, 139</sup> and alkynes<sup>131, 139, 140</sup> occurs rather smoothly and can be used as a convenient method for the preparation of some pyrrole and pyridine derivatives.



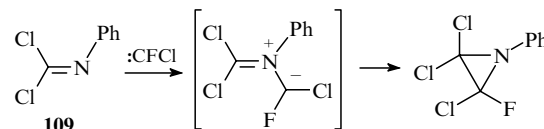
The relative yields of the reaction products, *viz.* pyrrole (**105**) and 2-pyridone (**106**), in the last-mentioned reaction can be changed by varying the ketene imine:dipolarophile ratio. Thus the use of a twofold excess of dimethyl fumarate has made it possible to obtain pyrrole (**105**) and pyridin-2-one (**106**) in 21% and 28% yields, whereas the use of a 20-fold excess afforded these compounds in 34% and 5% yields, respectively.

### 3. Ylides from chlorofluorocarbene

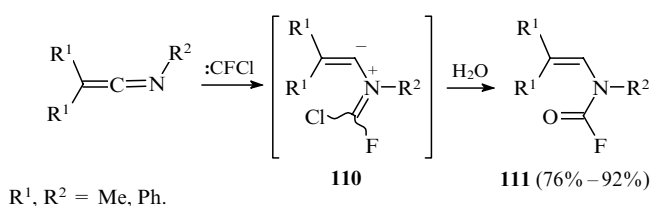
Iminiochlorofluoromethanides, *i.e.*, the intermediates in the addition of chlorofluorocarbene to the unshared electron pair of the nitrogen atom, have been studied less thoroughly. The data available suggest that the substitution of one fluorine atom for chlorine in dichloroazomethine ylides does not exert any noticeable changes in the properties of the intermediate ylides. Thus chlorofluorocarbene generated upon alkaline treatment of dichlorofluoromethane in the presence of TEBA is added to benzylideneaniline to give the corresponding *gem*-chlorofluoroazomethine ylide, which is easily cyclised to chlorofluoroaziridine **107**.<sup>141, 142</sup> Ethyl *N*-benzhydrylidene alaninate reacts similarly with chlorofluorocarbene to give aziridine **108** in 79% yield.<sup>115</sup>



Aziridine can also be prepared from the less nucleophilic imine **109**; however, in this case more drastic conditions should be used for the generation of fluorochlorocarbene, *i.e.*, thermolysis of (dichlorofluoromethyl)phenylmercury.<sup>143</sup>



The reactions of chlorofluorocarbene with ketene imines, which proceed *via* the intermediate ketene imine ylides **110** (chlorofluorocarbene was prepared from  $CH_2Cl_2$  and  $Bu^4OK$ ), are related to synthetically valuable reactions. The yields of carbamoyl fluorides **111** formed upon hydrolysis of ylides **110** are usually high, which makes these compounds, along with the above-mentioned carbamoyl chlorides, attractive for the synthesis of carbamic acid derivatives and various polynitrogenous heterocycles.<sup>144</sup>

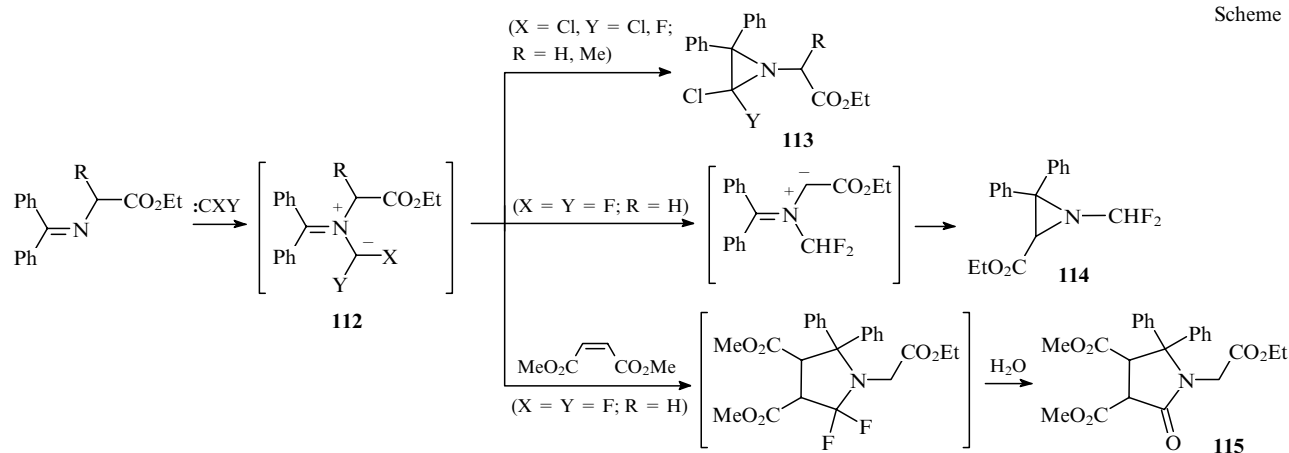


### 4. Ylides from difluorocarbene

#### a. Acyclic azomethine ylides from difluorocarbene

It is known that difluorocarbene is much less reactive than dichloro- and chlorofluorocarbenes.<sup>145</sup> Nevertheless, it is reactive enough for the addition to benzaldehyde and benzophenone *N*-alkyl- and *N*-arylimines to give the corresponding difluoromethylides. The presence of two highly electronegative fluorine atoms at the ylide carbon atom is the reason for the significant changes in the chemical properties of these intermediates in comparison with dichloro- and chlorofluoro-substituted analogues. The dependence of the reactivities of iminodihalogeno methanides on the nature of the halogen atoms is especially noticeable in the conversions of ylides generated from the corresponding dihalogeno carbenes and benzhydrylidene derivatives of amino acids (Scheme 7).<sup>146, 147</sup>

Scheme 7

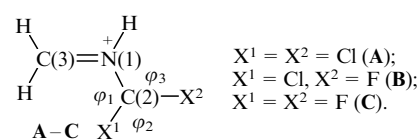


Dichloro- and chlorofluoro-substituted ylides **112** undergo cyclisation into aziridines **113** irrespective of the substituent R; the direction of the reaction does not change even in the presence of a 'dipole trap' (a dipolarophile). This conversion route is not characteristic of the difluoroylide from ethyl *N*-benzhydrylidene-glycinate, which undergoes ylide–ylide isomerisation in the absence of a dipolarophile with subsequent cyclisation to aziridine **114**, whereas in the presence of dimethyl maleate it undergoes cycloaddition reaction to give pyrrolidinone **115** after hydrolysis.

According to quantum-chemical calculations (B3LYP/6-31G\*), the presence of two geminal fluorine atoms in the ylide influences its geometry significantly, which changes from nearly planar (*i.e.*, characteristic of classical iminium ylides) to pyramidal (characteristic of ammonium ylides) on going from dichloro-substituted to difluoro-substituted ylides (Table 4). These results are consistent with the experimental results and *ab initio* calculations, which suggest that the presence of fluorine atoms brings about pyramidalisation of the radical centre.<sup>148</sup>

For this reason, difluoroylides do not cyclise to aziridines irrespective of their structures, while 1,3-dipolar cycloaddition reactions to multiple bonds, which will be considered below, are the main pathways of their conversions.

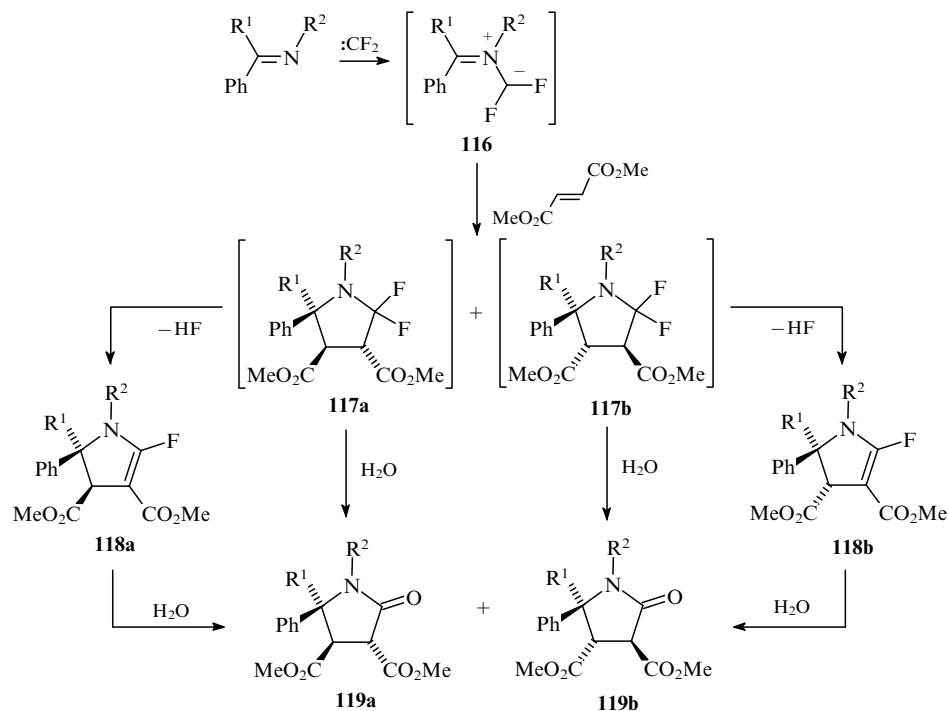
**Table 4.** The sum of angles  $\varphi_1 + \varphi_2 + \varphi_3$  and bond lengths in ylides A–C calculated by the B3LYP/6-31G\* method.



| Parameters                                       | A    | B    | C    |
|--------------------------------------------------|------|------|------|
| $\varphi_1 + \varphi_2 + \varphi_3 / \text{deg}$ | 349  | 339  | 328  |
| C(2)–N(1) / Å                                    | 1.35 | 1.36 | 1.39 |
| N(1)=C(3) / Å                                    | 1.33 | 1.33 | 1.32 |

**Addition of iminodifluoromethanides to the C=C bond.** Ylides **116** prepared by the reaction of difluorocarbene generated upon reduction of dibromodifluoromethane by lead in the presence of tetrabutylammonium bromide with benzaldehyde or benzophenone *N*-alkylimines add easily to electron-deficient alkenes, such as maleic acid esters and imides and fumaric acid esters (Scheme 8).<sup>149–151</sup> Primary cycloadducts formed from ylides

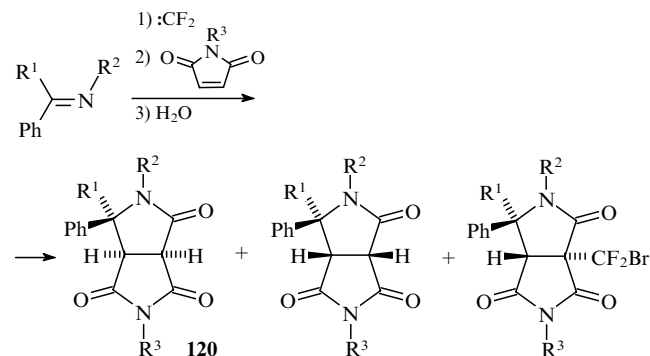
Scheme 8



R<sup>1</sup> = H, Ph; R<sup>2</sup> = Bn, CH<sub>2</sub>CO<sub>2</sub>Me, CH<sub>2</sub>SiMe<sub>3</sub>.

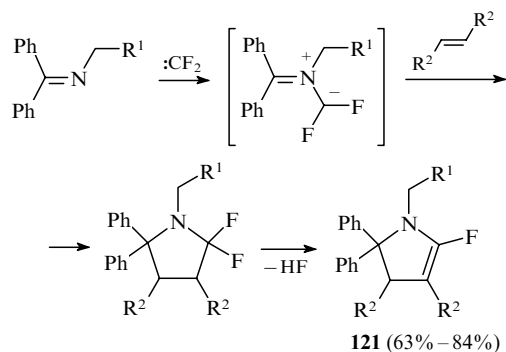
**116**, viz., pyrrolidines **117**, and their dehydrofluorination products, viz., dihydropyrroles **118**, are unstable and can only be detected by GC/MS. Only their hydrolytic products, viz., diastereomeric pyrrolidinones **119**, could be isolated.

Cycloaddition of difluoroylides prepared from benzaldehyde imines and difluorocarbene to *cis*-alkenes, e.g., *N*-phenylmaleimide, occurs *endo*-stereoselectively and gives predominantly pyrrolidinones of the type **120**, whereas *trans*-alkenes largely generate products of the type **119a**.<sup>151</sup> It should be noted that similar reactions with dichlorocarbene afford exclusively adducts of the type **119b**.<sup>114</sup>



$R^1 = \text{H, Ph; } R^2, R^3 = \text{Alk, Ar.}$

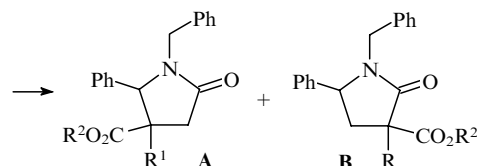
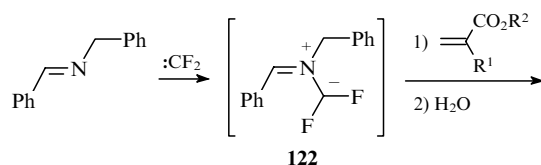
Fluorodihydropyrroles **121** prepared from benzophenone imines using fumaronitrile or dimethyl maleate as dipolarophiles are more stable and can be isolated in 63%–84% yields.<sup>152</sup>



$R^1 = \text{H, Bn, CO}_2\text{Me; } R^2 = \text{CN, CO}_2\text{Me.}$

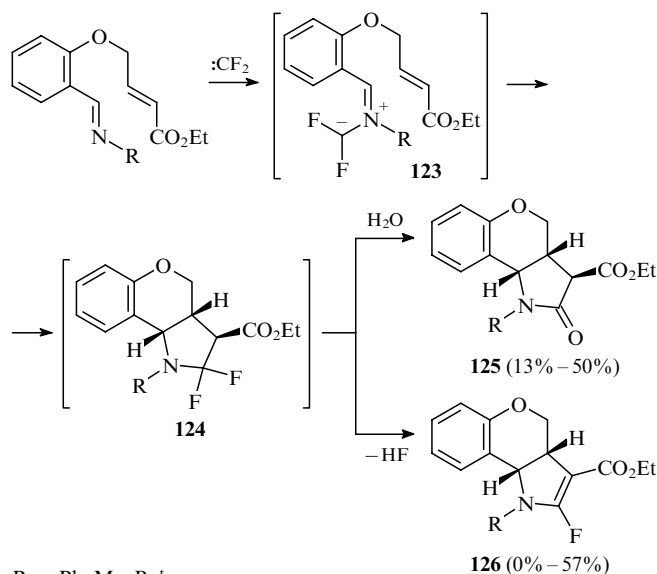
This methodology is applicable not only to Schiff bases, but also to substrates containing an endocyclic C=N bond. In the latter case, the reaction products represent cyclic systems that can be *ortho*-fused with fluorodihydropyrrole.<sup>152</sup>

Ylides of the type **122** react easily even with alkenes containing one electron-withdrawing group; the cycloaddition may occur with either complete regioselectivity, as in the case of methyl methacrylate (where isomer **A** is formed in 77% yield), or formation of both regioisomers **A** (62%) and **B** (21%), as in the case of ethyl acrylate.<sup>149</sup>



$R^1 = \text{H, } R^2 = \text{Et; } R^1 = R^2 = \text{Me.}$

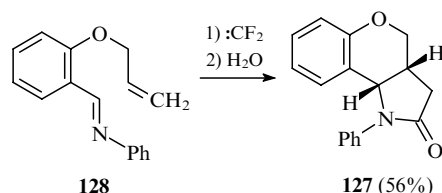
Intramolecular cycloaddition of difluoro-substituted ylides of the type **123** to the monoactivated multiple bond always gives only one regioisomeric difluoropyrrolidine **124**, which can be hydrolysed to the corresponding lactam **125**. In some cases, relatively stable fluorodihydropyrrole derivatives **126** can be isolated.<sup>153</sup>



$R = \text{Ph, Me, Bu}^t.$

Complete *cis*-stereoselectivity is a distinguishing feature of the synthesis of compounds of the type **125** by intramolecular cycloaddition of difluoro-substituted ylides **123** generated by the carbene method, which leads to the formation of systems with only *cis*-fused rings.<sup>†</sup> An explanation of such stereoselectivity is the specificity of the carbene method for the generation of azomethine ylides, which enables preparation of *Z*-configured dipoles, this configuration, in turn, being determined by the *E*-configuration of the starting imines.

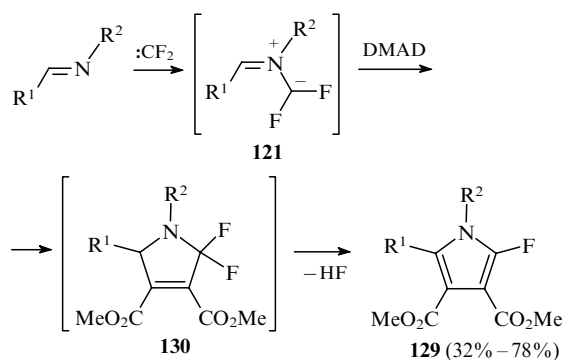
This reaction was successfully used for the synthesis of the derivative **127** containing no alkoxy carbonyl group, from imine **128** containing a terminal double bond.<sup>153</sup>



**Addition of iminodifluoromethanides to the C≡C bond.** Addition of difluoroylides to dimethyl acetylenedicarboxylate can be employed in the synthesis of substituted 2-fluoropyrrole-3,4-dicarboxylates **129**.<sup>158, 159</sup>

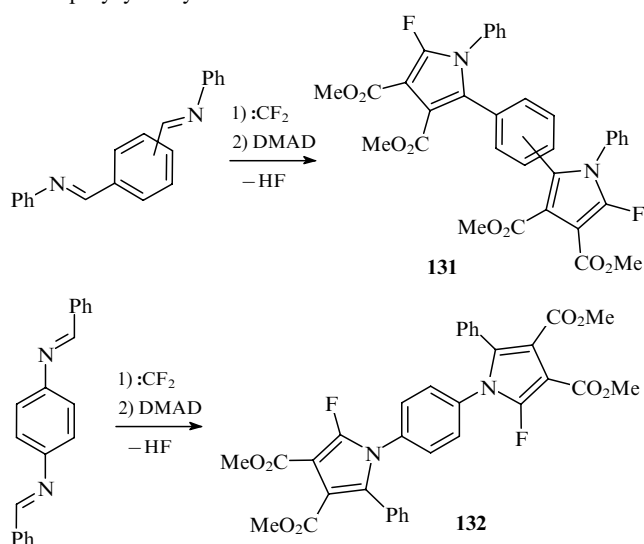
<sup>†</sup> The intramolecular cycloaddition, to the C=C bond, of non-halogenated azomethine ylides generated by non-carbene methods leading to chromeno[4,3-*b*]pyrrole derivatives has been studied.<sup>154–157</sup>



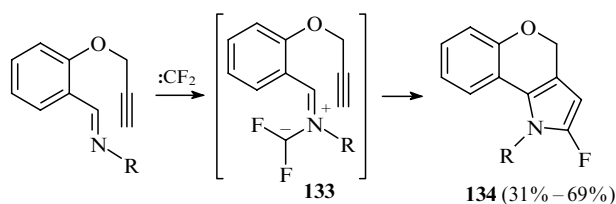


$R^1 = \text{Ar}$ ,  $R^2 = \text{Ar}$ , furyl, alkenyl, alkynyl.

Stabilisation of the addition products, *viz.*, difluorodihydropyrrole **130**, results from abstraction of HF to give a stable aromatic pyrrole system. This method was successfully used for the synthesis of compounds **131** and **132** containing two fluoropyrrole rings and the formation of a fluoropyrrole fragment in a fused polycyclic system.<sup>159</sup>

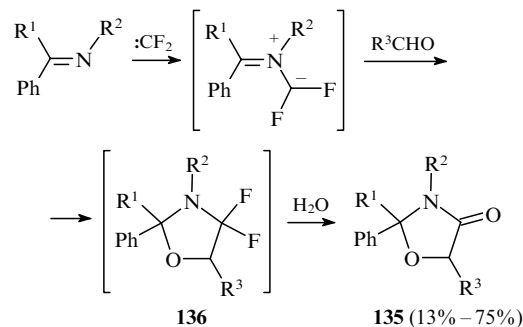


The addition of difluoroylides to non-symmetrical acetylenes occurs with both complete regioselectivity, as in the case of ethyl propiolate and methyl tetrolate, and the formation of both regioisomers, as in the case of methyl phenylpropiolate.<sup>159</sup> All these reactions include exclusive or predominant formation of 5-fluoropyrrole-3-carboxylic acid derivatives. It should be noted that the yields of the products of difluoroylide cycloaddition to this kind of monoactivated acetylene are significantly lower than those on addition to the diactivated triple bond (*e.g.*, dimethyl acetylenedicarboxylate). Difluoroylides do not add to non-activated triple bonds (*e.g.*, phenylacetylene). The situation is different on going to systems containing simultaneously an ylide and an acetylenic fragment. Thus the intramolecular cycloaddition of ylide **133** to a non-activated triple bond yields chromenopyrroles **134** in preparative yields.



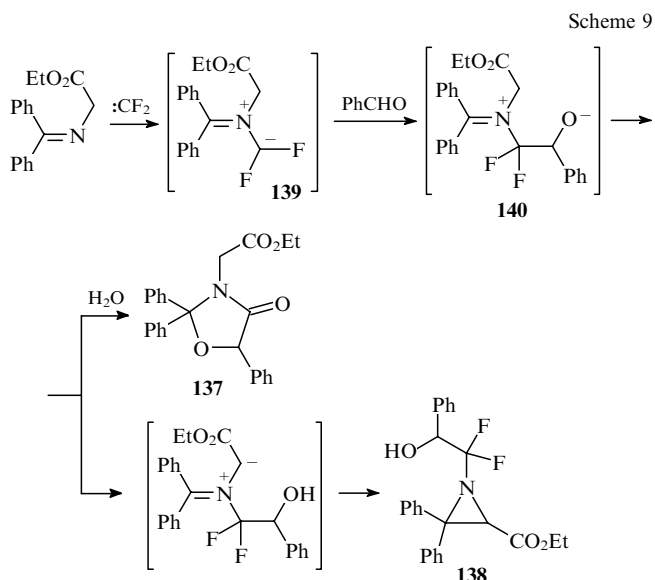
**Addition of iminodifluoromethanides to the C=O bond.** Studies of intermolecular cycloaddition of iminodifluoromethanides generated from imines and difluorocarbene to the C=O bonds of

various substrates have shown that these reactions usually give good yields only with aldehydes.<sup>160</sup> In this case, the process is characterised by complete regioselectivity and affords oxazolidin-4-one derivatives **135**, which represent hydrolysis products of the primary cycloadducts **136**. The stereoselectivity of the cycloaddition step is determined by the nature of the radical  $R^3$  in the aldehyde: acetaldehyde reacts non-stereoselectively, while aromatic aldehydes react with the predominant formation of the *trans*-product.



$R^1 = \text{H}$ , Ph;  $R^2 = \text{Bn}$ ,  $\text{CH}_2\text{CO}_2\text{Me}$ ,  $\text{CH}_2\text{SiMe}_3$ ;  $R^3 = \text{Alk}$ , Ar.

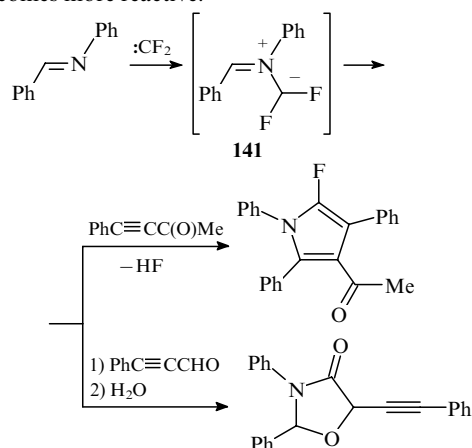
The reaction of ethyl *N*-benzhydrylidene glycinate with difluorocarbene in the presence of benzaldehyde yields, along with the expected cycloaddition product (oxazolidinone **137**), also aziridine **138**; it was assumed<sup>160</sup> that its formation includes a nucleophilic attack of the ylide on the carbon atom of the carbonyl group of benzaldehyde followed by a 1,5-H-shift and cyclisation (Scheme 9). This suggests a non-concerted cycloaddition mechanism of sterically crowded *C,C*-diphenyl-substituted *gem*-difluoroylides to strongly polarised multiple 'carbon–heteroatom' bonds containing a zwitter-ionic intermediate of the type **140**.



Scheme 9

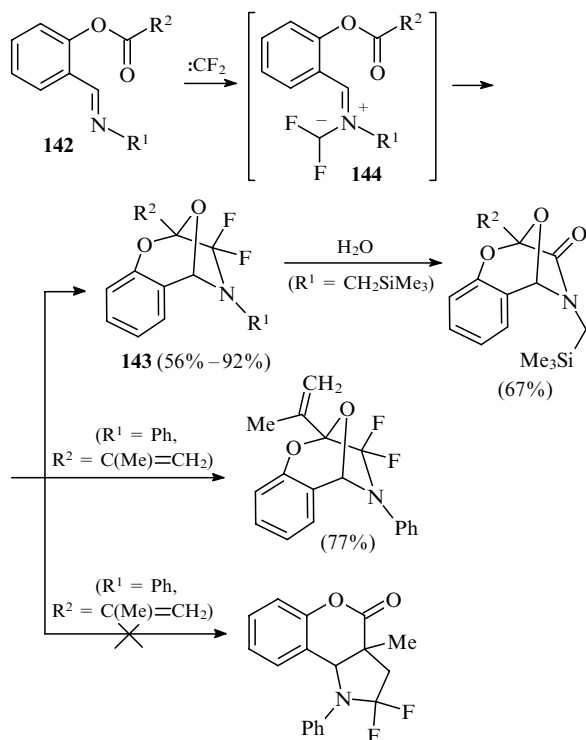
Ketones are significantly less active in the reaction with difluoro-substituted iminium ylides than aldehydes. Thus an oxazolidinone of the type **135** ( $R^1 = \text{H}$ ,  $R^2 = \text{Bn}$ ,  $R^3 = \text{Me}$ ), the addition product of the intermediate ylide to acetone, was prepared in as low yield as 3%, whereas the carbonyl group of benzophenone is generally inactive with respect to difluoroylides.<sup>160</sup> The data on the chemoselectivity of the cycloaddition of difluoroylide **141** to the C=O and C≡C bonds of phenylpropionaldehyde and methyl phenylethynyl ketone<sup>159</sup> suggest a higher reactivity of the aldehyde C=O group than the mono-activated C≡C group in the 1,3-dipolar cycloaddition. Substitution of the ketone for the aldehyde causes changes in the reaction

centre: thus the  $C\equiv C$  bond in methyl phenylethynyl ketone becomes more reactive.



The data from competitive cycloaddition of ylide **141** to various substrates containing  $C=O$  and  $C\equiv C$  bonds allowed the arrangement of dipolarophiles as regards their activities with respect to iminodifluoromethanides (generated upon reactions of difluorocarbene with aromatic imines) in the following series: the  $C=O$  bond of ketones  $<$  the monoactivated  $C\equiv C$  bond  $<$  the  $C=O$  bond of aldehydes  $<$  the deactivated  $C\equiv C$  bond.<sup>159</sup>

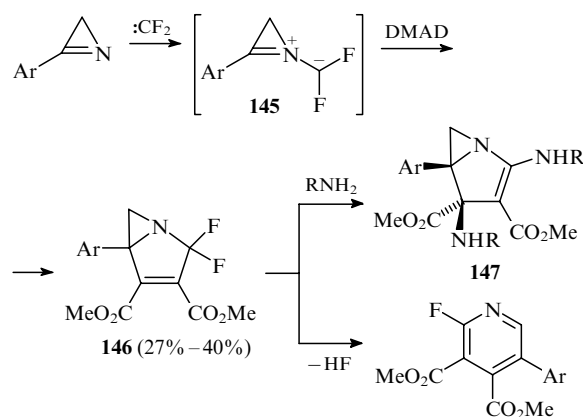
The carbonyl groups of esters are non-reactive with respect to difluoro-substituted ylides. However, the ester carbonyl can be involved in intramolecular cycloaddition reactions with a difluoroylide fragment as a dipolarophilic component. Thus azomethine ylides generated upon reaction of difluorocarbene with *N*-arylimines of the *O*-acylated salicylaldehyde **142** undergo intramolecular 1,3-dipolar cycloaddition with the ester carbonyl group. This reaction is completely regioselective and yields the 2,5-epoxy-1,4-benzoxazepine derivatives **143**.<sup>161</sup> The direction of a cycloaddition reaction is not changed in the presence of an alkenyl fragment on the acyl group as a competitive dipolarophile. Moreover, it has been shown that the rate of the intramolecular cycloaddition to the  $C=O$  bond of ylide **144** is comparable to the rate of intermolecular cycloaddition to one of the most reactive dipolarophiles, *viz.*, dimethyl acetylenedicarboxylate.<sup>162</sup>



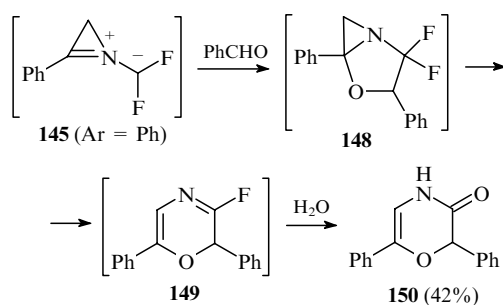
## b. Cyclic ylides from difluorocarbene

Various conversions of cyclic nitrogen ylides, in particular intermolecular 1,3-dipolar cycloadditions, underlie an approach to the synthesis of *ortho*-fused nitrogenous heterocycles. At present, only three-, six- and seven-membered cyclic systems containing an endocyclic  $C=N$  bond are known; ylides could be generated from these systems under conditions of generation of difluorocarbene.

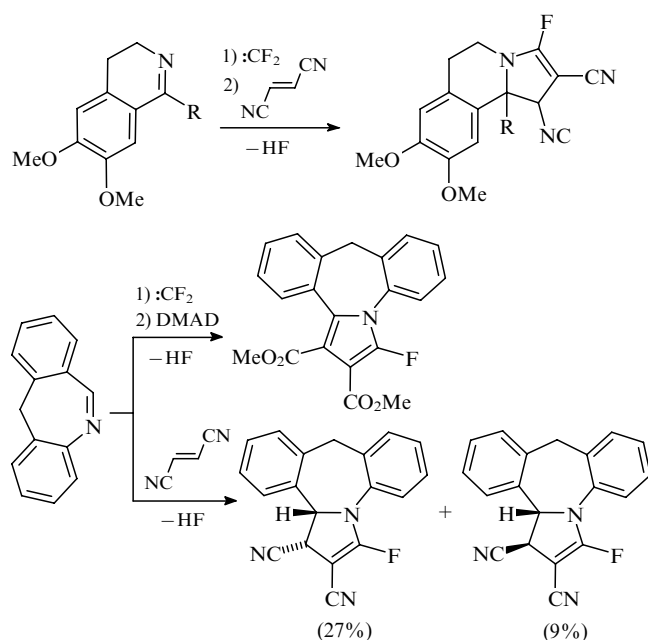
The formation of strained azirinium ylides **145** upon reaction of 3-aryl-2*H*-azirines with difluorocarbene obtained by reduction of  $CF_2Br_2$  with active lead was confirmed by 1,3-dipolar cycloaddition to dimethyl acetylenedicarboxylate.<sup>163</sup> Difluoro-substituted dihydroazirino[1,2-*a*]pyrroles **146** were isolated as the reaction products. An important feature of these unusual bicyclic compounds is that they can undergo either ring expansion to give quantitative yields of 2-fluoro-substituted pyridines as valuable intermediates for the preparation of miscellaneous pyridine derivatives or transformations with the retention of the bicyclic skeleton, *e.g.*, with the formation of diaminodicarboxylic acid derivatives **147**.



The reaction of ylide **145** ( $Ar = Ph$ ) with benzaldehyde does not stop at the step of formation of the bicyclic derivative **148**. Presumably, in the course of the reaction, the opening of the aziridine ring takes place with the formation of 3-fluorooxazine derivative **149**, which is easily hydrolysed upon chromatographic isolation to yield lactam **150**.<sup>163</sup>



This approach does not allow preparation of the corresponding fused *gem*-difluorodihydropyrrole derivatives similar to compounds **146** starting from six- and seven-membered heterocycles containing a  $C=N$  bond. Nevertheless, reactions of these heterocyclic compounds with difluorocarbene in the presence of but-2-enoic and acetylenedicarboxylic acid derivatives can be used for the synthesis of polycyclic systems containing fluorodihydropyrrole and fluoropyrrole fragments, respectively.<sup>152</sup>



## V. Conclusion

Considerable progress has been achieved in the past decade in the chemistry of 1,3-dipoles and in the study of reactivities and synthetic applications of unstable iminium ylides in particular. The perfection of the methods for matrix isolation of reactive intermediates (LFP and FVT) has made it possible to expand considerably the range of unstable ylides detected by spectroscopic methods. Recently, only analysis of 1,3-dipolar cycloaddition products to dipolarophiles has been used as indirect evidence for their existence. This trend will undoubtedly be developed in the near future, predominantly with respect to azomethine ylides; their spectral, kinetic and thermodynamic characteristics are not documented anywhere.

The great diversity of products of domino reactions of carbenes and ylides points to the high potential of this approach for designing the synthesis and assembly of the skeletons of nitrogen-containing molecules. The intramolecular 1,3-dipolar cycloaddition reaction is one of the most interesting synthetic approaches to the synthesis of polycyclic nitrogen-containing compounds and a potent tool for the stereoselective construction of complex polycyclic and bridged systems. This methodology will certainly find application in the syntheses of natural compounds and their analogues. In this context, a search for novel types of iminium ylides containing different combinations of synthetically important structural fragments (*e.g.*, functional groups, small and chemically labile rings, *etc.*) is becoming a topical task. Their conversions will lead to intermediates with high synthetic potentials, which can undergo further selective chemical transformations.

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<sup>b</sup> — *Mendeleev Chem. J. (Engl. Transl.)*

<sup>c</sup> — *Chem. Heterocycl. Compd. (Engl. Transl.)*

<sup>d</sup> — *Russ. J. Org. Chem. (Engl. Transl.)*

# Tautomerism and various coordination modes of typical chelating ligands with metals<sup>†</sup>

A D Garnovskii, I S Vasil'chenko

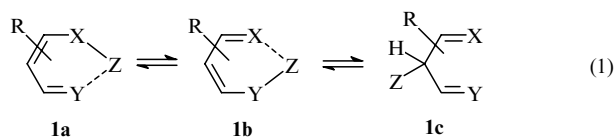
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**Abstract.** Data on the tautomerism of classical chelating ligands, *viz.*,  $\beta$ -diketones and nitrogen- and sulfur-containing analogues, are surveyed. The possibilities of the stabilisation of specific tautomers of these organic compounds due to coordination with metals are discussed. The bibliography includes 455 references.

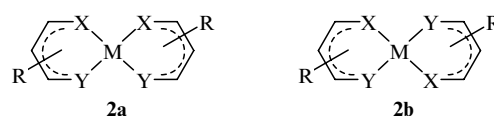
## I. Introduction

Investigations into tautomerism<sup>1–6</sup> and complex formation<sup>1,7–10</sup> is an important direction of the research activity of the Rostov school of chemists headed by V I Minkin. Proto- and elementotropic tautomerism<sup>1–3,11</sup> was elucidated, the acylotropy phenomenon (*i.e.*, the intramolecular transfer of a COMe group)<sup>5,12</sup> was discovered, and stereochemically non-rigid structures in their ground and electronically excited states were studied<sup>13,14</sup> using  $\beta$ -diketones and functionalised aliphatic, aromatic or heterocyclic azomethines **1** as examples of typical chelating ligands.



R = H, Alk, Ar; X, Y = O, S; Z = H, COR', MR', MR'\_2, MR'\_3  
(R' = Alk, Ar; M = Hg, B, Ga, Tl, In, Si, Sn, Sb).

V I Minkin and co-workers<sup>7,8</sup> developed original methods for the synthesis of azomethine intracomplex compounds with metal-lacycles containing chalcogen atoms (S, Se), and undertook fundamental investigations into the stereochemistry, stereodynamics<sup>13,14</sup> and photochemistry<sup>15,16</sup> of the type **2** metal chelates.



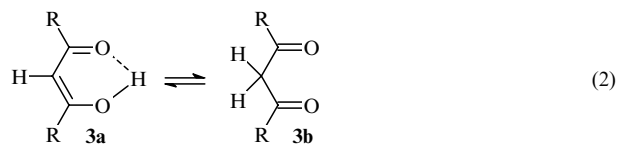
X = O, S, Se; Y = NR'; M = Be, Cd, Hg, Pb, Co, Ni, Cu, Zn.

The above aspects served as a background for the development of an important direction in modern coordination chemistry, *viz.*, the coordination-dependent stabilisation of specific tautomeric forms of organic compounds.<sup>6</sup>

The present review surveys the state-of-the-art structural studies of free and coordinated tautomeric chelating ligand systems, which are of great importance for the chemistry of not only complex compounds but of organic and organometallic compounds as well.

## II. $\beta$ -Diketones and their coordination compounds

The problem of stabilisation of a specific tautomeric form of  $\beta$ -diketones upon complexation with metal ions was discussed for the first time by Kukushkin.<sup>17</sup> It is known that  $\beta$ -diketones exist in two tautomeric forms, *viz.*, ketoenol (**3a**) and diketone (**3b**) with the former predominating.<sup>2–5</sup>



R = Alk, Ar.

Coordination compounds of these chelating ligands are widely represented by intracomplex compounds  $ML_n$  ( $L^-$  is an anionic ligand). Contributions of specific tautomeric forms of the ligands to the solid-state or solution structures of such complexes cannot be estimated due to the equality of the intrachelate bonds M—O (from X-ray diffraction data<sup>18–24</sup>).

In those cases where  $\beta$ -diketones act as neutral proton-containing ligands (LH),<sup>19–30</sup> the ketone form **3b** is realised (for instance, in complex **4**). This has been proved using X-ray

A D Garnovskii, I S Vasil'chenko Institute of Physical and Organic Chemistry, Rostov State University, prosp. Stachki 194/2, 344090 Rostov-on-Don, Russian Federation. Fax (7-8632) 43 46 67, tel. (7-8632) 43 47 76, e-mail: garn@ipoc.rsu.ru (A D Garnovskii), vas@ipoc.rsu.ru (I S Vasil'chenko)

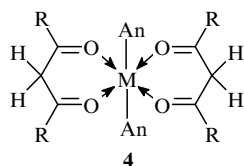
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<sup>†</sup> Dedicated to Academician Vladimir Minkin on the occasion of his 70th birthday.

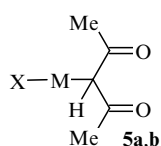


diffraction studies with the objective localisation of all hydrogen atoms.<sup>18, 25, 26</sup>

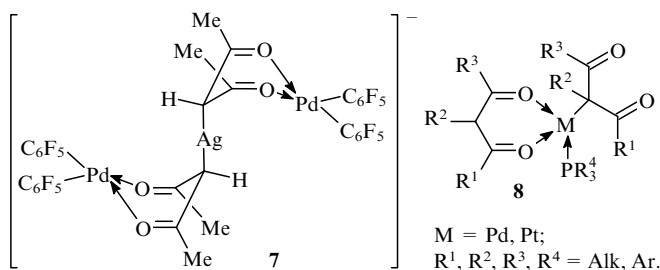
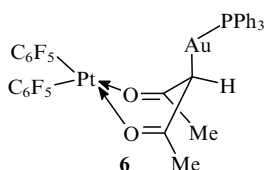


An is a monocharged anion.

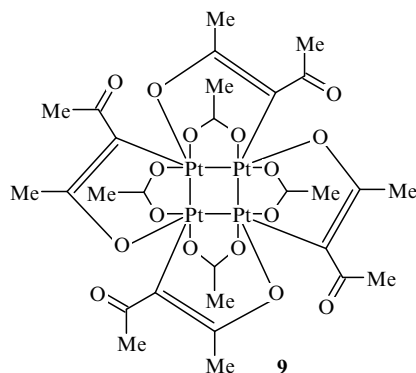
The same structure is typical of mono- (compounds **5**)<sup>18, 25, 26</sup> and polynuclear (compounds **6** and **7**)<sup>31, 32</sup> complexes as well as of compound **8**, in which two β-diketone fragments are differently bound to a metal atom.<sup>18</sup>



**5a:** M = Hg, X = Cl, OAc;  
**5b:** M = Au, X = Ph<sub>3</sub>P.

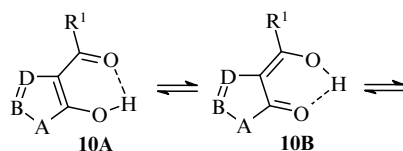


Unusual C,O-coordination of the β-diketone ligands was observed in complex **9**.<sup>33</sup>

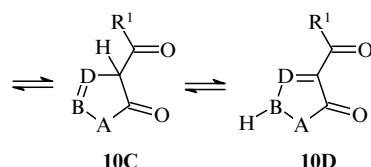


The type **2** (X = Y = O), **4** and **5** β-diketone complexes can be prepared by both chemical (from metal salts)<sup>34, 35</sup> and electrochemical (from zero-valent metals)<sup>34–37</sup> methods. The structures of coordination compounds **2**, **4**–**9** were unequivocally established by X-ray diffraction studies.

Studies of the tautomeric forms of heterocyclic β-diketone ligands **10** showed<sup>6, 21, 38, 39</sup> that the tautomeric equilibrium (3) in solution is shifted towards the formation of the ketoenol form **A**, which is typical of these ligand systems in the crystalline phase as well.<sup>6, 21, 38–44</sup>

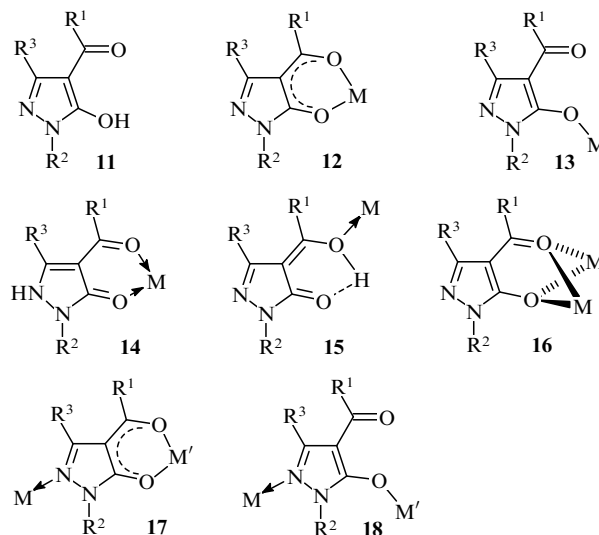


(3)



A = NR<sup>2</sup>, O, S, Se; B, D = CR<sup>3</sup>, N; R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> = H, Alk, Ar.

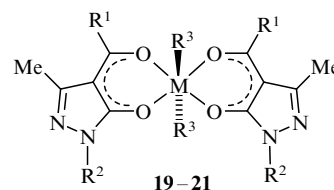
4-Acylpyrazol-5-ones **11** are the most studied ligands.<sup>6, 21, 38</sup> Characteristic types of their coordination with different metals are shown below. Different tautomeric forms of these ligand systems (complexes **12**–**18**) are realised depending on the nature of the metal atom.<sup>21</sup>



R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> = Alk, Ar.

Studies devoted to β-diketones **12** with equalised intrachelate bonds are most numerous.<sup>6, 21, 39–43, 45–48</sup>

Nearly identical M–O bond lengths in complexes **19**–**21** confirm the delocalisation of the intrachelate bonds within the ligands.<sup>48, 49</sup>

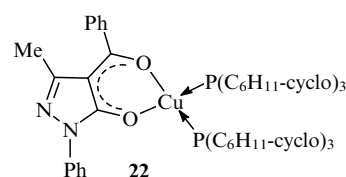


**19:** M = Sn, R<sup>1</sup>, R<sup>3</sup> = Alk, R<sup>2</sup> = 4-MeC<sub>6</sub>H<sub>4</sub>;

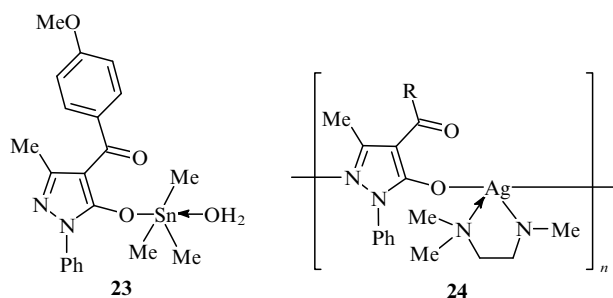
**20:** M = Zn, R<sup>1</sup> = R<sup>2</sup> = Ph, R<sup>3</sup> = DMF;

**21:** M = Cu, R<sup>1</sup> = CF<sub>3</sub>, R<sup>2</sup> = Ph, R<sup>3</sup> =

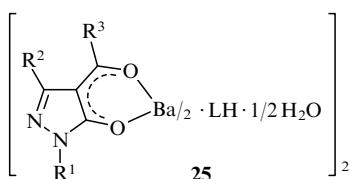
A similar type of coordination was also revealed in the monochelate complex **22** using X-ray diffraction.<sup>50</sup>



According to the X-ray diffraction data, the β-diketone ligand in the organometallic derivative **23**<sup>51, 52</sup> and in polymeric complex compounds **24** exists in the enol form.<sup>53</sup>

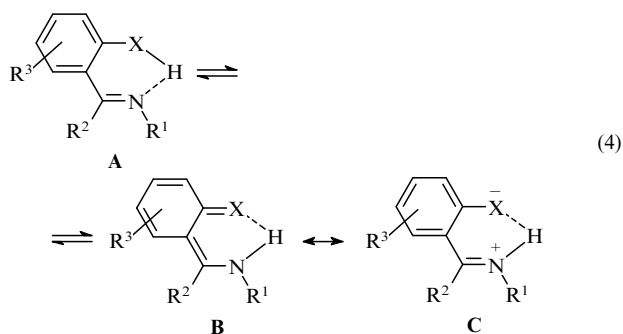


Of particular interest is complex **25** where the chelate form and the diketone form of the molecular ligand (LH) are simultaneously present.<sup>21</sup>



### III. Hydroxy-, amino-, thio- and seleno-substituted aromatic azomethines and their metal complexes

It is known that azomethines with the general formula  $o\text{-HXArC(R}^2\text{)=NR}^1$  can exist in three tautomeric forms **A**, **B** and **C** [equilibrium (4)].

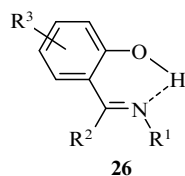


X = O, NR<sup>4</sup>, S, Se.

The tautomeric equilibrium (4) is strongly affected by the nature of the donor atom X.

#### 1. Schiff bases with one OH group

Among such tautomeric systems, azomethines of salicylaldehyde and *o*-hydroxynaphthaldehyde **26** are the most abundant.<sup>1–5, 8, 11, 54–58</sup>

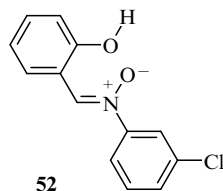


R<sup>1</sup> = Alk, Ar, Het; R<sup>2</sup> = H, Alk, Ar; R<sup>3</sup> = H, 5,6-benzo.

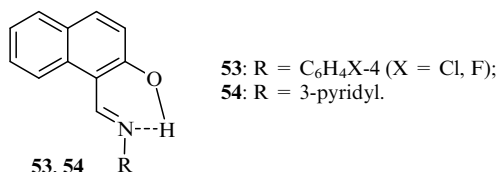
The existence of the tautomeric equilibrium (4) in solutions of azomethines **26** and of their derivatives has been confirmed by diverse physical methods,<sup>1–6, 8, 11, 54–56</sup> whereas its involvement in crystalline phases has been observed only in a few examples. The large body of X-ray diffraction studies on the structures of this class of compounds published in 1990–2000 (compounds **27–51**, Table 1) suggested that it is form **A** of the ligand that is virtually always realised in the crystalline phases.<sup>59–86</sup> It is of note that the presence of bulky substituents (compounds **31–36**)<sup>63–67</sup> or

coordinatively active fragments (compounds **37–49**)<sup>68–84</sup> at the nitrogen atom of the imino group does not affect the type of tautomeric form of the azomethine ligand.

The enolimine tautomeric form is also retained in other modifications of the imine; for instance, this was found in *o*-hydroxyazomethine *N*-oxide **52**.<sup>87</sup>

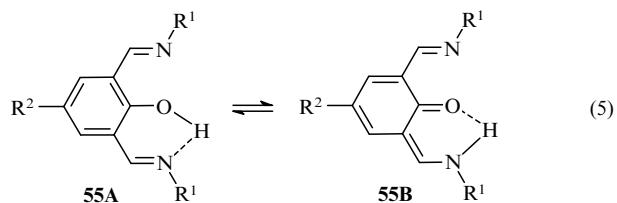


The structures of the Schiff bases of *o*-hydroxynaphthaldehyde are of particular interest.<sup>68, 88–94</sup> As has been established using <sup>1</sup>H, <sup>13</sup>C and <sup>15</sup>N NMR spectroscopy, UV and IR spectroscopy in solution,<sup>11, 55, 56, 68</sup> equilibrium (4) is shifted towards the formation of tautomer **B** (X = O)<sup>88</sup> with an increase in the bulk of the aromatic fragment annulated to the azomethine system of the aromatic fragment (*i.e.*, on going from salicylaldehyde to *o*-hydroxynaphthaldehyde). Meanwhile, tautomeric form **A** prevails<sup>89, 92–94</sup> in crystals (*e.g.*, in compounds **34**, **53**, **54**).



The study by Nazir *et al.*<sup>68</sup> is worth a special note: they synthesised both tautomers of the Schiff base of 2-hydroxy-1-naphthaldehyde and 2-aminopyridine and proved their co-existence in the crystalline phase using X-ray diffraction.

Substituted 2,6-diformylphenol diimines **55** are of significance as alterdentate<sup>13, 95, 96</sup> ligands.<sup>97–99</sup>



R<sup>1</sup> = Ph, Pr<sup>i</sup>, *p*-Tol, cyclo-C<sub>6</sub>H<sub>11</sub>; R<sup>2</sup> = Me, Bu<sup>n</sup>, OMe, Br, NO<sub>2</sub>.

A study of the photo- and thermochromic properties of compounds **55** with consideration of the character of the R<sup>1</sup> and R<sup>2</sup> substituents and the solvent nature has shown that equilibrium (5) is shifted towards the formation of the enolimine tautomer **55A**<sup>97</sup> (this form is also present in the crystalline phase according to X-ray diffraction data<sup>99</sup>) in nonpolar solvents, whereas it is shifted towards the formation of the quinomethide tautomer **55B** in polar solvents (*e.g.*, in DMSO). An increase in temperature shifts equilibrium (5) in a similar way. Alkyl substituents R<sup>1</sup> at the nitrogen atom shift the equilibrium towards the formation of tautomer **B**, whereas aryl substituents shift it towards tautomer **A**. The presence of donor substituents R<sup>2</sup> in the aldehyde fragment stabilises the enolimine form of ligand **55A**, whereas acceptor substituents shift equilibrium (5) to the right.

#### 2. Schiff bases with two and more hydroxy groups

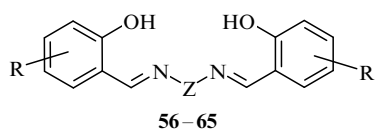
Many mono- and binuclear metal complexes containing Schiff bases with several OH groups as ligands are known.<sup>34, 35, 100, 101</sup> Among them, ligands with two hydroxy groups where two azomethine fragments are bound to each other by a bridge Z through the imine nitrogen atoms (compounds **56–65**),<sup>102–111</sup> or the carbon atoms of the aldehyde moieties (compounds **66a,b**,



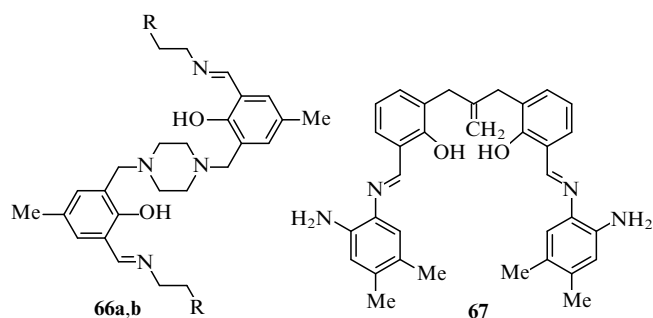
**Table 1.** Azomethines of salicylaldehyde and 2-hydroxynaphthaldehyde (type **26**) and their derivatives with known crystal structures.

| Com-<br>pound | R <sup>1</sup>                                                 | R <sup>2</sup> | R <sup>3</sup>                                | Ref.  | Com-<br>pound | R <sup>1</sup>                                  | R <sup>2</sup> | R <sup>3</sup>                                                                                         | Ref.   |
|---------------|----------------------------------------------------------------|----------------|-----------------------------------------------|-------|---------------|-------------------------------------------------|----------------|--------------------------------------------------------------------------------------------------------|--------|
| <b>27</b>     | Ph                                                             | H              | 5-Cl                                          | 59    | <b>41</b>     |                                                 | H              | 3-CH <sub>2</sub> NEt <sub>2</sub> -5-Br                                                               | 75     |
| <b>28</b>     | C <sub>6</sub> H <sub>4</sub> F                                | H              | H                                             | 60    | <b>42</b>     |                                                 | H              | 3-CHMePh-5-Me                                                                                          | 76     |
| <b>29</b>     | C <sub>6</sub> H <sub>4</sub> F                                | H              | OMe                                           | 61    | <b>43</b>     |                                                 | H              | H                                                                                                      | 77, 78 |
| <b>30</b>     |                                                                | H              | H                                             | 62    | <b>44</b>     |                                                 | H              | H                                                                                                      | 79     |
| <b>31</b>     | 2,6-Pr <sub>2</sub> <sup>1</sup> C <sub>6</sub> H <sub>3</sub> | H              | 3-Me                                          | 63    | <b>45</b>     |                                                 | H              | 5-Br                                                                                                   | 80     |
| <b>32</b>     | 2,6-Pr <sub>2</sub> <sup>2</sup> C <sub>6</sub> H <sub>3</sub> | H              | 3,5-Cl <sub>2</sub>                           | 64    | <b>46</b>     | 2-NH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> | H              | H, 5,6-benzo                                                                                           | 81, 82 |
| <b>33</b>     |                                                                | H              | H                                             | 65    | <b>47</b>     | 2-NH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> | Ph             | 5-Me                                                                                                   | 83     |
| <b>34</b>     |                                                                | H              | 4,5-benzo                                     | 66    | <b>48</b>     |                                                 | Me             | H                                                                                                      | 84     |
| <b>35</b>     |                                                                | H              | H                                             | 67    | <b>49</b>     |                                                 | Ph             | 5-Me                                                                                                   | 83     |
| <b>36</b>     |                                                                | H              | H                                             | 67    | <b>50</b>     | Pr <sup>n</sup>                                 | Me             | 4-Me-5-Cl                                                                                              | 85     |
| <b>37</b>     | 2-C <sub>5</sub> H <sub>4</sub> N                              | H              | H                                             | 68    | <b>51</b>     | CHMePh                                          | Ph             | 3,6-[(CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>2</sub> -p] | 86     |
| <b>38</b>     | 2-C <sub>5</sub> H <sub>4</sub> N                              | H              | 3,4-benzo                                     | 68    |               |                                                 |                |                                                                                                        |        |
| <b>39</b>     |                                                                | H              | H, 3,4- and<br>4,5-benzo,<br>4,5-(15-crown-5) | 69–73 |               |                                                 |                |                                                                                                        |        |
| <b>40</b>     |                                                                | H              | H                                             | 74    |               |                                                 |                |                                                                                                        |        |

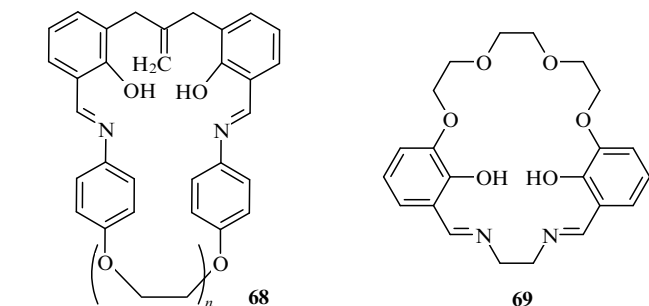
**67)** <sup>112–114</sup> or through the N and C atoms simultaneously (compounds **68**, **69**) <sup>112,115–117</sup> are the most abundant. Various alkyl, aryl, aralkyl, O-, N- and S-containing cyclic or acyclic fragments,



| Com-<br>pound | Z                               | R                                | Ref. | Com-<br>pound | Z | R     | Ref. |
|---------------|---------------------------------|----------------------------------|------|---------------|---|-------|------|
| <b>56</b>     | (CH <sub>2</sub> ) <sub>2</sub> | 5-Br                             | 102  | <b>61</b>     |   | 3-OEt | 107  |
| <b>57</b>     |                                 | 3,5-Bu <sub>2</sub> <sup>1</sup> | 103  | <b>62</b>     |   | 5-Br  | 108  |
| <b>58</b>     |                                 | 5-Br                             | 104  | <b>63</b>     |   | H     | 109  |
| <b>59</b>     |                                 | 3,5-Bu <sub>2</sub> <sup>1</sup> | 105  | <b>64</b>     |   | 3-OMe | 110  |
| <b>60</b>     |                                 | 3-OMe                            | 106  | <b>65</b>     |   | H     | 111  |



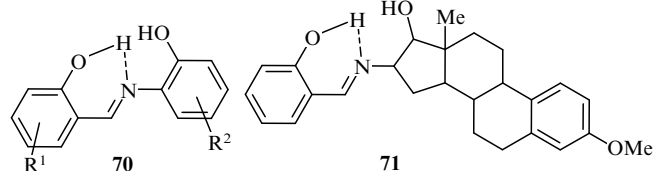
R = NMe<sub>2</sub> (a), OH (b).



$n = 3, 4$ .

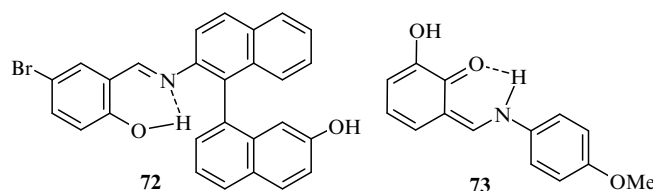
*etc.* can act as the bridges. The hydroxyimine tautomeric form of these ligands predominates in both solution and crystalline phases.

Salicylaldehyde derivatives with OH-containing substituents at the nitrogen atom, *e.g.*, compounds **70** and **71**,<sup>118, 119</sup> represent another class of azomethine ligands with two OH groups. They also exist as the enolimine form.



In these derivatives, the formation of intramolecular H-bonds can involve both OH groups giving rise to five- or six-membered rings. X-Ray diffraction studies have shown that six-membered rings are formed in bishydroxy imines **70** and **71**.

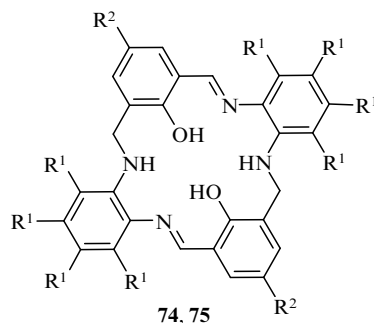
In the recently synthesised and structurally characterised<sup>120</sup> derivative **72**, only one of two possible H-bonded rings<sup>11, 58</sup> is formed, which involves the OH group of salicylaldehyde; the substituent at the nitrogen atom is rotated in such a way that the OH group is far from the nitrogen atom.



A similar situation occurs in the case of 2,3-dihydroxyazomethine **73**,<sup>121</sup> which exists in the ketoenamine form in the crystal. One of the OH groups of this compound, *viz.*, in the *ortho*-position with respect to the imino group, is involved in the intramolecular H-bonding (closure of a six-membered ring), while the second one forms H-bonds with the carbonyl oxygen atom of a neighbouring molecule. This gives rise to dimers with a ten-membered H-bonded pseudocycle. According to <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy, fast exchange between the ketoenamine and enolimine forms is observed in solution at room temperature.<sup>121</sup>

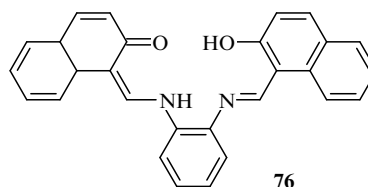
Macrocyclic azomethines (*e.g.*, compounds **74** and **75**)<sup>122–124</sup> and Schiff bases containing crown-ether fragments (*e.g.*, com-

pounds **68** and **69**)<sup>112, 115–117</sup> exist in the enolimine tautomeric form in both solution (as evidenced by <sup>1</sup>H NMR data) and the crystalline phase (according to X-ray diffraction).



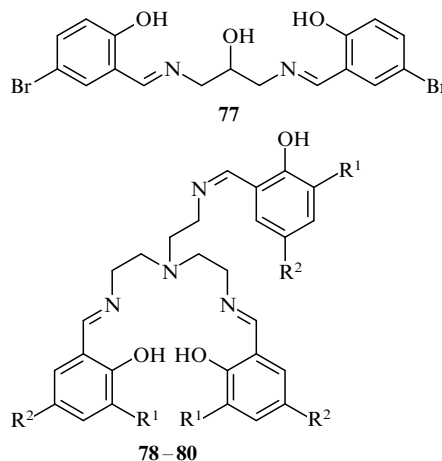
**74**: R<sup>1</sup> = F, R<sup>2</sup> = Bu<sup>t</sup>; **75**: R<sup>1</sup> = H, R<sup>2</sup> = Me.

The crystal structure of compound **76** is of considerable interest; this has been determined using X-ray diffraction and the positions of all hydrogen atoms have been revealed objectively. Two tautomeric forms, *viz.*, enolimine and ketoenamine, co-exist in molecules of **76** at 200 K.<sup>125</sup>



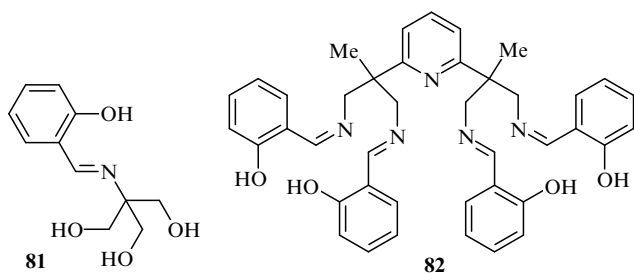
The co-existence of two tautomeric forms in one molecule of **76** is also supported by IR spectroscopy (KBr pellets): two bands at 1605 cm<sup>-1</sup> and 1622 cm<sup>-1</sup> are observed in the region 1600–1700 cm<sup>-1</sup>. Although Popovic *et al.*<sup>125</sup> attributed both bands to vibrations of the C=N bond (see Refs 126–129), there are reasons to re-assign the higher-frequency band to vibrations of the C=O group involved in the formation of the intramolecular H-bond. There is some experimental evidence that both of the above tautomeric forms also occur in solution (according to <sup>1</sup>H NMR spectroscopy). Nevertheless, the use of dimethylformamide, which is a strong donor, as a solvent in these spectral studies makes their results doubtful. In particular, a strict assignment of the signals to the fragments OH...N and O...HN is hardly possible.

Prototropic tautomerism is also observed for Schiff bases containing a larger number of OH groups. Typically, these compounds exist in the enolimine tautomeric form. Several Schiff bases containing three (compounds **77–80**)<sup>130–132</sup> and four (compounds **66b**, **81**, **82**)<sup>113, 133–135</sup> OH groups are listed below.

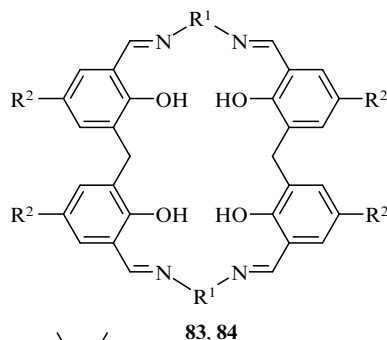


R<sup>1</sup> = H, R<sup>2</sup> = Cl (**78**); R<sup>1</sup> = Bu<sup>t</sup>, R<sup>2</sup> = H (**79**);

R<sup>1</sup> = CHO, R<sup>2</sup> = Me (**80**).



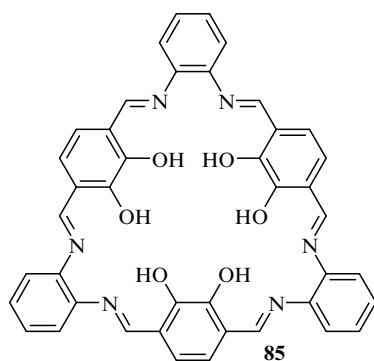
Macrocyclic compounds (e.g., ligands **83**, **84**, etc.)<sup>112, 114, 136–138</sup> constitute another group of tetrahydroxyazomethine derivatives.



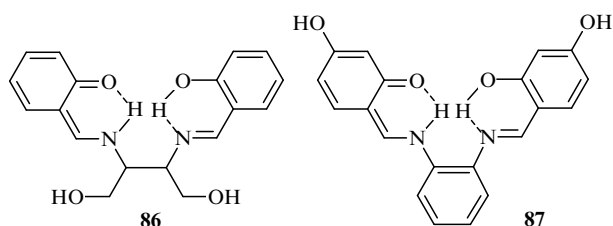
**83**:  $R^1 = \text{C}_6\text{H}_4$ ,  $R^2 = \text{Bu}^t$ ;

**84**:  $R^1 = -(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$ ,  $R^2 = \text{Me}$ .

To our knowledge, no pentahydroxyazomethine structures have been characterised so far; Schiff bases with six OH groups are represented by single macrocyclic structure **85**.<sup>139</sup>



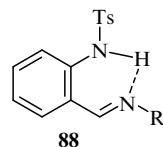
Derivatives **86**<sup>140</sup> and **87**<sup>141</sup> are worth a special note among the Schiff bases with four OH groups; their molecules contain two different tautomeric forms simultaneously, which co-exist both at room temperature and at 116 K (according to X-ray diffraction data). The reported <sup>1</sup>H NMR data (in CDCl<sub>3</sub>) concerned only the possibility of the existence of compound **86** in the open or cyclic forms rather than tautomeric equilibrium.



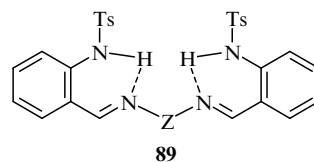
### 3. Tosylamino- and mercaptoazomethines

Tosylaminoazomethines ( $X = \text{NTs}$ ) exist predominantly in the benzenoid form **A** [like the hydroxyazomethines ( $X = \text{O}$ ) consid-

ered above], i.e., equilibrium (4) is shifted to the left.<sup>142–144</sup> This form is typical of the majority of tosylaminophenyl imines **88**<sup>143–146</sup> and bis-*o*-tosylaminobenzylidene derivatives **89** with various bridges **Z**.<sup>147–149</sup>

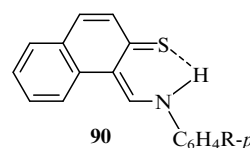


$R = \text{Ph}$ ,<sup>142</sup>  $\text{Bn}$ ,<sup>143</sup>  $\text{Bu}^t$ ,<sup>144</sup>  $\text{C}_6\text{H}_4\text{OH}-o$ ,<sup>145</sup> (see <sup>146</sup>).



$Z = \text{C}_2\text{H}_4$ ,<sup>147</sup> (see <sup>148</sup>), (see <sup>149</sup>).

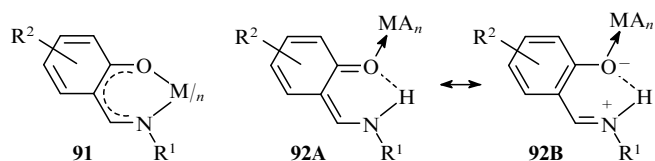
In contrast, in the case of sulfur-containing analogues of hydroxyazomethines ( $X = \text{S}$ ), equilibrium (4) is shifted towards tautomer **B**, as evidenced by data from UV, IR and <sup>1</sup>H NMR spectroscopy and supported by quantum-chemical calculations.<sup>150, 151</sup> The fraction of tautomer **B** increases with an increase in the polarity of the solvent, nucleophilicity of the substituent at the nitrogen atom ( $R^1$ ) and acceptor properties of the substituent  $R^3$  (see Ref. 150). In particular, it was established<sup>151</sup> that the thio-derivative **90** exists virtually exclusively in the tautomeric form **B** in solution (DMSO, ethanol).



$R = \text{H}, \text{Me}, \text{Cl}, \text{OMe}, \text{NO}_2$ .

### 4. Coordination compounds of azomethines

Coordination compounds of hydroxyazomethines can be subdivided<sup>1, 8, 22, 27, 28, 34, 35, 57, 58</sup> into traditional chelates **91** and non-standard molecular complexes **92A** and **92B**.



$R^1 = \text{Alk}, \text{Ar}$ ;  $R^2 = \text{H}, \text{Hal}, \text{NO}_3$ ;  $A = \text{Hal}, \text{NO}_3$ ;  $n = 3, 4$ .

There is experimental evidence<sup>58, 152, 153</sup> that interconversion is possible between the chelate (**91**) and molecular (**92**) complexes.<sup>‡</sup>

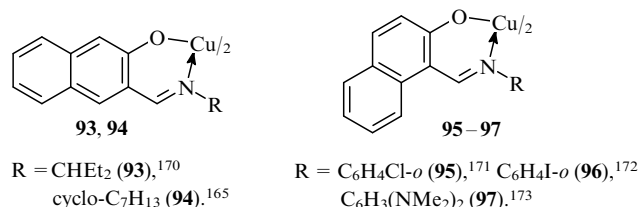
Intracomplex compounds of type **91** were the subject of numerous monographs<sup>34–37</sup> and reviews,<sup>8, 22, 58, 154–159</sup> thus only compounds with crystal structures established over the last five years will be considered below. The respective copper, zinc and cobalt intracomplex compounds (structural data published in 2000–2004)<sup>63, 152, 160–169</sup> are listed in Table 2.

<sup>‡</sup> In the majority of schematic drawings of chelate structures, the enol-imine tautomeric form **A** [equilibrium (4)] is depicted, although the bonds in anionic azomethine ligands (complex **91**) are substantially delocalised.

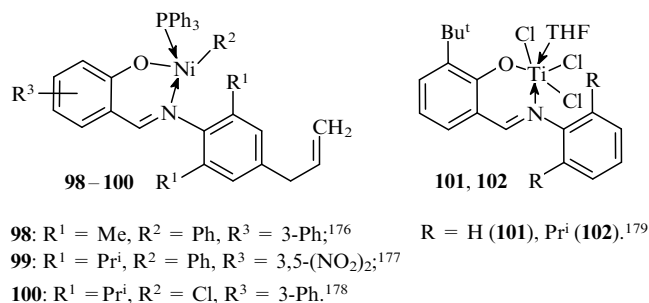
**Table 2.** Mononuclear chelate complexes of 3d metals with hydroxy-azomethine ligands of the type **91**.

| M  | R <sup>1</sup>                                                                    | R <sup>2</sup>                   | Ref. |
|----|-----------------------------------------------------------------------------------|----------------------------------|------|
| Cu | CHPh <sub>2</sub>                                                                 | H                                | 160  |
| Cu | n-C <sub>8</sub> H <sub>17</sub>                                                  | H                                | 161  |
| Cu | C <sub>6</sub> H <sub>4</sub> OMe- <i>p</i>                                       | H                                | 162  |
| Cu | C <sub>6</sub> H <sub>4</sub> F- <i>p</i>                                         | H                                | 163  |
| Cu | C <sub>6</sub> H <sub>4</sub> Cl- <i>p</i>                                        | H                                | 164  |
| Cu | C <sub>5</sub> H <sub>9</sub> -cyclo                                              | H                                | 165  |
| Cu | C <sub>6</sub> H <sub>11</sub> -cyclo                                             | H                                | 165  |
| Cu |  | 3,5-Bu <sub>2</sub> <sup>1</sup> | 166  |
| Zn | Pr <sup>n</sup>                                                                   | H                                | 152  |
| Zn | C <sub>6</sub> H <sub>3</sub> Pr <sub>2</sub> <sup>i</sup> -2,6                   | 3,5-Bu <sub>2</sub> <sup>1</sup> | 63   |
| Zn | CHMePh                                                                            | 4-OMe                            | 167  |
| Zn | CHMePh                                                                            | 4-NO <sub>2</sub>                | 167  |
| Zn | C <sub>6</sub> H <sub>3</sub> Pr <sub>2</sub> <sup>i</sup> -2,6                   | 4-NO <sub>2</sub>                | 168  |
| Co | cyclo-C <sub>6</sub> H <sub>9</sub> Pr <sup>i</sup> -2-Me-5                       | H                                | 169  |

A series of copper complexes **93–97** containing azomethines of naphthaldehyde as ligands have been characterised structurally.<sup>165, 170–173</sup>

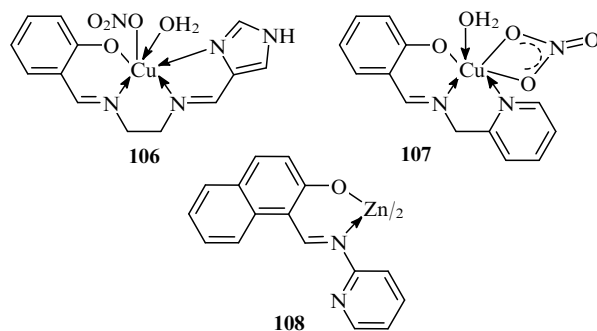
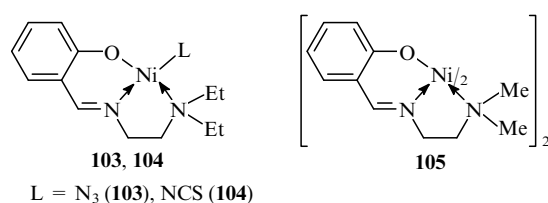


Monochelates **98–102**<sup>176–179</sup> are of great potential importance as catalysts of polymerisation processes.<sup>174, 175</sup>



In complexes **101** and **102**, trimethylsilyl derivatives of salicylideneaniline are used as ligands.<sup>179</sup>

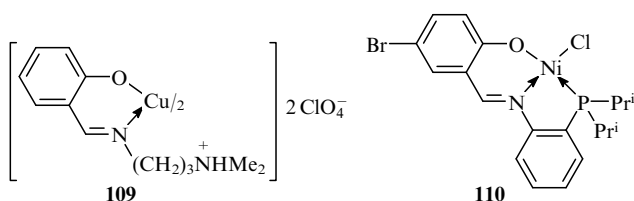
In complexes of hydroxyazomethines containing coordinatively active fragments with N-, P-, O- or S-donor centres at the nitrogen atom of the imino group,<sup>180–186</sup> additional coordination with the metal atom is observed. For instance, this is typical of complexes **103–108**.<sup>181, 184, 186–188</sup>



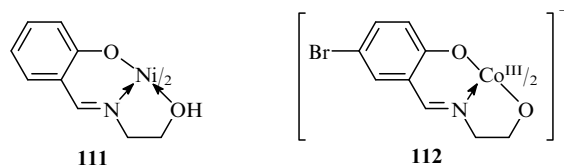
The dependence of the coordinative activity of the nitrogen atom of the pyridine fragment on the size of the metallacycle formed was analysed by several authors.<sup>34, 35, 57, 58</sup> It was found that five-membered rings are more stable than four-membered ones. The molecular structures of compounds **107** and **108** support this conclusion.

Protonation of the amino group in the coordinatively active substituent at the nitrogen atom of the imino group (compound **109**)<sup>189</sup> suppresses the donor properties of the substituent.

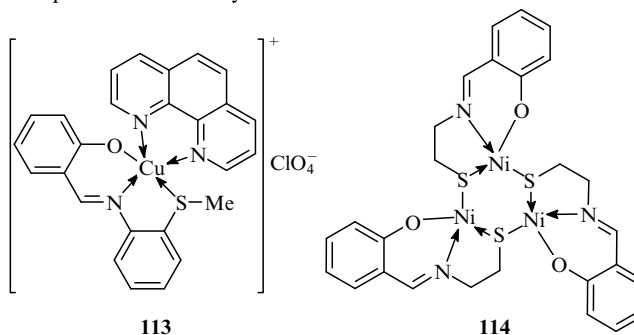
Among phosphorus-containing azomethine compounds, we are aware of only one complex **110** with the coordination core NiNPOCl.<sup>190</sup>



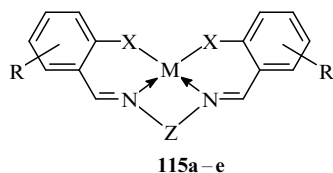
Intracomplex compounds of azomethines with coordinatively active oxygen-containing fragments<sup>57, 58, 191</sup> include mononuclear complexes with a protonated (compound **111**)<sup>192, 193</sup> or deprotonated (compound **112**)<sup>194</sup> OH group.



In the case of hydroxyazomethine ligands with sulfur-containing coordinatively active substituents, both mono- (compound **113**)<sup>195–197</sup> and polynuclear (compound **114**)<sup>198</sup> complexes have been synthesised.



The structures of chelates **115** for the Group III elements of the Periodic Table have recently been reviewed<sup>199</sup> and structures of complexes of 3d metals (copper, nickel, cobalt) are considered in Refs 200–204.



**115a:** M = Cu, Z = (CH<sub>2</sub>)<sub>3</sub>, X = O, R = H;<sup>200</sup>

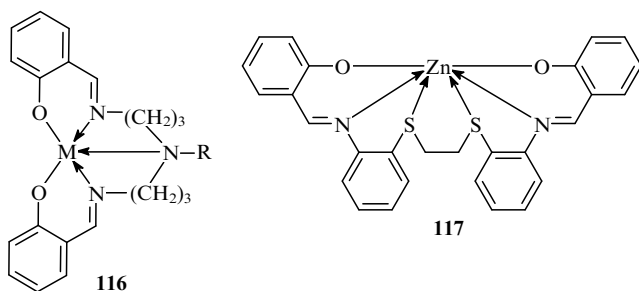
**115b:** M = Ni, Z = (CH<sub>2</sub>)<sub>3</sub>, X = O, R = 6-OMe;<sup>201</sup>

**115c:** M = Ni, Z = (CHPh)<sub>2</sub>, X = O, R = H;<sup>202</sup>

**115d:** M = Ni, Z = (CHPh)<sub>2</sub>, X = O, R = NEt<sub>2</sub>;<sup>203</sup>

**115e:** M = Co, Z = , X = O, R = 3,5-Bu<sub>2</sub>;<sup>204</sup>

If the bridge Z contains coordinatively active donor atoms, the dentate numbers of ligands and coordination numbers of the complex-forming metal atoms increase (complexes **116**<sup>205</sup> and **117**<sup>206</sup>).



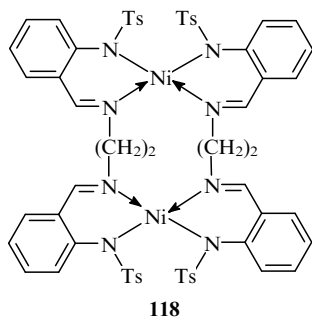
M = Co, Cu; R = H, Pr<sup>n</sup>, SiMe<sub>3</sub>, Si(OMe)<sub>3</sub>.

Azomethine compounds with three OH groups (*e.g.*, **78–80**) form complexes with lanthanides with the composition LnL (Ln = La, Ce, Sm, Tb, Y or Lu) where triply deprotonated molecules act as the ligands L<sup>3-</sup>. In these complexes, a complex-forming metal atom binds three nitrogen atoms of the C=N groups and a nitrogen atom of the amino group (according to X-ray diffraction data).<sup>132</sup>

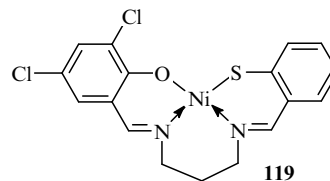
Coordination of ligand **86**, which exists in two tautomeric forms, gives rise to a series of chelates **115** (M = Mn, X = O, R = H, Z = CH<sub>2</sub>OH–CH<sub>2</sub>OH) with structures typical of bis-salicylideneiminates.<sup>140</sup>

Similar complexes are formed upon coordination of ligands **89**.<sup>207–211</sup> In particular, metal chelates with the coordination core MN<sub>4</sub> [Z = (CH<sub>2</sub>)<sub>3</sub>, M = Cu;<sup>208</sup> Z = (CH<sub>2</sub>)<sub>2</sub>CHOH, M = Zn;<sup>209</sup> Z = 1,2-C<sub>6</sub>H<sub>4</sub>, M = Ni;<sup>210</sup> Z = 1,2-C<sub>6</sub>H<sub>10</sub>, M = Ni;<sup>149</sup> Z = 1,2-C<sub>6</sub>H<sub>4</sub>, M = Cu (see Ref. 211)] analogous to **115** (X = NTs) have been prepared.

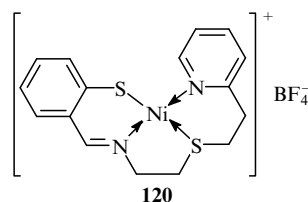
The ligands **89** (Z = C<sub>2</sub>H<sub>4</sub>) can form binuclear chelates in some specific cases as well (*e.g.*, complex **118**).<sup>212</sup>



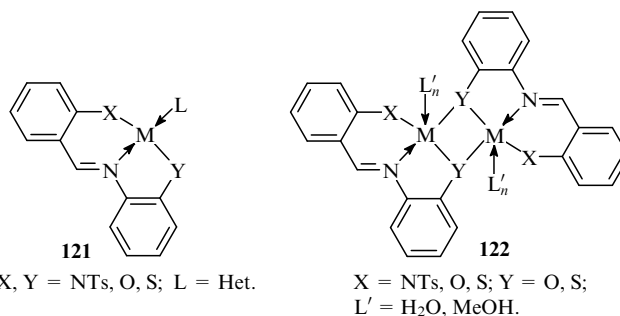
The Schiff bases with N,N,O,S- and N,N,S,S-donor centres form intracomplex compounds **119**<sup>213</sup> and **115** (X = S, M = Cu, Z = C<sub>2</sub>H<sub>4</sub>).<sup>214</sup> which are characterised by the *cis*-planar configuration of the coordination core.



The mercaptoazomethine ligand with the substituent (CH<sub>2</sub>)<sub>2</sub>S(CH<sub>2</sub>)<sub>2</sub>(C<sub>5</sub>H<sub>4</sub>N-2) with coordinatively active N and S atoms at the nitrogen atom of the imino group forms a nickel complex with the NiN<sub>2</sub>S<sub>2</sub> coordination core (complex **120**, X-ray diffraction data).<sup>215</sup>

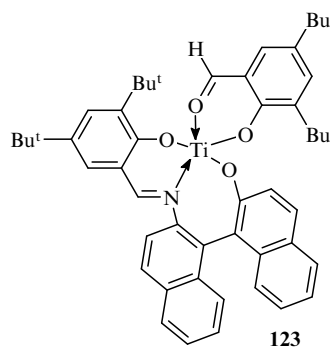


Numerous mono- (**121**) and binuclear (**122**) structures with tetra-, penta- and hexa-coordinated metal sites have been synthesised based on bishydroxyazomethines **70** (O,N,O-) and related N,N,N-, N,N,O-, N,N,S- and N,O,S-tridentate azomethines.

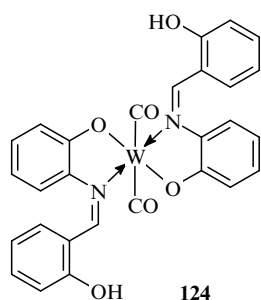


The structures of these complexes have been surveyed in several monographs<sup>34–37</sup> and a review<sup>58</sup>. Recently, the structures of nickel, copper and zinc complexes with tosylaminoazomethine ligands (X = NTs, L = 2-aminopyridine, L' = MeOH) have been reported.<sup>216–218</sup>

Compound **123**<sup>120</sup> containing six- and seven-membered metallocyclic fragments represents an interesting example of complex formation involving a tridentate azomethine ligand.

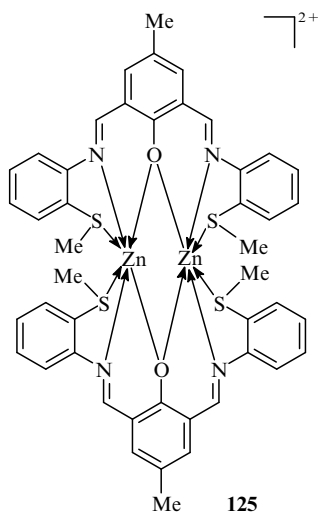


The presence of two OH groups in positions suitable for double chelation does not guarantee the realisation of structures **121** or **122**. For instance, ligand **71** afforded mononuclear intracomplex compounds due to coordination of only one hydroxy group of the hydroxyazomethine fragment.<sup>119</sup> An unusual structure of tungsten complex **124** was suggested by El-Medani.<sup>219</sup> Unfortunately, no reliable X-ray diffraction data confirming this structure are available for this compound.

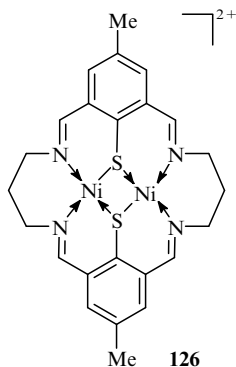


124

Complexes based on the alterdentate ligand systems **55** or on their sulfur-containing analogues<sup>220–222</sup> have predominantly binuclear structures. The metal atom is coordinated by both imine nitrogen atoms and an oxygen (complex **125**)<sup>221</sup> or sulfur (complex **126**) atom.<sup>222</sup> Similar complexes are formed with macrocyclic Schiff bases.<sup>158, 159, 220</sup>

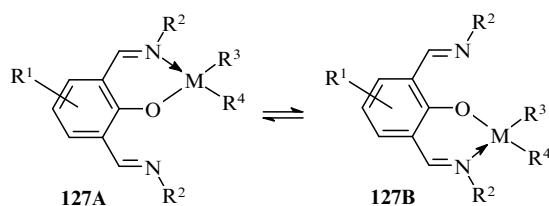


125



126

Sometimes, both imine nitrogen atoms of the alterdentate ligands **55**<sup>13, 14, 97</sup> cannot be involved in coordination with a metal atom simultaneously due to spatial restrictions. In these cases, intermediate structures (**127**) are formed with equally probable involvement of any of the two nitrogen atoms in coordination with the metal.



127A

127B

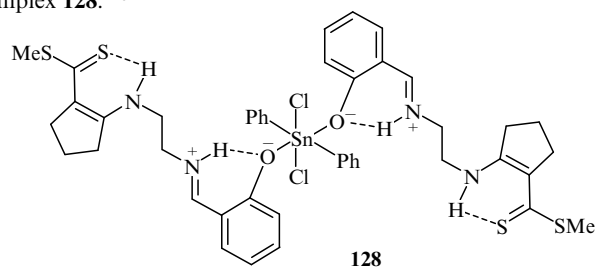
M = B, Ga, In; R<sup>1</sup> = H, 5-NO<sub>2</sub>, 5,6-benzo;

R<sup>2</sup> = Me, Pr<sup>i</sup>, Bn; R<sup>3</sup> = OMe, OPr<sup>i</sup>, OBn; R<sup>4</sup> = Ph, C<sub>6</sub>H<sub>4</sub>OMe-4.

Similar coordination is typical, for instance, of organoboron derivatives.<sup>223</sup>

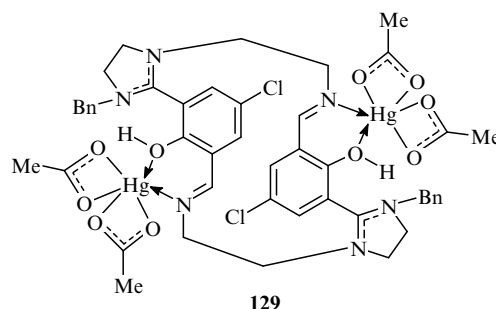
The intrachelate bonds in complexes **91** with anionic ligands are delocalised. Meanwhile, according to X-ray diffraction studies with objective localisation of all hydrogen atoms, the ligand exists in molecular complexes **92** in the ketoenamine (quinomethide) form.<sup>34, 35, 58</sup> This form was also revealed in complexes of salicylidene imines (**92**: R<sup>1</sup> = Ar, R<sup>2</sup> = H)<sup>152</sup> and hydroxynaphthylmethylidene (**92**: R<sup>1</sup> = Ph, R<sup>2</sup> = 4,5-benzo)<sup>89</sup> with zinc dichloride. Although the proton is reliably localised at the nitrogen atom and the coordination of the oxygen atom with the metal atom is confirmed in such complexes, the formation of enolimine<sup>224</sup> and

zwitter-ionic<sup>152</sup> structures cannot be totally ruled out. In particular, a zwitter-ionic structure was suggested for the molecular complex **128**.<sup>225</sup>



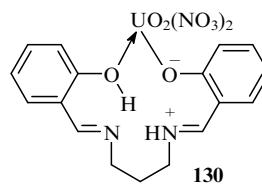
128

Compound **129**<sup>226</sup> manifests the N,O-chelate coordination that is unusual for molecular complexes of hydroxyazomethines.



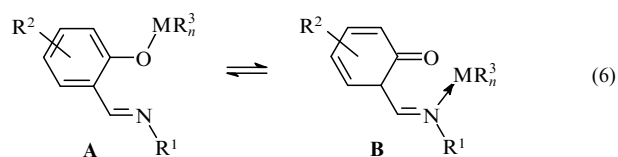
129

The structure of **130**<sup>227</sup> confirms the possibility of the co-existence of two tautomeric forms in one molecule of bishydroxyazomethine.



130

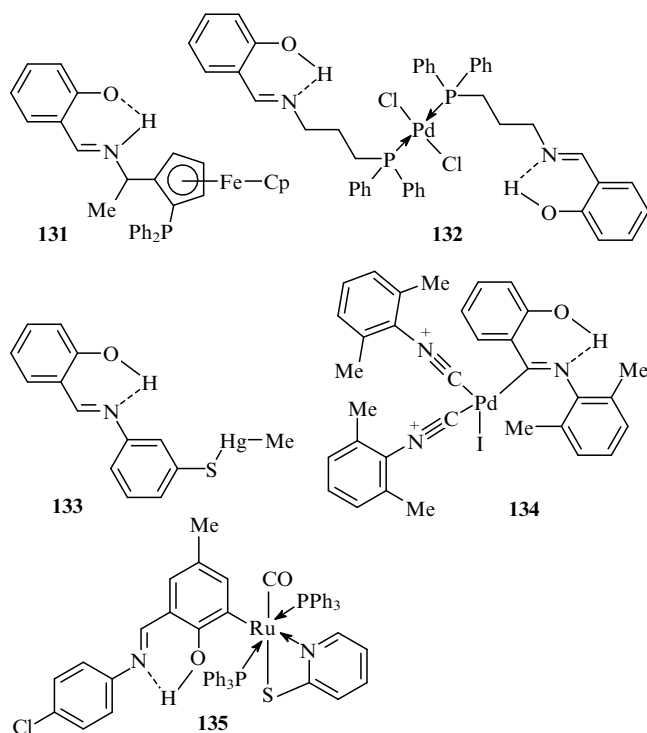
The tautomeric metallotropic equilibrium (6) involving organometallic derivatives of azomethines was studied using spectroscopic<sup>228</sup> and X-ray diffraction<sup>229</sup> methods. It was established that coordination of the oxygen atom with a metal atom stabilises the enolimine (benzenoid) form **A**, whereas coordination of the nitrogen atom stabilises the ketoenamine (quinomethide) tautomeric form **B**.



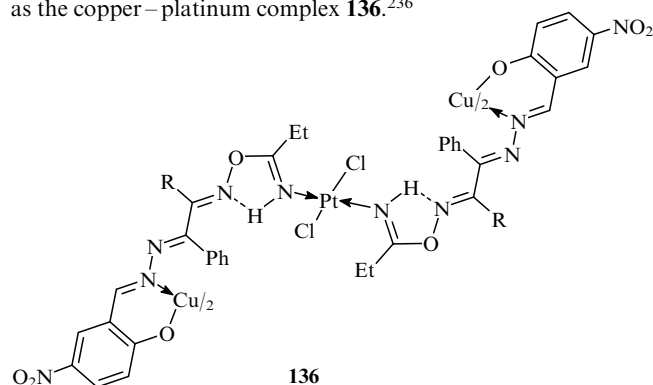
(6)

R<sup>1</sup> = H, Me, C<sub>6</sub>H<sub>4</sub>OMe-*p*; R<sup>2</sup> = H, 5,6-benzo; R<sup>3</sup> = Me, Ph; M = Hg, Tl; n = 1, 2.

The fraction of the latter increases with an increase in the solvent polarity (*e.g.*, DMSO) and with a lowering of the temperature.<sup>228</sup> Apparently, both tautomeric forms occur in crystalline phases.<sup>229</sup> Although the tautomeric equilibrium (6) has not been studied in detail with other organometallic derivatives of hydroxyazomethines, X-ray diffraction data indicate the predominance of the enolimine tautomers **A**. The enolimine form of the ligand is also realised in complexes **131–135**<sup>230–235</sup> where substituents at the nitrogen (compounds **131–133**) or carbon (compound **134**) atoms of the imino group or at the carbon atom of salicylaldehyde (compound **135**) contain metal-bearing fragments.



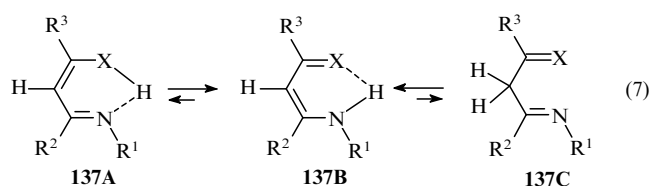
Compounds similar to **131–135** can be used as metal-containing ligands for the synthesis of heteronuclear complexes, such as the copper–platinum complex **136**.<sup>236</sup>



Thus, functionalised azomethines exist predominantly in the enolimine tautomeric form independently of the nature of the substituents. Intracomplex compounds **91** containing this ligand system are characterised by delocalised intrachelate bonds, whereas the ketoenamine tautomeric form of ligand **92** is stabilised in molecular complexes due to metal coordination.

#### IV. $\beta$ -Aminovinyl ketones, thiones, imines and their complexes

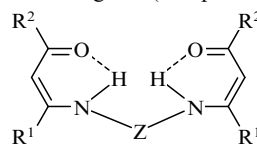
In contrast to the functionalised aromatic Schiff bases, the tautomeric equilibrium (7) in solutions of enamino ketones ( $X = O$ ), thiones ( $X = S$ ) and imines ( $X = NR^4$ ) **137** is shifted towards form **B**, as evidenced by data from NMR and electronic spectroscopy and supported by quantum-chemical calculations.<sup>11, 55, 56, 237, 238</sup>



$X = NR^4, O, S; R^1 - R^4 = H, \text{Alk}, \text{cyclo-Alk}, \text{Ar}.$

X-Ray diffraction studies<sup>239–253</sup> of enamino ketones ( $X = O$ ) **138–153** confirmed the existence of form **B** in the crystalline phases as well (Table 3).

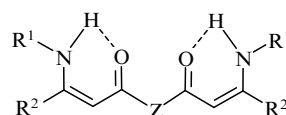
This form is also typical of bisenamino ketones containing various bridges  $Z$  (compounds **154–159**).<sup>254–261</sup>



**154–157**

**154:**  $Z = C_2H_4$ ,  $R^1 = R^2 = \text{Me}, \text{Ph}, \text{Bn}$ ; **155:**  $Z = o\text{-}C_6H_4$ ,  $R^1 = \text{Me}$ ,  $R^2 = \text{Ph}$ ; **156:**  $Z = p\text{-}C_6H_4$ ,  $R^1 = \text{CO}_2\text{Et}$ ,  $R^2 = (\eta^5\text{-}C_5H_4)\text{FeCp}$ ;

**157:**  $Z = (\eta^5\text{-}C_5H_4)_2\text{Fe}$ ,  $R^1 = R^2 = \text{Me}$ .



**158, 159**

**158:**  $Z = (CF_2)_4$ ,  $R^1 = \text{Pr}^i$ ,  $R^2 = \text{Me}$ ;

**159:**  $Z = (\eta^5\text{-}C_5H_4)_2\text{Fe}$ ,  $R^1 = \text{Ph}$ ,  $R^2 = \text{CO}_2\text{Et}$ .

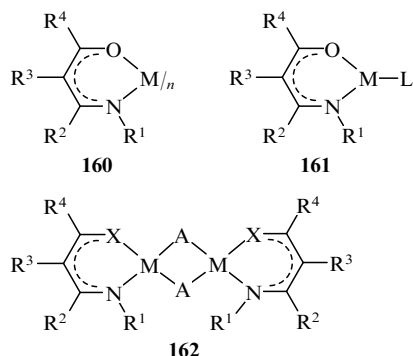
**Table 3.**  $\beta$ -Aminovinyl ketones (type **137**) with known crystal structures.

| Compound    | $R^1$                                                               | $R^2$                                           | $R^3$                          | Ref. |
|-------------|---------------------------------------------------------------------|-------------------------------------------------|--------------------------------|------|
| <b>138</b>  | 4-BrC <sub>6</sub> H <sub>4</sub>                                   | Me                                              | Me                             | 239  |
| <b>139</b>  | 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>                     | Me                                              | Me                             | 240  |
| <b>140</b>  | C <sub>6</sub> F <sub>5</sub>                                       | Me                                              | Me                             | 241  |
| <b>141</b>  | XC <sub>6</sub> H <sub>4</sub> ( $X = H, \text{Br}, \text{NEt}_2$ ) | C(O)Ph                                          | Ph                             | 242  |
| <b>142</b>  | 2-MeC <sub>6</sub> H <sub>4</sub>                                   | Bz                                              | Ph                             | 243  |
| <b>143</b>  | Bu <sup>n</sup>                                                     | CO <sub>2</sub> Et                              | ( $\eta^5\text{-}C_5H_4$ )FeCp | 245  |
| <b>144</b>  |                                                                     | Me                                              | Me                             | 119  |
| <b>145</b>  |                                                                     | CO <sub>2</sub> Et                              |                                | 246  |
| <b>146</b>  | 2-NH <sub>2</sub> -5-NO <sub>2</sub> C <sub>6</sub> H <sub>3</sub>  | 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> | Ph                             | 247  |
| <b>147</b>  | 2-C <sub>5</sub> H <sub>4</sub> N                                   | Me                                              | Ph                             | 248  |
| <b>148</b>  | 2-HOC <sub>6</sub> H <sub>4</sub>                                   | Me                                              | Ph                             | 249  |
| <b>149</b>  | 2-HOC <sub>6</sub> H <sub>4</sub>                                   | Me                                              | Me                             | 250  |
| <b>150</b>  |                                                                     | Me                                              | Me                             | 251  |
| <b>151a</b> | 1-C <sub>10</sub> H <sub>7</sub>                                    | Me                                              |                                | 252  |
| <b>151b</b> | 1-C <sub>10</sub> H <sub>7</sub>                                    | CO <sub>2</sub> Et                              |                                | 252  |
| <b>152</b>  | 4-MeOC <sub>6</sub> H <sub>4</sub>                                  | Me                                              |                                | 253  |
| <b>153</b>  | 4-MeOC <sub>6</sub> H <sub>4</sub>                                  | CO <sub>2</sub> Et                              |                                | 253  |

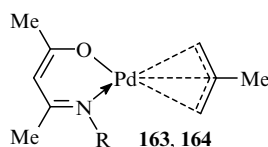


Metal chelates **160** are the most common complex compounds of  $\beta$ -aminovinyl ketones; their structures have been considered in numerous publications, including reviews,<sup>8, 27, 58, 262</sup> theses<sup>263–265</sup> and monographs.<sup>35, 36</sup> Metal chelates of the type **160** are widely used for the deposition of metal films; thus they attract undying interest. For instance, the structures of copper and palladium metal chelates have recently been reported.<sup>266–268</sup>

In addition to intracomplex compounds **160**, the deprotonated ligands also form mononuclear complexes **161**<sup>269, 270</sup> and binuclear bridged complexes **162**.<sup>264</sup>

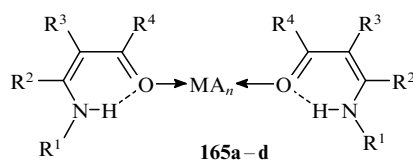


Organopalladium compounds **163** and **164**<sup>269, 270</sup> can be considered as examples of mono- $\beta$ -aminovinylketonate complexes.



R = CHMePh (**163**), Ph (**164**).

Neutral  $\beta$ -aminovinylketonate ligands (LH) form molecular adducts **165** with the stoichiometry  $(\text{LH})_2 \cdot \text{MA}_n$ .<sup>8</sup> As in the case of free molecules of these enamino ketones, the amino ketone form of the ligands was found<sup>271–276</sup> in these complexes.



**165a**:  $\text{MA}_n = \text{TiCl}_4$ ,  $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{R}^4 = \text{Me}$ ,  $\text{R}^3 = \text{H}$  (taken from Ref. 8);

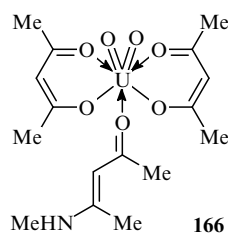
**165b**:  $\text{MA}_n = \text{ZnI}_2$ ,  $\text{R}^1 = \text{Bu}^i$ ,  $\text{R}^2 = \text{R}^4 = \text{Me}$ ,  $\text{R}^3 = \text{H}$  (see Ref. 271);

**165c**:  $\text{MA}_n = \text{MoO}_2\text{Cl}_2$ ,  $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{R}^4 = \text{Me}$ ,  $\text{R}^3 = \text{H}$  (see Refs 272 and 273);

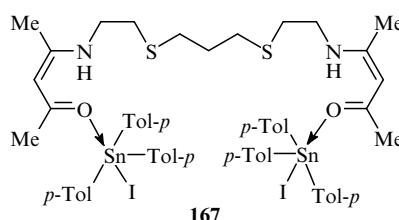
**165d**:  $\text{MA}_n = \text{ZrCl}_4$ ,  $\text{R}^1 = \text{Pr}^i$ ,  $\text{R}^2 = \text{R}^4 = \text{Me}$ ,  $\text{R}^3 = \text{H}$  (see Ref. 274).

A spectroscopic study of the adduct **165a** has been performed<sup>8</sup> in order to determine the type of ligand coordination (*i.e.*, through the N or O atom). A decrease in the frequency of the stretching vibrations of the carbonyl group in the range 1610–1650  $\text{cm}^{-1}$  (which can be due to the formation of a M–O bond) was used as the criterion for localisation of the coordination bond. Notwithstanding, it should be taken into account that the absorption band of the azomethine group shifted to higher frequencies due to M–N coordination can also fall in the same range. This problem was unambiguously solved by X-ray structural investigation of the adducts **165**.

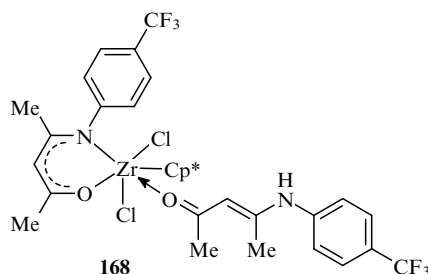
For the first time, coordination of the neutral ligand LH through the oxygen atom was established for a mixed-ligand complex **166**.<sup>271</sup>



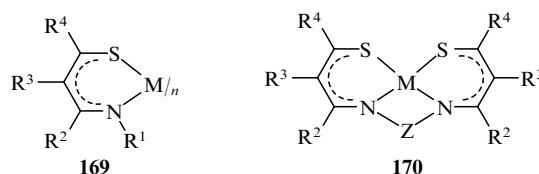
The bisenaminoketone adduct **167**<sup>276</sup> reveals similar coordination of the ligand.



Complex **168** is of particular interest since it contains the ligand system in the anionic and neutral forms simultaneously.<sup>277</sup>



Like enamino ketones, their sulfur-containing analogues, enamino thiones **137** (X = S), exist in the  $\beta$ -aminovinylthione tautomeric form **B**.<sup>278–281</sup> Metal salts and deprotonated ligands yield complex compounds **169** and **170** with delocalised chelate bonds.



Depending on the nature of the metal atom and the substituent  $\text{R}^1$  at the nitrogen atom, the metal cores in chelates **169** adopt the *cis*-planar (M = Ni;  $\text{R}^1 = \text{Me}$ , Et),<sup>281</sup> tetrahedral (M = Zn,  $\text{R}^1 = \text{cyclo-C}_6\text{H}_{11}$ )<sup>8, 282</sup> or square-pyramidal (M = Cu,  $\text{R}^1 = 8\text{-quinolyl}$ )<sup>283</sup> configurations. Despite the fact that octahedral coordination of the copper atom might be expected for copper complex with the  $\beta$ -aminovinylthione ligand containing a coordinatively active quinoline fragment, X-ray diffraction data indicated that only one nitrogen atom of the azine substituent is involved in coordination.<sup>264</sup>

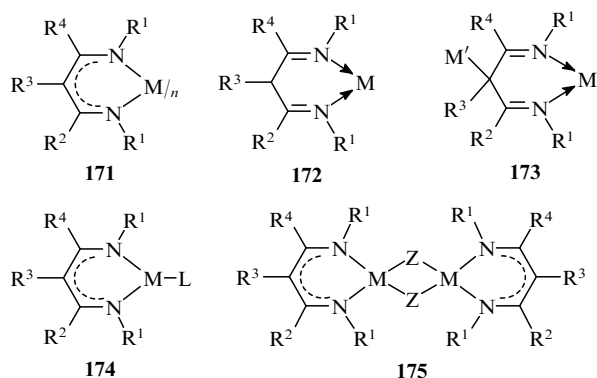
The nickel complex **169** ( $n = 2$ ) possesses the *cis*-planar structure, whereas analogous copper ( $n = 2$ ) and zinc ( $n = 2, 4$ ) complexes are characterised by tetrahedral chelate structures.<sup>8</sup>

It was assumed that neutral  $\beta$ -aminovinylthione ligands form molecular complexes of the type **165** with metal salts (*e.g.*, with  $\text{MoO}_2\text{Cl}_2$ ).<sup>8</sup> The formation of an Mo–S bond therein was suggested based on IR data (which cannot be considered reliable since the frequency of the stretching vibrations of the C=S bond is not characteristic), thus this requires independent confirmation using X-ray diffraction.

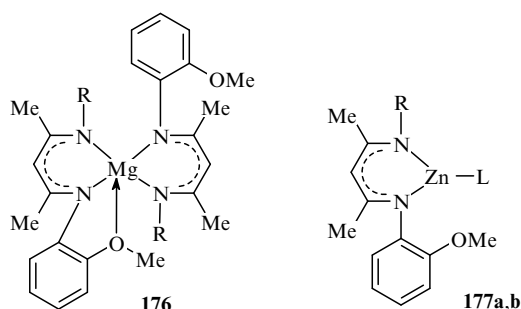
According to X-ray diffraction studies,<sup>284–287</sup> the tautomeric forms **A** and **B** for  $\beta$ -aminovinyl imines **137** (X =  $\text{NR}^4$ ) can hardly

be distinguished, especially in the case of similar types of substituents  $R^1$  and  $R^4$ ; form **C** has never been detected.

A series of coordination compounds synthesised from  $\beta$ -aminovinyl imines ( $X = NR^1$ ) has been analysed by Bourget-Merle *et al.*;<sup>288</sup> they proposed that their structures can be classified into several types with **171**–**173** being the most interesting.



Examples of metal chelates of anionic  $\beta$ -aminovinylimine ligands with delocalised coordination bonds include both mono- (types **171** and **174**) and binuclear (type **175**) structures.<sup>288–291</sup> Recently reported synthesis<sup>292</sup> of a non-symmetrically substituted  $\beta$ -aminovinyl imine [2-(2-methoxyphenylimino)-4-(2,6-diisopropylphenylimido)pent-2-ene, BDI] and its magnesium and zinc complexes  $(BDI)_2Mg$ ,  $(BDI)MgPr^i$ ,  $(BDI)MgNPr_2^i$ ,  $(BDI)ZnN(SiMe_3)_2$  and  $(BDI)ZnEt$  are worth a special note. The structures of the bischelatate magnesium complex (**176**) and two monochelate zinc complexes were determined using X-ray diffraction.



$R = C_6H_3Pr_2^{i-2,6}$ .  $R = C_6H_3Pr_2^{i-2,6}$ ;  $L = Et$  (**a**),  $N(SiMe_3)_2$  (**b**).

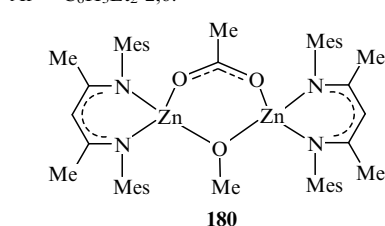
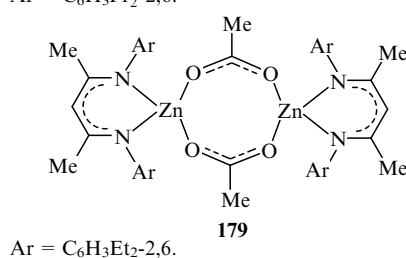
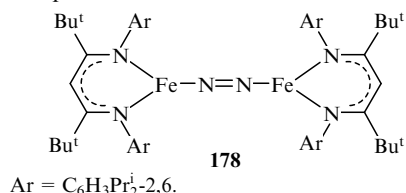
It was found that the two BDI ligands in the bischelatate magnesium complex are coordinated differently to the metal atom.

Since the number of publications devoted to monochelate anionic complexes **174** is very large, we mention here only recent structural studies of tricoordinated iron [ $R^1 = 2,6-Pr_2^iC_6H_3$ ,  $R^2 = Bu^t$ ,  $L = Me$ ;<sup>293</sup>  $R^1 = 2,6-Pr_2^iC_6H_3$ ,  $C_6F_5$ ,  $Mes$ ,  $2,6-Me_2C_6H_3$ ,  $2,6-Cl_2C_6H_3$ ,  $R^2 = Me$ ,  $L = N(SiMe_3)_2$ ;<sup>294</sup>  $R^1 = Ar$ ,  $R^2 = Alk$ ,  $L = Et$ ,  $CH_2Bu^t$ ,  $Pr^i$ ;<sup>295</sup>  $R^1 = 2,6-Pr_2^iC_6H_3$ ,  $R^2 = Me$ ,  $Bu^t$ ,  $L = Et$ ,  $Bu^i$ ,  $Bu^t$  (see Ref. 296)], cobalt [ $R^1 = 2,6-Pr_2^iC_6H_3$ ,  $R^2 = Bu^t$ ,  $L = Cl$ ,  $Me$ ;<sup>293</sup>  $R^1 = 2,6-Pr_2^iC_6H_3$ ,  $R^2 = Me$ ,  $L = N(SiMe_3)_2$ ;<sup>294</sup>  $R^1 = 2,6-Cl_2C_6H_3$ ,  $R^2 = Bu^t$ ,  $L = Cl$ ,  $THF$ ;<sup>293</sup>  $R^1 = 2,6-Cl_2C_6H_3$ ,  $R^2 = Me$ ,  $L = Cl$ ,  $N(SiMe_3)_2$  (see Ref. 297)], manganese [ $R^1 = 2,6-Pr_2^iC_6H_3$ ,  $R^2 = Me$ ,  $L = N(SiMe_3)_2$  (see Ref. 294)], copper [ $R^1 = Mes$ ,  $R^2 = H$ ,  $L = OAc$ ;<sup>298</sup>  $R^1 = 2,6-Pr_2^iC_6H_3$ ,  $R^2 = Me$ ,  $L = SCPh_3$ ,  $Py$  (see Ref. 299)] and zinc [ $R^1 = 2,6-Pr_2^iC_6H_3$ ,  $R^2 = Me$ ,  $L = NPr_2$ ,  $OBu^t$  (see Ref. 300)] complexes and tetracoordinated nickel  $(Dipp)NiR(2,4-Lut)$  ( $Dipp = CH[CMEN(C_6H_3Pr_2^{i-2,6})_2]$ ,  $2,4-Lut = 2,4-lutidine$ ,  $R = Me$ ,  $Et$ ,  $Pr$ ),<sup>301</sup> zinc  $(Dipp)Zn(OSiPh_3)(THF)$ <sup>300</sup> and magnesium  $(Dipp)Mg(NPr_2)(THF)$  and  $(Dipp)Mg(OBu^t)(THF)$ <sup>300</sup> complexes.

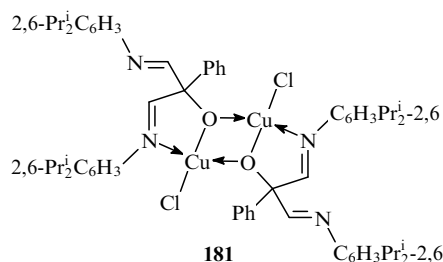
Compounds **174** can form binuclear complexes **175** containing two monoatomic bridges  $Z$  [ $Z = H$ ,<sup>302</sup>  $Hal$ ,<sup>297, 301–304</sup>  $O$ ,<sup>305</sup>  $OR$

( $R = H$ ,  $Alk$ ,  $Ac$ ),<sup>303, 305–308</sup>  $NR_2$ , *etc.*]. For instance, monochelate zinc  $\beta$ -aminovinyliminates with the composition  $(BDI)ZnL$  [ $BDI$ :  $R^1 = 2,6-Pr_2^iC_6H_3$ ,  $R^2 = H$  or  $R^1 = 2,6-Et_2C_6H_3$ ,  $R^2 = H$ ;  $L = Br$ ,  $Cl$ ,  $Et$ ,  $N(SiMe_3)_2$ ,  $OH$ ,  $OMe$ ,  $OPr^i$ ,  $OAc$ ] were studied.<sup>303</sup> It was established that all these complexes except for ones with  $L = Et$  and  $N(SiMe_3)_2$  exist in the dimeric form  $(BDI)Zn(\mu-L)_2Zn(BDI)$ .

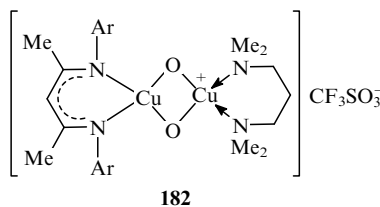
Furthermore, other binuclear chelates with longer bridges are known. In particular, two monochelate fragments are linked through one diatomic bridge  $N_2$  in the iron complex **178**,<sup>309</sup> through two triatomic bridges  $O=C(Me)=O$  in the zinc complex **179**<sup>310</sup> and through one triatomic and one monoatomic bridge in complex **180**.<sup>311</sup>

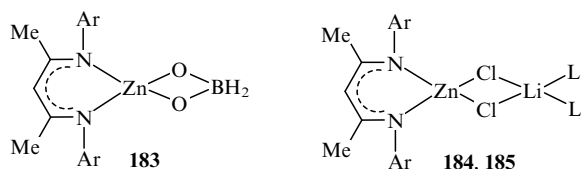


Complexes with unusual structures were obtained instead of the expected  $\beta$ -aminovinyliminates in the reaction of 1,3-bis(2,6-diisopropylphenylimido)-2-phenylpropane with  $Cu^{2+}$  salts in methanol or ethanol. In particular, copper bis- $\beta$ -diketonate and the dimer **181** were obtained from  $Cu(ClO_4)_2 \cdot 6H_2O$  and  $CuCl_2 \cdot 2H_2O$ , respectively; the structure of the latter was established using X-ray diffraction.<sup>312</sup>



Yet another large class of binuclear metal complexes with  $\beta$ -aminovinyl imines as ligands is represented by compounds where two metal atoms linked through a bridge have different ligand environments. For example, complexes **182**–**185**<sup>313, 314</sup> fall into this class.



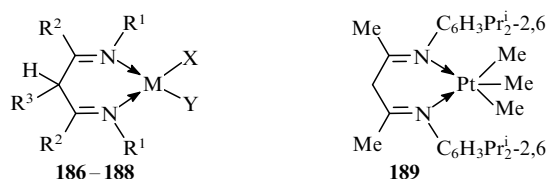


Ar = C<sub>6</sub>H<sub>3</sub>Pr<sub>2</sub><sup>i</sup>-2,6.

L = OEt (**184**), THF (**185**);

Ar = C<sub>6</sub>H<sub>3</sub>Pr<sub>2</sub><sup>i</sup>-2,6.

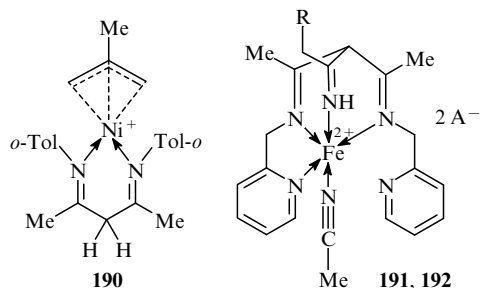
The complexes considered above contain a  $\beta$ -aminovinylimine ligand in the deprotonated form. In addition, complexes are known with the ligands in neutral form; coordination with a metal stabilises the diimine tautomeric form **172**, which is not typical of free enamino imines.<sup>288</sup> This form of the ligand was found both in mononuclear (**186–192**<sup>315–321</sup>) and binuclear (**193**<sup>317</sup> and **194**<sup>286, 322</sup>) complexes.



**186:** M = Ir, X = CO, Y = PPh<sub>3</sub>, R<sup>1</sup> = H, R<sup>2</sup> = CF<sub>3</sub>, R<sup>3</sup> = Allyl;<sup>315</sup>

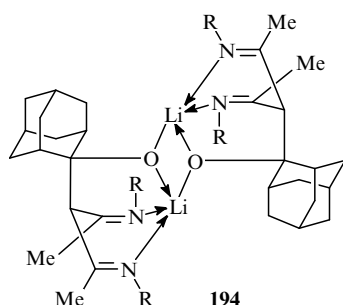
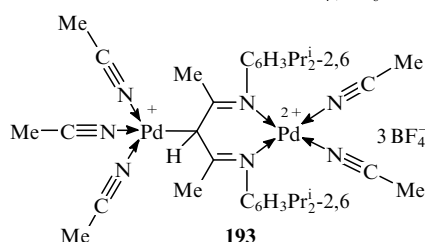
**187:** M = Rh<sup>+</sup>, X = Y = CO, R<sup>1</sup> = R<sup>3</sup> = H, R<sup>2</sup> = Me;<sup>316</sup>

**188:** M = Ni, X = Y = Br, R<sup>1</sup> = C<sub>6</sub>H<sub>3</sub>Pr<sub>2</sub><sup>i</sup>-2,6, R<sup>2</sup> = Me, R<sup>3</sup> = H.<sup>317</sup>



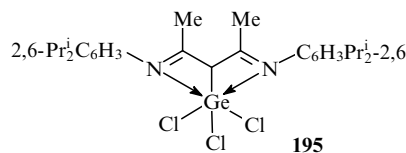
R = Me (**191**), Ph (**192**);

A = ClO<sub>4</sub><sup>-</sup>, PF<sub>6</sub><sup>-</sup>.

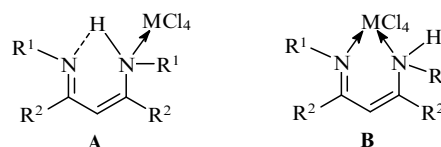


R = C<sub>6</sub>H<sub>3</sub>Pr<sub>2</sub><sup>i</sup>-2,6.

Apparently, this form of the ligand is also typical of complex **195**, where the  $\beta$ -aminovinylimine ligand is tridentate.<sup>323</sup>

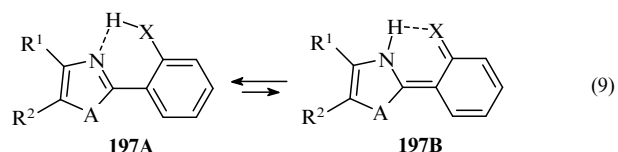
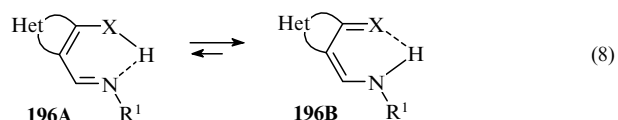


The structures of adducts of  $\beta$ -aminovinyl imines with MCl<sub>4</sub> (M = Sn, Ti)<sup>263</sup> are of interest. Although formation of the M–N-coordinated forms **A** or **B** was suggested for them, the question remains open due to a lack of X-ray diffraction data.



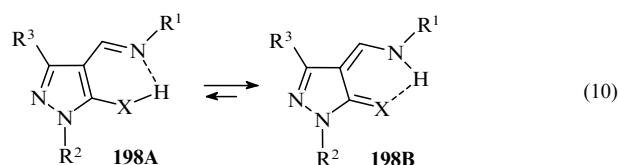
## V. Heterocyclic azomethines and their complexes

Amino-, hydroxy(oxo)- and thio-substituted heterocyclic azomethines can be subdivided into two groups depending on the type of imine bond, viz., compounds with exo- (**196**) and endocyclic (**197**) C = N bonds.<sup>6, 8, 11, 38, 55, 56, 324–327</sup>



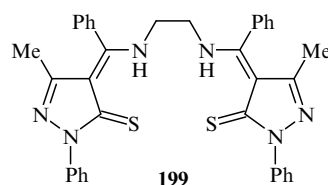
X, A = NR<sup>3</sup>, O, S.

The best studied class of chelating ligands of type **196** is the pyrazole derivatives **198**. Compounds with X = NR<sup>3</sup> exist exclusively in the imine form **A**, whereas those with X = O and S exist in the amine form **B** [equilibrium (10)].

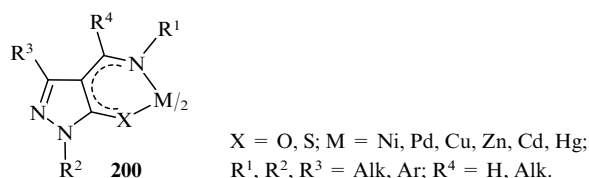


X = NR<sup>4</sup>, O, S; R<sup>1</sup> = H, Alk, Ar, Het; R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> = H, Alk, Ar.

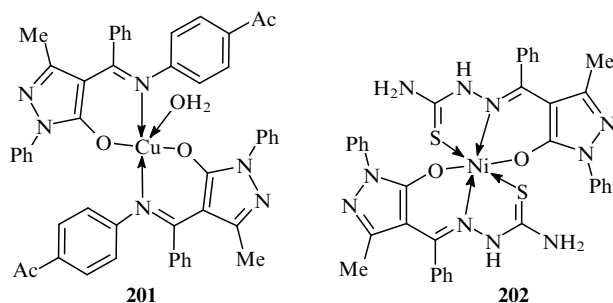
The latter form is realised in both solution and the crystalline phase, as evidenced by X-ray diffraction data. For instance, this form was found in a series of hydroxypyrazoles **198** (X = O) with coordinatively active substituents R<sup>1</sup> (R<sup>1</sup> = C<sub>6</sub>H<sub>4</sub>SMe-2,<sup>328</sup> COCH<sub>2</sub>Cl,<sup>329</sup> 8-quinolyl,<sup>330</sup> C<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>-2,<sup>331</sup> C<sub>6</sub>H<sub>4</sub>OH-2<sup>332</sup> and antipyril<sup>333</sup>) and for pyrazolethione **199** derivatives.<sup>334</sup>



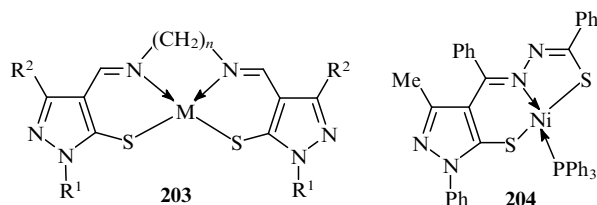
Complex compounds synthesised based on compounds **198** include exclusively chelates **200** with anionic ligands<sup>6, 8, 58, 324, 326, 335</sup> that are characterised by virtually delocalised intrachelate bonds.



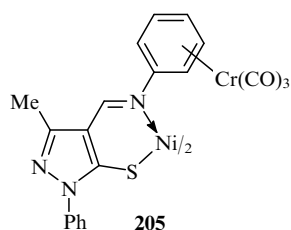
Only a few metal complexes with hydroxypyrazole ligands ( $X = O$ ) have been studied (*e.g.*, compounds **201**<sup>336</sup> and **202**<sup>337</sup>).



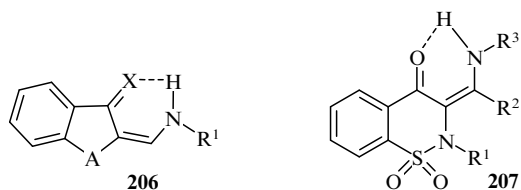
Meanwhile, mercaptopyrazole complexes are quite numerous.<sup>8, 158, 264, 338–353</sup> These include bischelate structures **200** ( $R^1 = Alk, Ar, Ph, cyclo-C_6H_{11}, pyridyl, crown-ether$  substituent), tricyclic chelates **203** with ethylene,<sup>8, 349, 350</sup> trimethylene<sup>8, 349</sup> or tetramethylene<sup>8</sup> bridges, bicyclic complexes **204** formed due to additional coordination of the metal atom with a coordinatively active substituent  $R^1$  and heteronuclear structures **205**.<sup>352, 353</sup>



$M = Ni, Cu; n = 2, 3, 4.$



Investigations into the tautomeric equilibrium (8) of azomethines of the pyrrole, furan, thiophene, their benzo-analogues<sup>10, 11, 55, 56</sup> (compounds **206**)<sup>354</sup> and benzothiazinone (compounds **207**)<sup>355</sup> series indicate that they predominantly exist in the enaminothione (thione) tautomeric form.



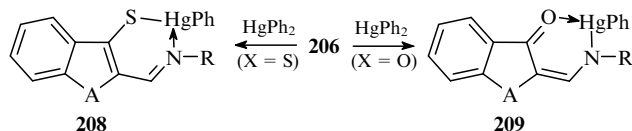
$A = NR^2, O, S; X = O, S;$   
 $R^1 = H, Alk, Ar.$

$R^1, R^2 = Alk, Ar; R^3 = Ar,$   
 8-quinolyl, 4-antipyril.

This suggestion is supported by the X-ray diffraction data for the respective complexes.<sup>8, 356–360</sup>

The possibility of the coordination-dependent stabilisation of specific tautomeric forms was deduced from the data on the tautomeric equilibrium (elementotropy)<sup>2–4</sup> of organometallic derivatives of ligands of the type **206** ( $A, X = O, S$ ). It was

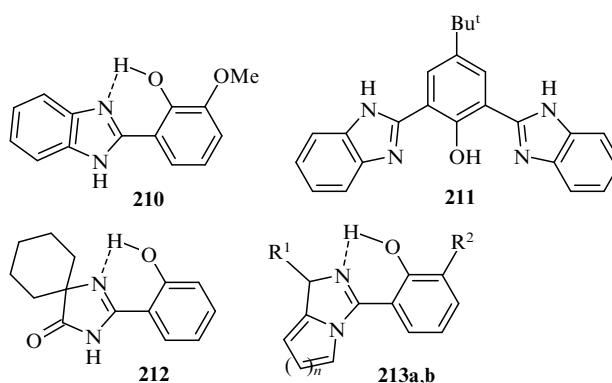
found<sup>55, 361–363</sup> that the interaction of enaminothione **206** ( $X = S$ ) with a soft acid (in terms of the Hard and Soft Acids and Bases, or HSAB, principle)<sup>34, 35, 364–366</sup> stabilises the imine form of the ligand (compound **208**), whereas the similar reaction of enamino ketone **206** ( $X = O$ ) gives rise to the amine form **209**.<sup>55, 56</sup>



The tautomers formed possess the maximum stability within the HSAB principle.<sup>34, 35, 365</sup>

Ligands of the type **197** manifest photo(thermo)-activated tautomerism [equilibrium (9)] with the tautomeric form **A** prevailing (see reviews<sup>6, 367</sup>). According to X-ray diffraction data, this form is also observed in the crystalline phase.

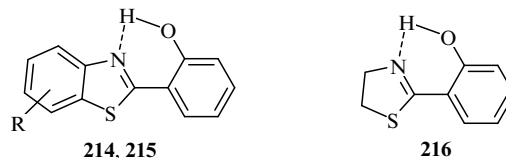
Among compounds **197**, benzoxazole ( $A = O$ ;  $R^1 - R^2 = benzo$ ),<sup>368</sup> oxazoline<sup>369, 370</sup> and imidazole [ $A = NH$ ;  $R^1 = R^2 = H$ ;<sup>371</sup>  $R^1 = Ph, R^2 = NO_2$  (see Ref. 372)] derivatives have been studied using X-ray diffraction. The structures of benzimidazoles **210** and **211**,<sup>373</sup> spiro- (**212**)<sup>374</sup> and polyheterocyclic (**213a,b**) imidazoles<sup>375, 376</sup> have been determined.



**213a:**  $R^1 = 2-C_5H_4N, R^2 = OMe; n = 1;$

**213b:**  $R^1 = N\text{-methylimidazol-2-yl}, R^2 = H; n = 2.$

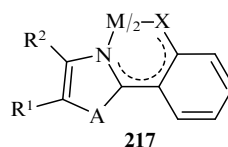
The tautomeric form **A** is also typical of benzothiazoles **214**,<sup>377</sup> **215**<sup>378</sup> and thiazolines **216**.<sup>379</sup>



$R = H$  (**214**); 5,6-benzo (**215**).

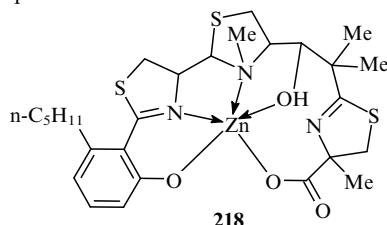
Ligand systems of the type **197** form chelates **217** with delocalised chelate bonds in nearly all cases; this prevents an analysis of the tautomeric forms of the ligands, as in the systems discussed above. The first complexes of this type<sup>380</sup> were synthesised based on 2-tosylaminophenylbenzoimid(ox)azole.<sup>381</sup>

Structural data on complexes **217** ( $X = NTs$ ) with the coordination core  $MN_4$  are rather scarce.<sup>369, 370, 382</sup>



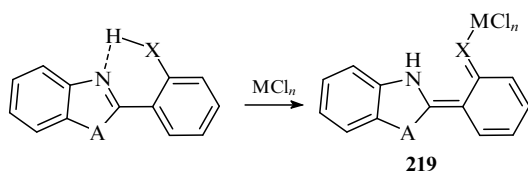
$A, X = NTs, O, S, Se.$

Complexes based on 2-hydroxyphenylazole systems similar to **217** ( $X = O$ ) are more numerous. These include chelates **217** with  $A = NH$ ,  $M = Cu, Co$ ,  $R^1 = R^2 = Ph$ ; <sup>383</sup>  $A = NH$ ,  $M = Cu, Co$ ,  $R^1 - R^2 = benzo$ ; <sup>384, 385</sup>  $A = O$ ,  $M = Cu, Co, Ni, Zn$ ,  $R^1 = H$ ,  $R^2 = H, Me, Ph$ ; <sup>386–388</sup>  $A = O$ ,  $M = Cu$ ,  $R^1 - R^2 = benzo$ ; <sup>389, 390</sup>  $A = S$ ,  $M = Cu$ ,  $R^1 - R^2 = benzo$  <sup>391, 392</sup> and the thiazoline complex **218**. <sup>393</sup>



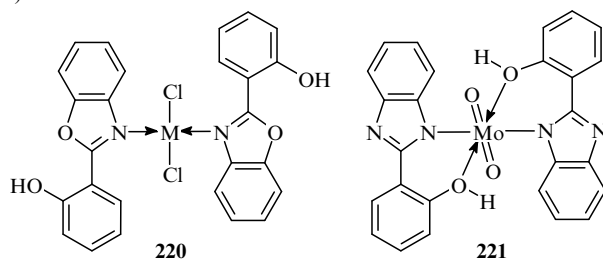
Several complexes based on mercaptophenylazoles (**217**,  $X = S$ ,  $M = Zn$ ,  $A = O$ ,  $R^1 = H$ ,  $R^2 = Me$ ) <sup>394</sup> and their hydro-seleno-derivatives (**217**,  $X = Se$ ,  $M = Zn$ ,  $A = O$ ,  $R^1 = H$ ,  $R^2 = Me$ ) <sup>395</sup> have been reported.

IR spectroscopic studies of molecular complexes of metal halides **219** produced in the following reaction: <sup>6, 396, 397</sup>



$A = NH, O$ ;  $X = NTs, O$ ;  $M = Sn, Ti, Co, Cu, Zn$ ;  $n = 2, 4$ .

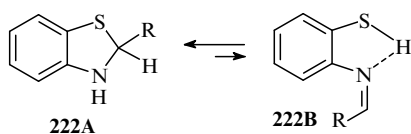
suggest stabilisation of the non-typical quinoid form **197B** due to coordination. However, this suggestion requires more reliable X-ray diffraction confirmation, since the enol form of the ligand was shown to be retained in analogous structurally characterised complexes **220** and **221** with N- (**220**) <sup>398, 399</sup> or N,O-coordination (**221**). <sup>400</sup>



$M = Pd, Pt$ .

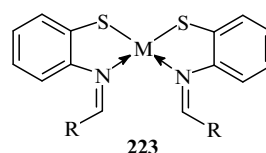
The structure of compound **221** is of note; the metal atom therein replaces the hydrogen atom at the endocyclic nitrogen atom rather than the exocyclic phenolic proton.

The stabilisation of specific tautomeric forms of azomethine ligands can be achieved not only for proto- and elementotropic tautomerism but for the ring-chain tautomerism of azole ligand systems **222** <sup>6, 401–403</sup> as well.



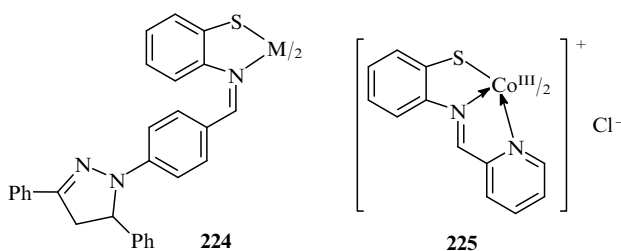
$R = Ar, Het$ .

Compound **222** in the free state (in both solution and the crystalline phase) exists predominantly in the closed tautomeric form **A**. Coordination stabilises form **B** (complex **223**). <sup>6, 8, 34, 35, 58, 157</sup>



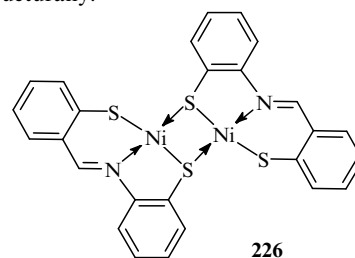
$M = Ni, Pd, Pt$ ;  $R = Ar, Het$ .

Recently, five-membered chelates with the coordination core  $MN_2S_2$  [compounds **223** ( $R = Ar$ ), <sup>404–406</sup> **224** <sup>407</sup> and **225** <sup>408</sup>] have been synthesised based on benzothiazolines.



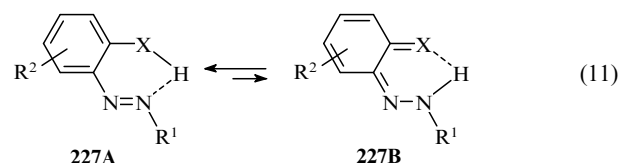
$M = Co, Ni, Zn, Cd$ .

One binuclear mercaptoazomethine chelate **226** with an S-bridge and the coordination core  $MNS_3$  has been characterised structurally. <sup>409</sup>



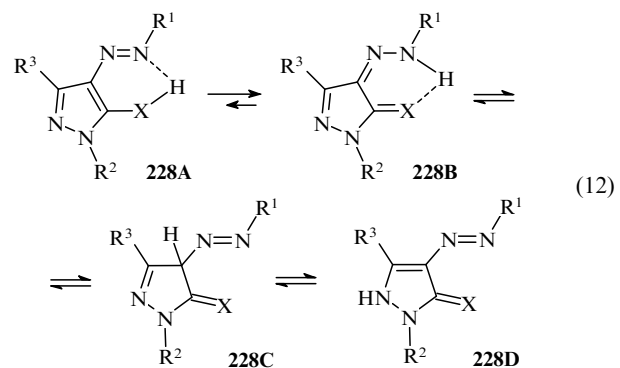
## VI. Hydroxy(mercapto)azo-compounds and metal chelates based on them

Tautomeric transformations occur also in diazo-analogues of azomethines, viz., hydroxy(mercapto)-derivatives of aromatic **227** and heterocyclic **228** azo-compounds. <sup>6, 34, 35, 410, 411</sup>



$R^1 = Ar, Het$ ;  $R^2 = benzo, OAlk, Hal, NO_2$ ;

$X = O, NR^3$  ( $R^3 = Alk, Ts$ ).

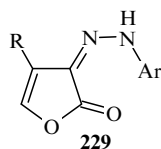


$X = NR^4, O, S, Se$ ;  $R^1 = Ar, Het$ ;  $R^2 = R^3 = R^4 = H, Alk, Ar$ .

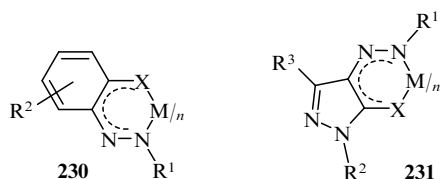
Ligands **227** and **228** manifest the azo–hydrazone tautomerism [equilibrium (11)]. The equilibrium is shifted towards the azo-tautomer **A** in the case of aromatic amino- (**227**,  $X = \text{NR}^3$ ,  $\text{R}^1 = \text{Ar}$ ) and hydroxyazo-compounds (**227**,  $X = \text{O}$ ,  $\text{R}^1 = \text{Ar}$ ) **A**.<sup>411–414</sup> Pyrazole compounds **228**<sup>6, 34, 35, 38, 411, 415</sup> exhibit a more complex equilibrium (12) with the tautomer **B**<sup>6, 38, 411, 412</sup> prevailing. According to a combined <sup>15</sup>N NMR (in CDCl<sub>3</sub>) and X-ray diffraction study,<sup>416</sup> complexes **227** exist predominantly in the azophenol form (**227A**), whereas compound **228** exists in the oxohydrazone (**228B**) tautomeric form. A similar situation is observed in the crystalline phases of compounds **227** and **228**.

In particular, compounds **228** ( $X = \text{O}$ ) exist in the solid phase exclusively in the form **228B** ( $\text{R}^1 = \text{C}_6\text{H}_3\text{Me}_2\text{-2,4}$ ,  $\text{R}^2 = \text{Ph}$ ,  $\text{R}^3 = \text{Me}$ ;<sup>417, 418</sup>  $\text{R}^1 = \text{C}_6\text{H}_4\text{NO}_2\text{-4}$ ,  $\text{R}^2 = \text{Ph}$ ,  $\text{R}^3 = \text{Me}$ ;<sup>419</sup>  $\text{R}^1 = \text{C}_6\text{H}_4\text{Cl-4}$ ,  $\text{R}^2 = \text{Ph}$ ,  $\text{R}^3 = \text{Me}$ ;<sup>420</sup>  $\text{R}^1 = \text{C}_6\text{H}_3\text{Cl}_2\text{-2,4}$ ,  $\text{R}^2 = \text{Ph}$ ,  $\text{R}^3 = \text{Me}$ ;<sup>421</sup>  $\text{R}^1 = \text{R}^2 = \text{Ph}$ ,  $\text{R}^3 = \text{COOPr}$ ;<sup>422</sup>  $\text{R}^1 = \text{R}^2 = \text{C}_6\text{H}_4\text{OMe-4}$ ,  $\text{R}^3 = \text{CO}_2\text{Et}$ <sup>423</sup>); the same form is typical of mercaptopyrazole derivatives ( $X = \text{S}$ ,  $\text{R}^1 = \text{R}^2 = \text{Ph}$ ,  $\text{R}^3 = \text{Me}$ ).<sup>424</sup> Meanwhile, amino-derivatives exist in the azo-form (**228A**,  $X = \text{NR}^4$ ).<sup>6, 425</sup>

The oxohydrazone tautomeric form is also typical of hydroxy-azo-derivatives of isoxazole **229**.<sup>426</sup>



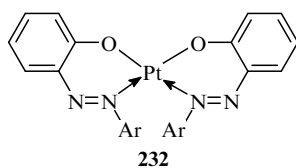
A large number of metal complexes of the types **230** and **231** with hydroxy(mercapto)azo-ligands have been reported, which are characterised by virtually delocalised intrachelate bonds.



$X = \text{NR}^4$ ,  $\text{O}$ ,  $\text{S}$ ;  $n = 2, 3$ ;  $\text{R}^1 = \text{Ar}$ ,  $\text{Het}$ ;  $\text{R}^2, \text{R}^3, \text{R}^4 = \text{H}$ ,  $\text{Alk}$ ,  $\text{Ar}$ .

According to a suggestion by Price,<sup>427</sup> two five-membered metallacycles are realised in a newly synthesised cobalt complex **230** ( $X = \text{NH}$ ,  $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{H}$ ,  $\text{M} = \text{Co}$ ). This suggestion needs to be verified, since it was two six-membered metallacycles that were revealed in a similar nickel complex using X-ray diffraction,<sup>428</sup> while five- and a six-membered metallacycles were shown to co-exist in a chelate with  $X = \text{NTs}$ .<sup>429</sup> Six-membered metallacyclic structures are also realised in coordination compounds based on hydroxyaromatic azo-compounds **230** ( $X = \text{O}$ ,  $\text{M} = \text{Ni}$ ,<sup>430</sup>  $\text{Cu}$ ,<sup>431</sup>  $\text{Pt}$ <sup>432</sup>).

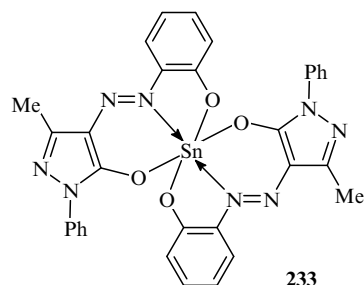
Typically, complexes **230** have *trans*-planar structures; however, in the case of a Pt-complex it was possible to isolate and determine the structure of the *cis*-isomer **232**.<sup>432</sup>



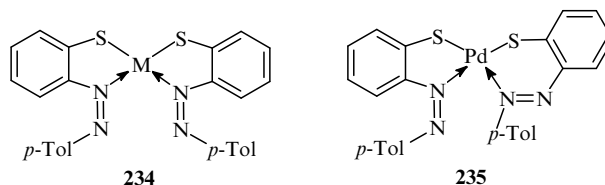
The formation of six-membered chelate structures is also typical of nickel complexes with aminoazo-ligands of the pyrazole series **231** ( $X = \text{NR}^4$ ,  $\text{M} = \text{Ni}$ ).<sup>425, 433</sup>

According to the <sup>1</sup>H NMR data and measurements of the dipole and magnetic moments, nickel pyrazole complexes (**231**,

$X = \text{O}$ ,  $\text{R}^1, \text{R}^2, \text{R}^3 = \text{Alk}$ ,  $\text{Ar}$ ) adopt tetrahedral structures in solution and the crystalline state.<sup>434</sup> According to X-ray diffraction data, the copper complex **231** ( $\text{M} = \text{Cu}$ ,  $n = 2$ ,  $\text{R}^1 = \text{R}^2 = \text{Ph}$ ,  $\text{R}^3 = \text{Me}$ ) is characterised<sup>435</sup> by planar structure, whereas the corresponding zinc complex is pseudotetrahedral; octahedral structures are observed for cobalt and nickel complexes ( $[\text{CoL}_3] \cdot 3 \text{ MeOH}$ ,  $[\text{NiL}_2] \cdot 2 \text{ MeOH}$ ;  $\text{LH}$  is the ligand **220**). The octahedral structure is also realised in the chelate **233**.<sup>436</sup>

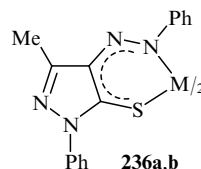


Complexes with ligand **227** ( $X = \text{S}$ ) can contain two five-membered metallacycles (compound **234**)<sup>437–441</sup> or a five- and a six-membered (compound **235**)<sup>411, 442</sup> metallacycle (intrachelate isomerism).



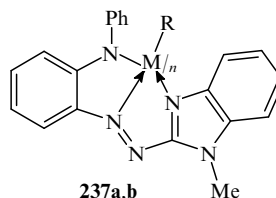
$\text{M} = \text{Ni}$ ,  $\text{Zn}$ .

Meanwhile, chelates based on 4-azo-derivatives of pyrazole-5-thione (**228**,  $X = \text{S}$ ) contain only six-membered metallacycles, as in complex **236**.<sup>443, 444</sup>



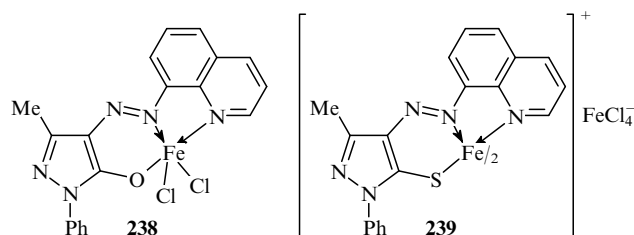
$\text{M} = \text{Zn}$ ,  $n = 2$  (**a**);  $\text{M} = \text{Ru}$ ;  $n = 3$  (**b**).

Chelates based on aromatic azo-compounds **227** with coordinatively active substituents ( $\text{R}^1$  is a derivative of a nitrogen heterocycle  $\text{Het}$ ) manifest intrachelate isomerism due to the possibility of the closure of metallacycles with different numbers of atoms. For instance, complexes **237a,b** synthesised based on aminoazo-ligands of the type **227** contain two five-membered metallacycles **187**,<sup>445, 446</sup> as evidenced by X-ray diffraction.



$\text{M} = \text{Pd}$ ,  $n = 1$ ,  $\text{R} = \text{OAc}$  (**a**);  $\text{M} = \text{Ni}$ ,  $n = 2$ , no  $\text{R}$  (**b**).

Pyrazole aza-ligands of the type **228** ( $X = \text{O}$ ,  $\text{S}$ ;  $\text{R} = 8\text{-quinolyl}$ ) form five- and six-membered metallacycles (compounds **238** and **239**)<sup>447</sup> upon coordination with metal atoms.



The structure of complex **239** was confirmed by X-ray diffraction.<sup>447</sup>

## VII. Conclusion

The ligand systems discussed in the present review are widely employed in the synthesis of typical metal chelate complexes. These complexes contain the ligands in the deprotonated ( $L^-$ ) form with delocalised intrachelate bonds. The involvement of the protonated ligand (LH) in coordination with a metal atom gives rise to molecular complexes containing the ligand in a non-standard tautomeric form. The experimental evidence summarised above implies that coordination with a metal represents an efficient means for stabilisation of non-standard tautomeric forms of these chelating ligand systems.<sup>27–30, 58</sup>

To intensify research in the field of coordination-dependent stabilisation of tautomers, it would be desirable to extend the range of prototropic ligand systems under study.<sup>34, 35, 448</sup> In addition to the chelating ligands mentioned in the present review, heterocyclic amino-, hydroxy- and thio-derivatives<sup>6, 28, 326, 327, 449–452</sup> as well as tosylamino-<sup>453</sup> and hydroxy-phenylazines<sup>454, 455</sup> can be considered. Taking into account that complex formation can stabilise not only prototropic but other tautomeric forms as well, the range of ligand systems can be extended to include those manifesting elementotropic (see Section III.4), photo- and thermochromic (see Section V), ring-chain (see Section V) and azido-tetrazole<sup>6</sup> tautomerism. Studies of such tautomeric systems are still in the maturation stage.

The competitive coordination (see Ref. 326) and stabilisation of non-classical organometallic structures are worth special attention.

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# The latest achievements in thienothiophene chemistry †

V P Litvinov

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**Abstract.** Data on methods of synthesis, physicochemical characteristics, reactivity and biological activities of isomeric thienothiophenes and their analogues and some of their properties of practical importance are summarised and analysed. The present review covers the last 25 years. The bibliography includes 417 references.

## I. Introduction

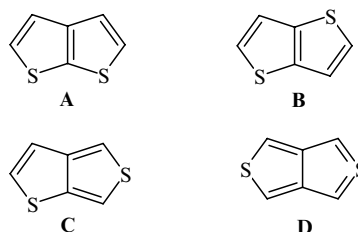
In the last 25 years, annelated heterocyclic systems have attracted considerable attention both from a theoretical standpoint and in view of their various practical applications. This interest is evidenced by a sharply increasing number of publications devoted to various aspects of the chemistry of fused thiophenes. For example, about 300 papers have been published during 90 years since the discovery of thienothiophenes (in 1886)<sup>1</sup> up to the publication of the most recent reviews devoted to this field of chemistry,<sup>2–5</sup> whereas the number of such papers has considerably increased in the last 10–15 years. The character of publications has also changed. In recent years, procedures for the synthesis of annelated derivatives and the physicochemical properties, reactivity and potentially useful properties of isomeric thienothiophenes and their analogues have attracted growing interest. In particular, the percentage of studies on practical applications of such systems exceeded 30% of the total number of publications. To represent information on the chemistry of this class of fused heterocycles in more detail, it is worthwhile to discuss not only investigations performed in the last decade but also earlier studies, which have not been included in the latest review<sup>2</sup> on this problem or those reported more recently.

## II. Methods of synthesis

Data presented in this Section are classified according to the nature of the starting compounds involved in the synthesis of isomeric thienothiophenes.

V P Litvinov N D Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prosp. 47, 119991 Moscow, Russian Federation. Fax (7-095) 135 53 28, tel. (7-095) 135 88 37, e-mail: vpl@ioc.ac.ru

Compounds characterised by three modes of fusion of the thiophene rings, *viz.*, [2,3-*b*] (structure **A**), [3,2-*b*] (**B**) and [3,4-*b*] (**C**), have attracted most attention. These isomers are referred to as conventional (or classical) thienothiophenes, because structures of the type **D** ([3,4-*c*]-fusion) are much less accessible.



For isomeric thienothiophenes, both general methods of synthesis and original procedures applicable only to the preparation of particular types of compounds have been developed. In recent years, along with conventional methods based on thiophene derivatives as substrates, other approaches using, in particular, cyclopropenethiones, dithiynes and dithiolium salts have been successfully designed. Special sections in the review deal with high-temperature synthesis of annelated thienothiophenes and procedures used for the preparation of particular representatives of this class of heterocycles.

### 1. Thiophene derivatives in the synthesis of thienothiophenes

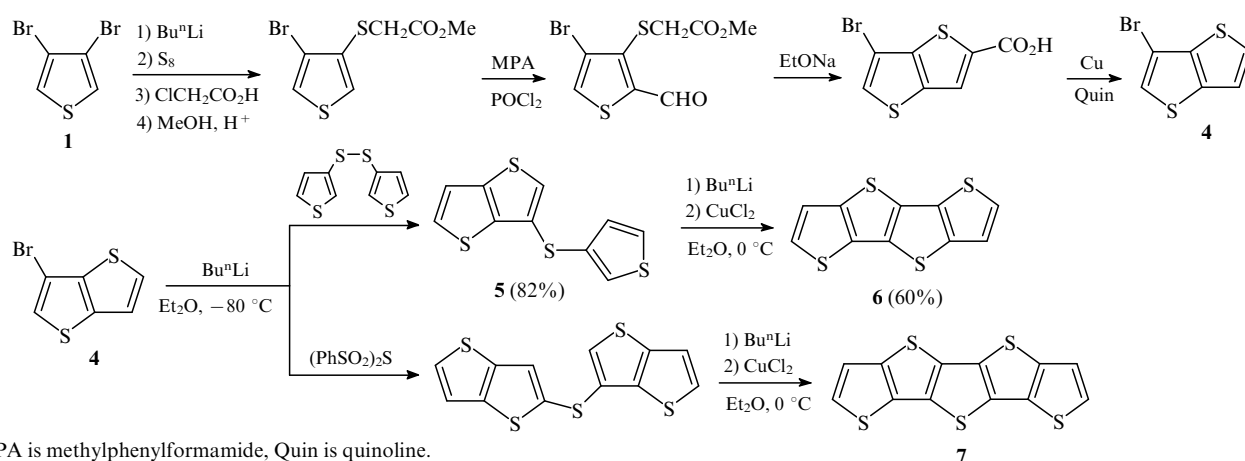
Bromine derivatives of thiophene are most widely used for the preparation of isomeric thienothiophenes and related systems. A classical example of this approach is illustrated by the following transformation sequence: formylation of 3,4-dibromothiophene (**1**) through a lithium derivative, repeated metallation and treatment with elemental sulfur and methyl bromoacetate. The closure of the second heterocycle occurs in the presence of sodium alkoxide. Decarboxylation of the resulting 4-bromothiopheno[2,3-*b*]thiophene-2-carboxylic acid (**2a**) affords 3-bromothiopheno[2,3-*b*]thiophene (**3a**).<sup>6</sup> The reaction with the use of selenium instead of sulfur produced 4-bromoselenopheno[2,3-*b*]thiophene-2-carboxylic acid (**2b**) and 4-bromoselenopheno[2,3-*b*]thiophene (**3b**).

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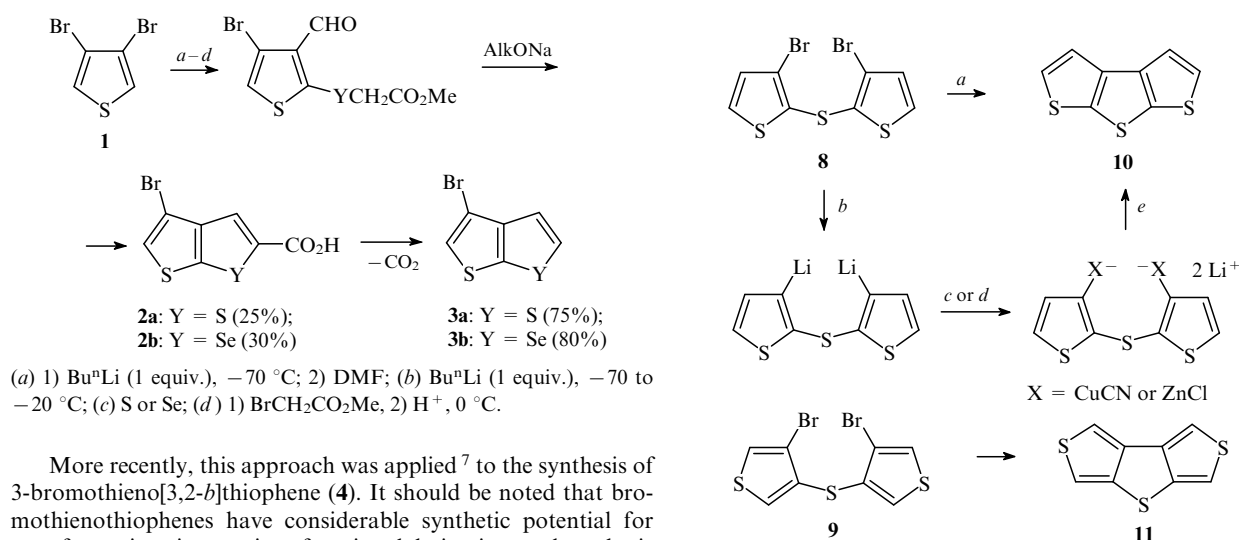
† Dedicated to Academician Yuriy Bubnov on the occasion of his 70th birthday.

Scheme 1



MPA is methylphenylformamide, Quin is quinoline.

Scheme 2



More recently, this approach was applied<sup>7</sup> to the synthesis of 3-bromothiopheno[3,2-*b*]thiophene (**4**). It should be noted that bromothiophenothiophenes have considerable synthetic potential for transformations into various functional derivatives and synthesis of polyannulated thiophenes. For example, treatment of bromide **4** with Bu<sup>n</sup>Li and then with di(3-thienyl) disulfide affords sulfide **5**. Oxidative cyclisation of the latter gives tetrathienocene **6**. Penta-thienocene **7** was prepared according to an analogous scheme (Scheme 1).

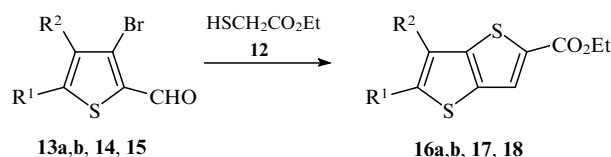
Three approaches to the synthesis of dithieno[2,3-*b*:3',2'-*d*]thiophene (**10**) and dithieno[3,4-*b*:3',4'-*d*]thiophene (**11**) starting from di(bromothieryl) sulfides **8** and **9** were developed.<sup>8,9</sup> One procedure (conditions *a*) involves cyclisation of sulfides **8** and **9** with hexamethyldistannane catalysed by a palladium complex. Two other procedures involve lithiation, the formation of organo-copper (conditions *b*, *c*, *e*) or organozinc (conditions *b*, *d*, *e*) derivatives and their oxidation by molecular oxygen (Scheme 2).

Bromine-substituted thiophenecarbaldehydes were used as the starting compounds in the synthesis of isomeric thienothiophenes.<sup>10</sup> The second sulfur-containing ring can be constructed using ethyl thioglycolate (**12**). The reactions of 3-bromine-substituted thiophene-2-carbaldehydes **13–15** with ester **12** are most often carried out in DMF in the presence of K<sub>2</sub>CO<sub>3</sub> as a base.<sup>10–15</sup> These reactions produce thieno[3,2-*b*]thiophene-5-carboxylates **16–18**, whose yields vary substantially depending on the structure of the starting aldehyde. The reaction of 3,4,5-tribromo derivative **15** with ethyl thioglycolate **12** was studied under different conditions. It should be noted that the reaction in boiling anhydrous ethanol in the presence of EtONa afforded ethyl 2,3-dibromothiopheno[3,2-*b*]thiophene-5-carboxylate (**18**), whereas the reaction in the presence of even traces of water *in situ* was accompanied by hydrolysis of ester **18** to the corresponding carboxylic acid. In

(a) Pd(PPh<sub>3</sub>)<sub>4</sub> (20 mol.%), (Me<sub>3</sub>Sn)<sub>2</sub> (0.9 equiv.), dioxane, 110–116 °C; (b) Bu<sup>n</sup>Li, THF, –78 °C; (c) CuCN; (d) ZnCl<sub>2</sub>, –50 °C; (e) 1) O<sub>2</sub>; 2) CuCl<sub>2</sub>, –70 °C.

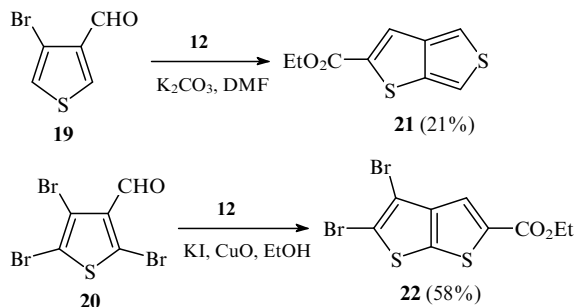
| Conditions                     | Yield (%) |     |
|--------------------------------|-----------|-----|
|                                | 10        | 11  |
| <i>a</i>                       | 75        | 78  |
| <i>b</i> , <i>c</i> , <i>e</i> | 37        | 40  |
| <i>b</i> , <i>d</i> , <i>e</i> | ~70       | ~70 |

liquid ammonia, the reaction proceeds apparently through the replacement of the bromine atom (by an S<sub>RN</sub>1 mechanism).

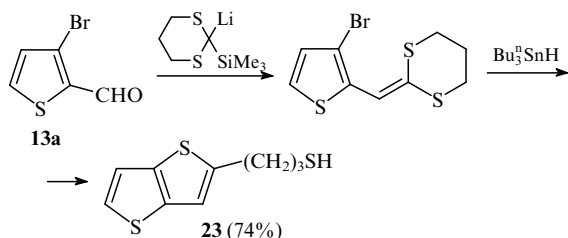


| Substrate (product) | R <sup>1</sup> | R <sup>2</sup> | Reaction conditions                         | Yield (%) | Ref.  |
|---------------------|----------------|----------------|---------------------------------------------|-----------|-------|
| 13a (16a)           | H              | H              | DMF, K <sub>2</sub> CO <sub>3</sub> , 20 °C | 95        | 11–13 |
| 13b (16b)           | Me             | Br             | DMF, K <sub>2</sub> CO <sub>3</sub> , 20 °C | 73        | 15    |
| 14 (17)             | Br             | H              | DMF, K <sub>2</sub> CO <sub>3</sub> , 20 °C | 8         | 10    |
| 15 (18)             | Br             | Br             | DMF, K <sub>2</sub> CO <sub>3</sub> , 20 °C | 61        | 10    |
| 15 (18)             | Br             | Br             | EtONa, EtOH (anhydr.), 78 °C                | 72        | 10    |
| 15 (18)             | Br             | Br             | NH <sub>3</sub> (liquid)                    | 66        | 10    |

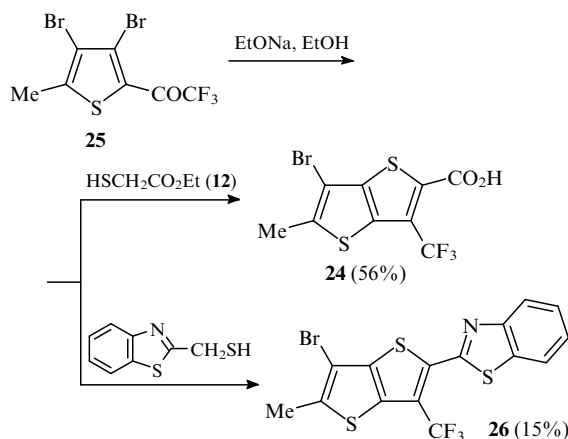
Analogously, thienothiophene systems **21** and **22** were derived from thiophene-3-carbaldehydes **19** and **20**, respectively<sup>10</sup> (cf. Ref. 16). Compounds **18**, **21** and **22** provide examples of isomeric thienothiophenes, which were prepared according to the same procedure but are characterised by different modes of fusion of the five-membered sulfur-containing heteroaromatic rings.



3-Bromothiophene-2-carbaldehyde **13a** served also as the starting compound in the synthesis of thieno[3,2-*b*]thiophene **23** containing the mercaptopropyl substituent.<sup>17</sup>

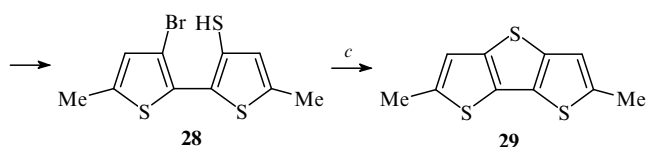
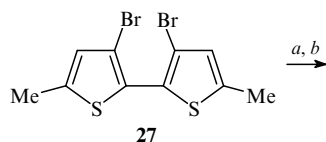


6-Bromo-5-methyl-3-trifluoromethylthieno[3,2-*b*]thiophene-2-carboxylic acid (**24**) was synthesised by the reaction of dibromo-substituted thienyl ketone **25** with ethyl thioglycolate **12** in an ethanolic solution of sodium alkoxide.



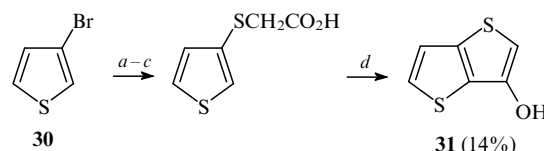
Under analogous conditions, the reaction with 2-mercapto-methylbenzothiazole afforded the corresponding 2-(benzothiazol-2-yl)thieno[3,2-*b*]thiophene derivative **26**.<sup>14, 15</sup>

Treatment of 3,3'-dibromo-5,5'-dimethyl-2,2'-bithiophene (**27**) with  $\text{Bu}^n\text{Li}$  and then with elemental sulfur produced 3-bromo-3'-mercapto-5,5'-dimethyl-2,2'-bithiophene (**28**). In the presence of  $\text{Cu}_2\text{O}$  and alkali, the latter undergoes cyclisation to 2,6-dimethyldithieno[3,2-*b*:2',3'-*d'*]thiophene (**29**).<sup>14, 18</sup> Compounds **26** and **29** were used to design new photochromic substances.<sup>14, 15, 18</sup>



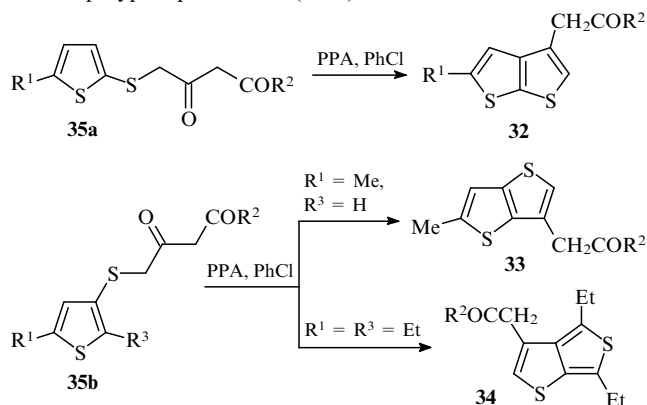
(a)  $\text{Bu}^n\text{Li}$ ,  $\text{C}_6\text{H}_{14}$ ,  $-70^\circ\text{C}$ ; (b)  $\text{S}_8$ ,  $-35^\circ\text{C}$ ; (c)  $\text{Cu}_2\text{O}$ ,  $\text{KOH}$ ,  $\text{DMF}$ .

An analogous method was used<sup>19</sup> to introduce the thiol group into 3-bromothiophene **30** in the synthesis of 3-hydroxy-thieno[3,2-*b*]thiophene (**31**).



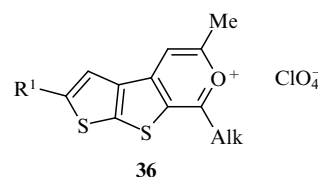
(a)  $\text{Bu}^n\text{Li}$ ,  $-70^\circ\text{C}$ ; (b)  $\text{S}_8$ ,  $-70^\circ\text{C}$ , 20%  $\text{NH}_4\text{Cl}$ ; (c)  $\text{ClCH}_2\text{CO}_2\text{H}$ ,  $40-45^\circ\text{C}$ ; (d)  $\text{H}_2\text{SO}_4$ ,  $95-100^\circ\text{C}$ .

Procedures were developed<sup>20-22</sup> for the preparation of isomeric thienothiophenes **32-34** by cyclisation of methyl  $\gamma$ -thienylthioacetates **35a,b** derived from substituted 3-bromothiophenes. Cyclisation occurs in chlorobenzene in the presence of polyphosphoric acid (PPA).



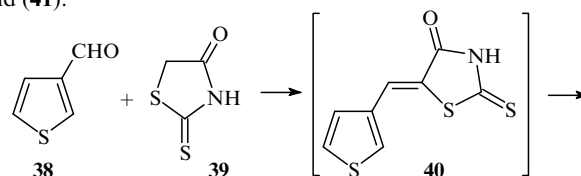
$\text{R}^1 = \text{Me}$ ,  $\text{Et}$ ;  $\text{R}^2 = \text{Me}$ ,  $\text{OMe}$ ;  $\text{R}^3 = \text{H}$ ,  $\text{Et}$ .

Acylation of thienothiophene derivatives **32** and **33** in an aliphatic acid anhydride–70% perchloric acid system was demonstrated to give the corresponding pyrylium salts **36** (for compounds **32**,  $\text{R}^2 = \text{Me}$ ).

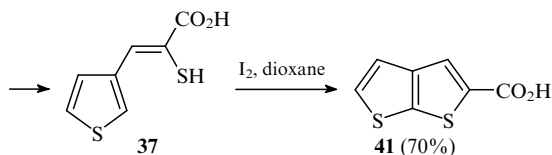


$\text{R}^1 = \text{Me}$ ,  $\text{Et}$ .

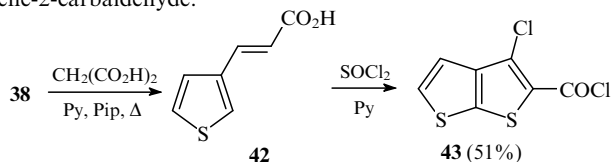
The synthesis of isomeric thienothiophenes and benzothienothiophenes was successfully carried out starting from thiophene-carbaldehydes and their derivatives. Treatment of 2-mercapto-3-(3-thienyl)acrylic acid (**37**), which was prepared in quantitative yield from thiophene-3-carbaldehyde (**38**) and 2-thioxothiazolidin-4-one (**39**) through intermediate **40**, with two equivalents of iodine in dioxane afforded thieno[2,3-*b*]thiophene-2-carboxylic acid (**41**).<sup>23</sup>



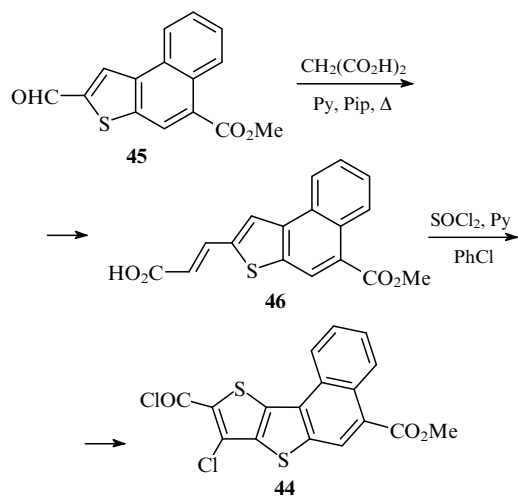




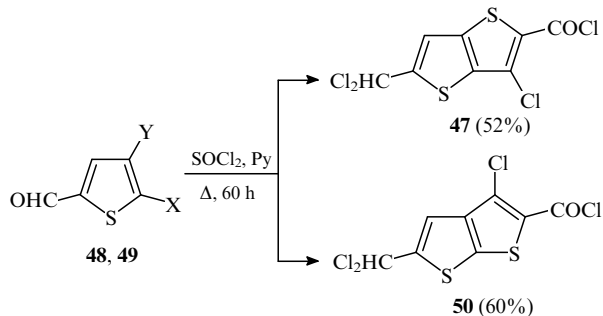
Condensation of thiophene-3-carbaldehyde **38** with malonic acid (Doebner reaction) in a mixture of pyridine (Py) and piperidine (Pip) performed with heating affords (*E*)-3-(3-thienyl)acrylic acid (**42**), whose treatment with thionyl chloride in pyridine produces 3-chlorothiopheno[2,3-*b*]thiophene-2-carboxylic acid chloride (**43**).<sup>24,25</sup> Analogously, 3,5-dichlorothiopheno[3,2-*b*]thiophene-2-carboxylic acid chloride was prepared from thiophene-2-carbaldehyde.<sup>24–26</sup>



The same methodology was employed in the synthesis of a more complex heterocyclic system, *viz.*, 3-chloro-6-methoxycarbonylnaphtho[2',1':2,3-*b*]thieno[4,5-*d*]thiophene-2-carboxylic acid chloride (**44**). Annulated thiophenecarbaldehyde **45** reacts with malonic acid in boiling pyridine containing two drops of piperidine to give unsaturated acid **46**, which undergoes cyclisation to acid chloride **44** upon mixing with thionyl chloride in chlorobenzene with a small admixture of pyridine.<sup>27</sup>

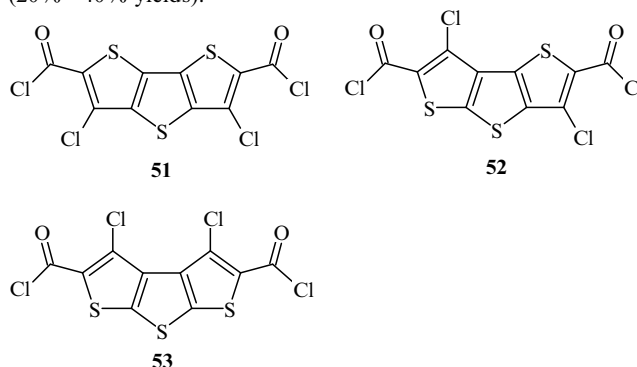


3-Chloro-5-dichloromethylthieno[3,2-*b*]thiophene-2-carboxylic acid chloride (**47**) was synthesised by the reaction of thionyl chloride in pyridine with 5-formylthiophen-2-ylacrylic acid **48**.<sup>28</sup> 3-Chloro-5-dichloromethylthieno[2,3-*b*]thiophene-2-carboxylic acid chloride (**50**) was prepared analogously starting from isomer **49**.

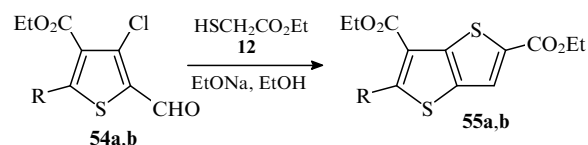


X = CH=CHCO<sub>2</sub>H, Y = H (**48**); X = H, Y = CH=CHCO<sub>2</sub>H (**49**).

This method was applied to the synthesis of dithienothiophenes **51–53** from isomeric thiophenediacrylic acids (20%–40% yields).

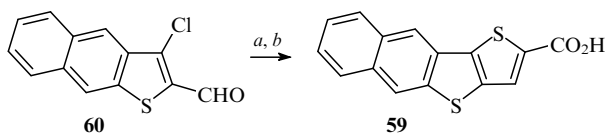
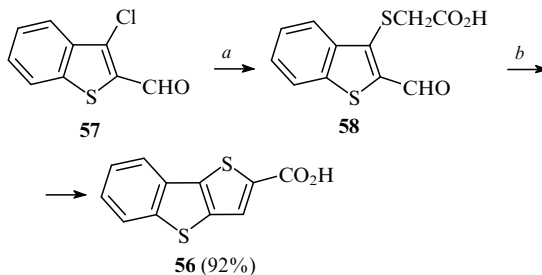


The synthesis of thieno[3,2-*b*]thiophenes and their benzo- and naphthoannelated analogues was carried out starting from 4-chloro-5-formylthiophene-3-carboxylic esters. For example, the reaction of 2-substituted ethyl 4-chloro-5-formylthiophene-3-carboxylates **54a,b** with ethyl thioglycolate **12** afforded the corresponding thieno[3,2-*b*]thiophene derivatives **55a,b** in rather high yields.<sup>29,30</sup>



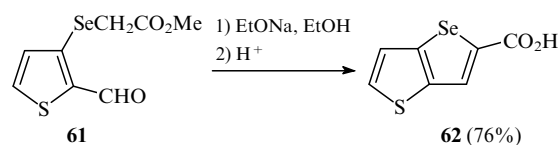
R = Me (**a**), PhNH (**b**).

An analogous approach was employed in the synthesis of benzo[*b*]thieno[3,2-*b*]thiophene-2-carboxylic acid (**56**) and naphtho[2,3-*b*]thieno[3,2-*b*]thiophene-2-carboxylic acid (**59**) from substituted benzo[*b*]thiophene-2-carbaldehyde **57**<sup>31</sup> (through thioglycolic acid derivative **58**) and naphtho[2,3-*b*]thiophene-2-carbaldehyde **60**, respectively.<sup>32</sup>

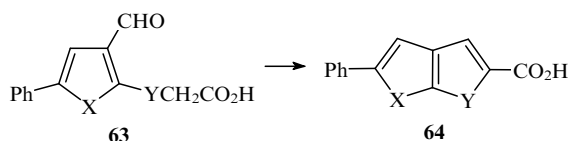


(a) HSCH<sub>2</sub>CO<sub>2</sub>H; (b) 30% KOH, 80–90 °C, 30 min.

Substituted thiophenecarbaldehydes were also used in the synthesis of thienothiophene-related systems. For example, cyclisation of thiophene-containing methyl selenylacetate **61** in the presence of EtONa in ethanol afforded selenopheno[3,2-*b*]thiophene-5-carboxylic acid (**62**).<sup>33,34</sup>

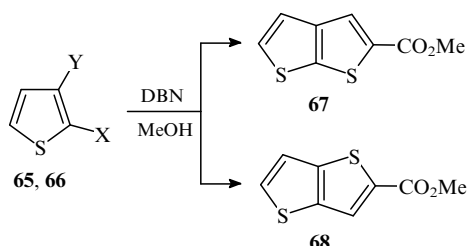


Furo-, pyrrolo-, selenopheno- and thieno[2,3-*b*]thiophene-2-carboxylic acids **64** were synthesised from various heterocyclic 2-chalcogenoacetic acids **63**.<sup>35</sup>



X = NMe, O, S; Y = S, Se.

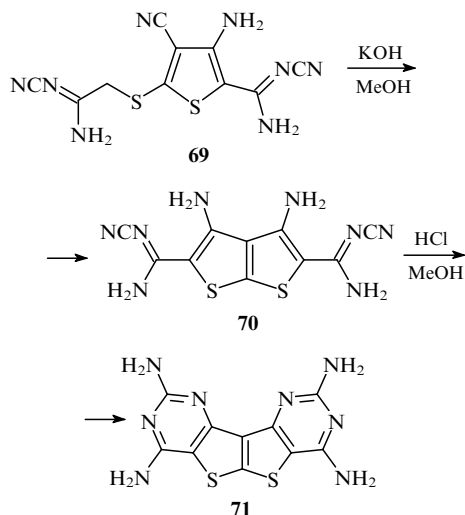
Cyclisation of isomeric thiophenes **65** and **66** containing the aldehyde function and the SCH<sub>2</sub>CO<sub>2</sub>Me group at positions 2 and 3 by the reactions with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) affords methyl thieno[2,3-*b*]thiophene-2-carboxylates (**67**) and -[3,2-*b*]thiophene-2-carboxylates (**68**), respectively.<sup>36</sup>



X = SCH<sub>2</sub>CO<sub>2</sub>Me, Y = CHO (**65**);

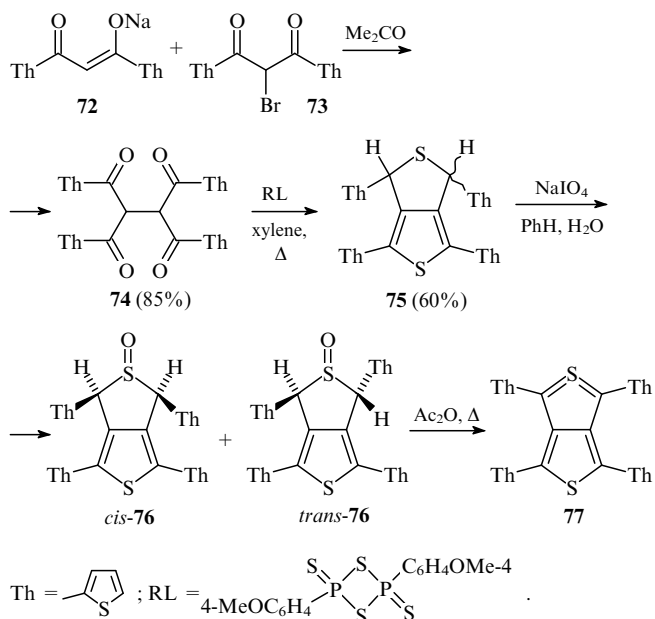
X = CHO, Y = SCH<sub>2</sub>CO<sub>2</sub>Me (**66**).

Intramolecular condensation was used also in the synthesis of more complex substances, including thienothiophenes containing various functional groups. The ester and nitrile functions can serve as the 'carbonyl component'.<sup>37,38</sup> Among examples of the synthesis of the thienothiophene system, worthy of mention is the transformation of thiophene-4-carbonitrile **69** in the reaction with KOH giving rise to 3,4-diamino-2,5-di[amino(cyanoimine)methyl]thieno[2,3-*b*]thiophene (**70**), which is cyclised to symmetrical tetracycle **71**.<sup>39,40</sup>

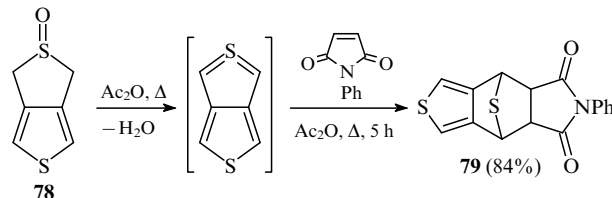


Thiophene derivatives were also used in the synthesis of derivatives of the fourth, the so-called non-classical, isomer of thienothiophene, *viz.*, thieno[3,4-*c*]thiophene.<sup>41,42</sup> For example, the reaction of a sodium salt of dithenoylmethane (**72**) and bromodithenoylmethane (**73**) in acetone produced 1,1,2,2-tetra-2-thenylethane (**74**). Sulfonation of the latter with Lawesson's reagent (RL) in boiling xylene afforded a mixture of two stereoisomeric 1,3-dihydrothieno[3,4-*c*]thiophenes (**75**). This mixture was oxidised without purification and then chromatographed on silica gel (CCl<sub>4</sub> as the eluent) to isolate individual *cis*- and *trans*-sulfoxides **76**. Dehydration of an unseparated mixture of isomers **76** in boiling acetic anhydride under nitrogen produced 1,3,4,6-

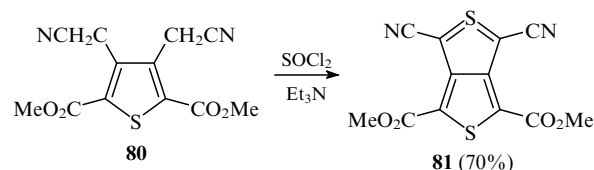
tetra-2-thienylthieno[3,4-*c*]thiophene (**77**) in 84% yield, whereas the yield of the product in an analogous transformation of the *cis*-isomer of **76** decreased to 68%.<sup>41</sup>



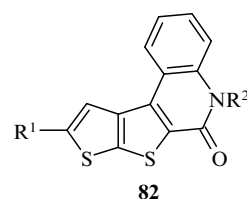
Unsubstituted thieno[3,4-*c*]thiophene was synthesised for the first time by Pummerer dehydration of 1*H*,3*H*-thieno[3,4-*c*]thiophene 2-oxide (**78**).<sup>42</sup> This compound was characterised using chemical traps (for example, as adduct **79** with *N*-phenylmaleimide).<sup>43</sup>



The reaction of thienyldinitrile **80** with thionyl chloride in the presence of triethylamine gives thieno[3,4-*c*]thiophene **81** containing only electron-withdrawing substituents.<sup>44,45</sup> This compound is very stable in the solid state.

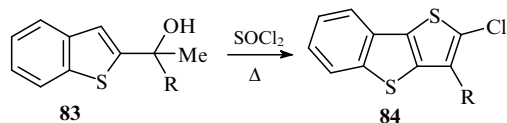


Multistep syntheses involving aldol condensation of thiophene-3-carbaldehyde **38** with malonic acid or the Heck reaction using 3-bromothiophene **30** or 4-bromothiophene-2-carboxylate produced thieno[3',2':4,5]thieno[2,3-*c*]quinolones **82**, which exhibit high antitumour activity.<sup>46</sup>



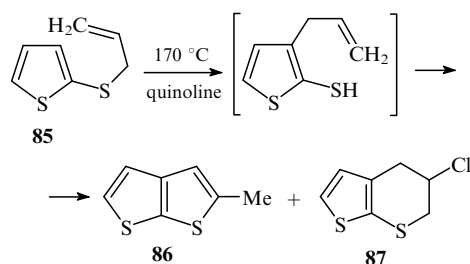
R<sup>1</sup> = H, MeO<sub>2</sub>C, Me<sub>2</sub>N(CH<sub>2</sub>)<sub>3</sub>NH, Me<sub>2</sub>N(CH<sub>2</sub>)<sub>3</sub>NPh;  
R<sup>2</sup> = H, Me<sub>2</sub>N(CH<sub>2</sub>)<sub>3</sub>.

Benzothiophenes **83** containing the tertiary alcoholic group undergo cyclisation in the presence of thionyl chloride.<sup>47</sup> The reaction affords benzo[*b*]thieno[3,2-*b*]thiophenes **84**.

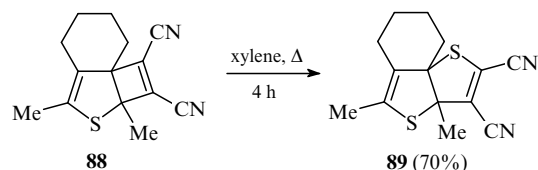


R = Pr<sup>i</sup>, Bu<sup>t</sup>.

Isomeric thienothiophenes can also be synthesised from other thiophene derivatives. In the studies of the 3,3-sigmatropic rearrangement of allyl 2-thienyl sulfide (**85**), 2-methylthieno[2,3-*b*]thiophene (**86**) and 3-chloro-3,4-dihydro-2*H*-thieno[2,3-*b*]thiopyran (**87**) were isolated from the reaction mixture in a total yield of up to 60%.<sup>48–50</sup>



Refluxing of sulfur-containing tricyclic dinitrile **88** in xylene was found to give 3*a*,5-dimethyl-3*aH*-6,7,8,9-tetrahydrobenzo[*c*]thieno[3,2-*b*]thiophene (**89**).<sup>51</sup>

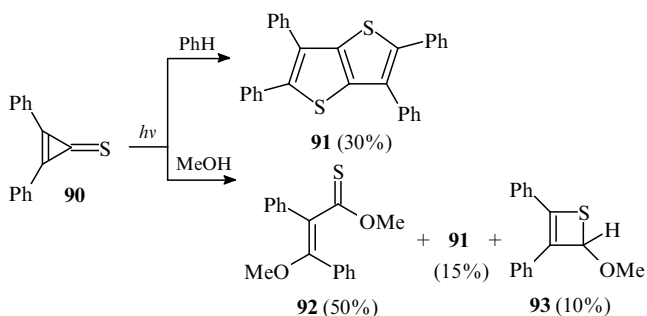


Analysis of the above methods for the synthesis of thienothiophenes and their analogues based on thiophene derivatives demonstrates that mono- and dibromo-substituted thiophenes are most often and successfully used as the starting compounds. It should be noted that intramolecular cyclisation of compounds derived from the above-mentioned thiophenes serves as the key step in this approach. In this step, vicinal carbonyl functions (generally, formyl or acyl) interact with fragments containing the activated methylene group.

## 2. Cyclopropenethiones in the synthesis of thienothiophenes

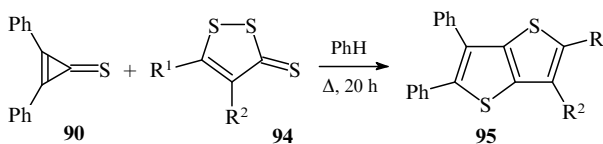
Cyclopropenethiones are transformed into thienothiophenes both under irradiation and on heating. However, this method has not received wide acceptance because the starting compounds are difficult to prepare and also because of low yields of the desired products.

Photodimerisation of 2,3-diphenylcyclopropenethione (**90**) in benzene<sup>52</sup> occurs regioselectively to give the expected 2,3,5,6-tetraphenylthieno[3,2-*b*]thiophene (**91**). This reaction in methanol



afforded methyl 1-methoxy-2-phenylthiocinnamate (**92**) as the major product; in addition, thienothiophene **91** and 3,4-diphenyl-2-methoxythiethane (**93**) were isolated as by-products.<sup>53, 54</sup>

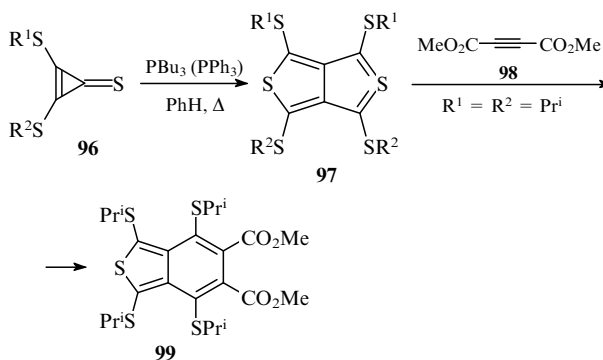
Refluxing of cyclopropenethione **90** with 4,5-disubstituted 1,2-dithiol-3-thiones **94** in anhydrous benzene in the dark is accompanied by elimination of two sulfur atoms to form thieno[3,2-*b*]thiophenes **95**.<sup>55</sup>



R<sup>1</sup> = R<sup>2</sup> = Me, Ph; R<sup>1</sup>–R<sup>2</sup> = (CH<sub>2</sub>)<sub>4</sub>, (CH = CH)<sub>2</sub>.

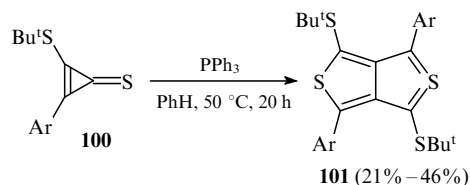
Refluxing of 1,2-dithiole-3-thione **94** (R<sup>1</sup> = R<sup>2</sup> = Ph) with powdered copper in chlorobenzene (6.5 h) led to its cyclisation to thienothiophene **91** in 39% yield.<sup>56, 57</sup>

In the presence of triphenyl- or tributylphosphine, 2,3-di-(alkylthio)cyclopropenethiones **96** are dimerised (refluxing in benzene under nitrogen, 4 h) to 1,3,4,6-tetra(alkylthio)-thieno[3,4-*c*]thiophenes (**97**) in moderate yields.<sup>58, 59</sup> The authors of the cited study also demonstrated that thienothiophene **97** (R<sup>1</sup> = R<sup>2</sup> = Pr<sup>i</sup>) is involved in cycloaddition with dimethyl acetylenedicarboxylate (**98**) to form 5,6-dimethoxycarbonylbenzo[*c*]thiophene (**99**).



R<sup>1</sup> = Pr<sup>i</sup>, Bu<sup>t</sup>; R<sup>2</sup> = Me, Et, Pr<sup>i</sup>, Bu<sup>t</sup>.

More recently,<sup>60, 61</sup> 1,4-bis(*tert*-butylthio)-3,6-diarylthieno[3,4-*c*]thiophenes **101** were prepared by treatment of cyclopropenethiones **100** with triphenylphosphine (benzene, 50 °C, argon atmosphere).



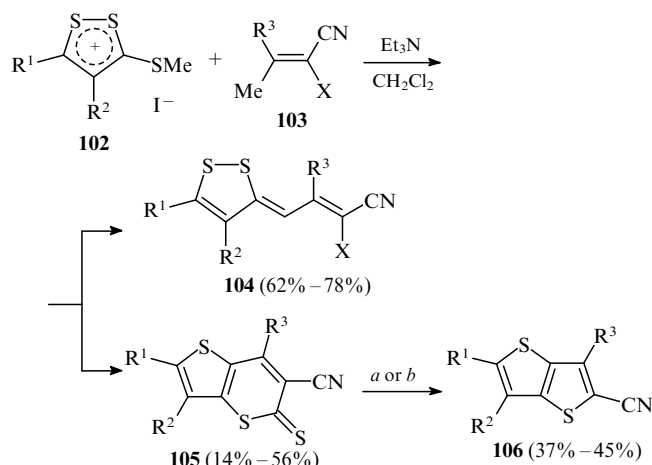
Ar = Ph, thien-2-yl.

An analogous procedure involving the reaction of cyclopropenethiones with tributylphosphine was employed in the synthesis of substituted thieno[3,2-*b*]thiophenes.<sup>62</sup>

## 3. Dithiynes in the synthesis of thienothiophenes

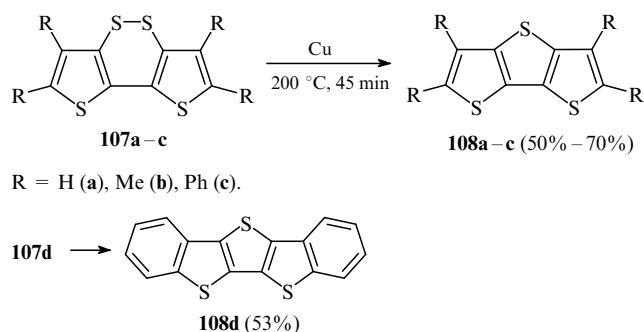
The use of dithiynes for the preparation of thienothiophenes is exemplified by four types of reactions. For example, 3-methylthio-1,2-dithiolium ions **102** react with malonic acid derivatives **103** to give  $\gamma$ -dithiolydene nitriles **104** and 6-cyanothieno[3,2-*b*]thiopyranones **105**. Oxidation of the latter with H<sub>2</sub>O<sub>2</sub> in acetic acid or successive treatment of **104** and **105** with NaOH and BrCH<sub>2</sub>CN affords 2-cyanothieno[3,2-*b*]thiophenes **106**.<sup>63</sup> This method was

applied to the synthesis of a rather broad range of nitrile-containing thienothiophenes promising for further modifications.



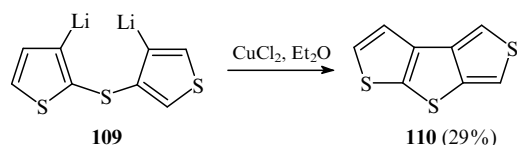
$\text{R}^1 = \text{H, Bu, SMe, Ph, 4-MeOC}_6\text{H}_4$ ;  $\text{R}^2, \text{R}^3 = \text{Ph, 4-MeOC}_6\text{H}_4$ ;  
 $\text{X} = \text{CN, CO}_2\text{Et}$ ; (a)  $\text{H}_2\text{O}_2$ ,  $\text{AcOH}$ ; (b) 1)  $\text{NaOH}$ , 2)  $\text{BrCH}_2\text{CN}$ .

Heating of dithienoannulated 1,2-dithiynes **107a–c** with powdered copper (200 °C, 45 min) afforded dithieno[3,2-*b*:2',3'-*d*]thiophenes **108a–c**.<sup>64,65</sup> An analogous transformation of benzoannulated dithiyn **107d** [ $\text{R}-\text{R} = (\text{CH}=\text{CH})_2$ ] produced bis(benzo[4,5]thieno)[3,2-*b*:2',3'-*d*]thiophene (**108d**).<sup>66</sup>

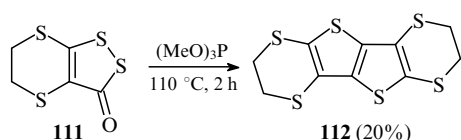


$\text{R} = \text{H (a), Me (b), Ph (c)}$ .

Unsubstituted dithienothiophene **108a** has been synthesised earlier by treating 2,2'-dilithium 3,3'-dithienyl sulfide with copper dichloride in diethyl ether.<sup>67</sup> This method was also successfully applied to oxidative cyclisation of the corresponding dilithium dithienyl sulfide **109** giving rise to dithieno[2,3-*b*:3',4'-*d*]thiophene (**110**) (29% yield).<sup>68</sup> The above-described dithieno[2,3-*b*:3',2'-*d*]thiophene (**10**) (32%) and dithieno[3,4-*b*:3',4'-*d*]thiophene (**11**) (31%) were synthesised analogously (see Section II.1).<sup>68</sup>



Heating of a suspension of 4,5-ethylenedithio-1,2-dithiol-3-one (**111**) in trimethylphosphite under nitrogen (110 °C, 2 h) afforded 2,3:5,6-bis(ethylenedithio)thieno[3,2-*b*]thiophene (**112**).<sup>69</sup>

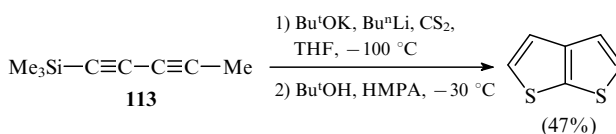


It should be noted that almost all the above-described reactions gave products in low yields. Hence, this approach is of theoretical rather than preparative interest.

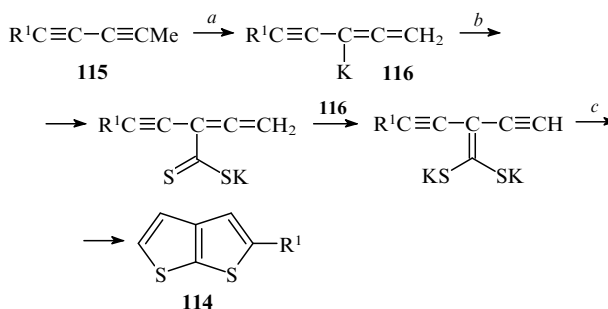
#### 4. Carbon disulfide in the synthesis of thienothiophenes

Methods based on the reactions of carbon disulfide with compounds containing conjugated triple-bond systems or the active methylene group are rather successfully employed in the synthesis of thienothiophenes. Generally, these procedures involve many steps, which require a thorough preparation and purification of the reagents and solvents.

Unsubstituted thieno[2,3-*b*]thiophene was synthesised in satisfactory yield from trimethylsilylpenta-1,3-diyne (**113**) under very mild conditions. In this procedure, the reagents should be added in a reverse order: *n*-butyllithium is initially added to a suspension of  $\text{Bu}^t\text{OK}$  in dry THF at –100 °C followed by the addition of alkyne at –80 °C,  $\text{CS}_2$  at –100 °C and a solution of  $\text{Bu}^t\text{OH}$  in dry HMPA at –30 °C.<sup>70</sup>

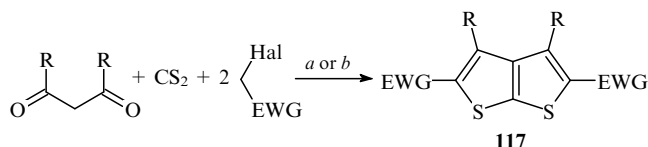


In the studies,<sup>71–73</sup> a one-pot procedure was developed for the synthesis of thieno[2,3-*b*]thiophenes **114** using diynes **115** and  $\text{CS}_2$  as the building blocks (in 44%–48% yields). Allene derivative **116** was detected as an intermediate. If the trimethylsilyl group is present as a substituent at the triple bond, it is eliminated during the reaction (as in the above-considered reaction).



$\text{R}^1 = \text{Me}_3\text{Si}$  (H for **114**), Alk,  $\text{N(Alk)}_2$ , SAlk;  
 (a)  $\text{Bu}^n\text{Li}$ ,  $\text{Bu}^t\text{OK}$ , THF,  $\text{C}_6\text{H}_{14}$ ; (b)  $\text{CS}_2$ , –100 °C; (c)  $\text{Bu}^t\text{OH}$ , HMPT (HMPT is hexamethylphosphorous triamide).

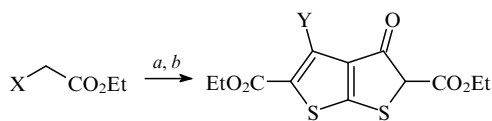
A technologically convenient one-pot synthesis of 2,5-functionalised thieno[2,3-*b*]thiophenes **117** starting from 1,3-diketones was proposed. In this procedure, carbon disulfide and alkylating agents containing electron-withdrawing groups are used. The reaction proceeds either in dry DMF in the presence of anhydrous  $\text{KF}$  as a promoter for condensation (36%–67% yields)<sup>74</sup> or under phase-transfer catalysis conditions (78%–93% yields)<sup>75</sup> (see also Ref. 76).



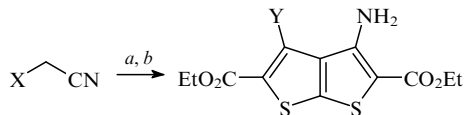
$\text{R} = \text{Me, Ph, 4-MeC}_6\text{H}_4$  (*p*-Tol); Hal = Br, Cl; EWG = CN, Ac,  $\text{CO}_2\text{Et}$ , CONHPh, CONH-thiazol-2-yl;  
 (a)  $\text{KF}$ , DMF; (b)  $\text{K}_2\text{CO}_3$ ,  $\text{Bu}_4\text{NBr}$ , PhH,  $\text{H}_2\text{O}$ .

More recently,<sup>77</sup> this approach was extended to the synthesis of oxo- and amino-substituted thieno[2,3-*b*]thiophenes. Compounds containing the active methylene group (3-keto esters, malononitrile, ethyl cyanoacetate or 3-ketonitrile) were used as the starting reagents, and ethyl bromoacetate or bromoacetic acid

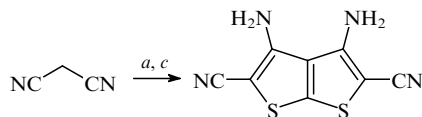
nitrile served as the alkylating agent. The yields of thienothiophenes were 61%–87%.



X = Ac, CN; Y = Me, NH<sub>2</sub>;

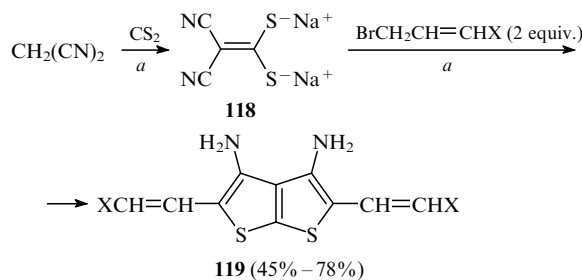


X = Piv, CN; Y = Bu<sup>t</sup>, NH<sub>2</sub>;



(a) CS<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, DMF; (b) BrCH<sub>2</sub>CO<sub>2</sub>Et (2 equiv.); (c) BrCH<sub>2</sub>CN (2 equiv.); Piv = Bu<sup>t</sup>C(O).

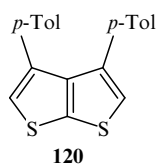
The reactions of carbon disulfide with malononitrile in the presence of sodium methoxide in methanol followed by treatment of the resulting dicyanodithioacetate **118** with  $\gamma$ -bromocrotonic acid derivatives can also be assigned to this reaction type.<sup>78</sup> These reactions give diamino-substituted thienothiophenes **119** as the final products.



X = CN, CO<sub>2</sub>Me; (a) MeONa, MeOH.

Dinitrile **118** was also used in the synthesis of other thieno[2,3-*b*]thiophene derivatives.<sup>79</sup> Various tri- and tetrasubstituted thieno[2,3-*b*]thiophenes were prepared according to modifications of this procedure.<sup>80–83</sup>

The synthesis of *peri*-substituted 3,4-diarylthienothiophene **120** from (4-MeC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>)<sub>2</sub>CO through the corresponding ketene dithioacetal, Dieckmann cyclisation, hydrolysis and decarboxylation was described in the study.<sup>84</sup>

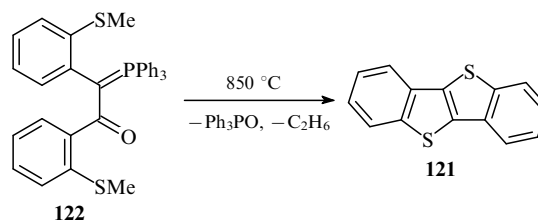


## 5. High-temperature synthesis

High-temperature synthesis of sulfur-containing heteroaromatic systems has attracted attention of researchers (predominantly, of Russian scientists) in the last 30 years. This method assumes the use of both a broad range of the starting substrates (aliphatic, aromatic, heteroaromatic compounds) and various sulfur donors (elemental sulfur, hydrogen sulfide, dialkyl sulfides).

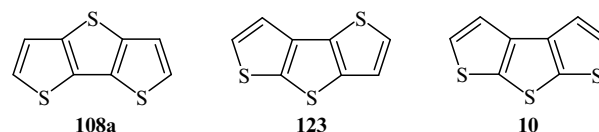
Friedmann was the first to describe the formation of thienothiophenes under pyrolysis conditions in 1916.<sup>85–88</sup> The reaction of aliphatic or aromatic hydrocarbons with sulfur proceeds at 270–320 °C and high pressure. More recently, this method was applied to the synthesis of benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene (**121**) in yields of up to 50% starting from benzyl bromide

and its derivatives,<sup>89,90</sup> 1,2,3-trichloro-1,2-diphenylethane<sup>91</sup> or *o*-halotoluenes<sup>92</sup> at 200–280 °C. Compound **121** was also prepared in 36% yield by tandem radical cyclisation of 2-methylthiophenyl-substituted phosphorus ylide **122** under conditions of flash vacuum pyrolysis at 850 °C.<sup>93,94</sup>



In addition, thienothiophene **121** was synthesised by gas-phase pyrolysis of benzotrichloride at 400 °C in a hydrogen sulfide atmosphere (67% yield).<sup>95</sup>

1,2-Dichloroethylene reacts with hydrogen sulfide in the gas phase at 420–520 °C in a quartz tube. The reaction produced a complex mixture, in which thieno[2,3-*b*]thiophene and thieno[3,2-*b*]thiophene were detected (in a total yield of 4.5%).<sup>96,97</sup> Thieno[2,3-*b*]thiophene was prepared by the gas-phase reaction of 2-chlorothiophene with hydrogen sulfide and acetylene at 600 °C.<sup>98</sup> The reaction with the use of dimethyl selenide instead of acetylene afforded a mixture of dithienothiophene **108a** and dithieno[3,2-*b*;2,3-*d*]thiophene (**123**) (3% yield).<sup>99</sup> The formation of dithienothiophene **10** along with other products was observed upon thermolysis (500–600 °C) of 2,2'-dithienyl sulfide under an atmosphere of nitrogen and hydrogen sulfide,<sup>100</sup> whereas dithienothiophenes **10** and **108a** were generated in a hydrogen sulfide atmosphere.<sup>101</sup>



Thieno[2,3-*b*]thiophene was also prepared by the high-temperature reaction of 2-chlorothiophene with acetylene and hydrogen sulfide<sup>102,103</sup> or dimethyl sulfide<sup>103</sup> and by the reaction of thiophene-2-thiol with acetylene.<sup>104</sup> An analogous reaction of 2-chlorothiophene with a mixture of diethyl di- and trisulfides produces a mixture of thieno[2,3-*b*]thiophene and thieno[3,2-*b*]thiophene in 10%–32% yields.<sup>105</sup> This reaction in the presence of acetylene affords a mixture of thienothiophenes in somewhat higher yield (36%).<sup>106</sup>

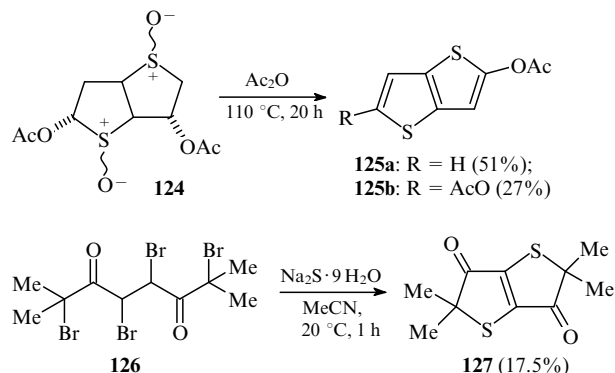
A mixture of thiophene and isomeric thienothiophenes (in a total yield of 85%) was prepared by the gas-phase reaction of dimethyl sulfide, diethyl disulfide, diethyl trisulfide and diethyl tetrasulfide with acetylene.<sup>107</sup> It was also found that gaseous allyl 2-thienyl sulfide is transformed into a mixture of thiophene-2-thiol, bis(2-thienyl) sulfide and 2-methylthieno[2,3-*b*]thiophene at 350–410 °C; in the presence of acetylene, the reaction gives these products along with thieno[2,3-*b*]thiophene.<sup>108</sup> Thermolysis (at 540 °C) of a mixture of di(prop-1-enyl) sulfide and 2-chloro(or bromo)thiophene affords a mixture of thieno[2,3-*b*]thiophene and thieno[3,2-*b*]thiophene.<sup>109</sup>

Therefore, the advantage of this method is that the starting compounds are readily available. Among the drawbacks are the necessity of using special apparatus, the formation of a large number of by-products in almost all reactions and low yields of the desired compounds.

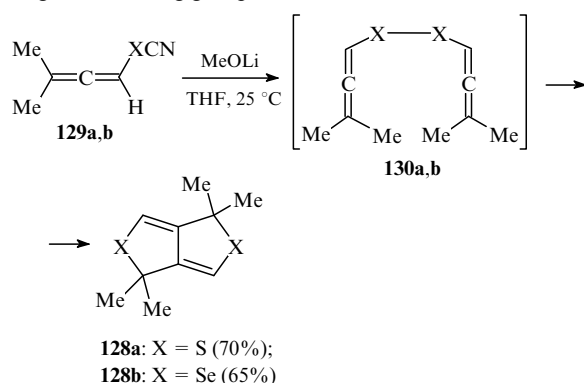
## 6. Other methods for the synthesis of thienothiophenes and their analogues

There are a few original procedures, which were used to prepare particular representatives of this class of heterocyclic compounds and their selenium and tellurium-containing analogues. The most interesting procedures are considered below.

Among other approaches to the synthesis of thienothiophenes, worthy of mention are the Pummerer rearrangement of disulfoxide **124** giving a mixture of 2-acetylthieno[3,2-*b*]thiophenes **125a,b**<sup>110</sup> and the reaction of 2,4,5,7-tetrabromo-2,7-dimethyl-3,6-octanedione (**126**) with sodium sulfide hydrate yielding 2,2,5,5-tetramethyl-2,3,5,6-tetrahydrothieno[3,2-*b*]thiophene-3,6-dione (**127**).<sup>111</sup>

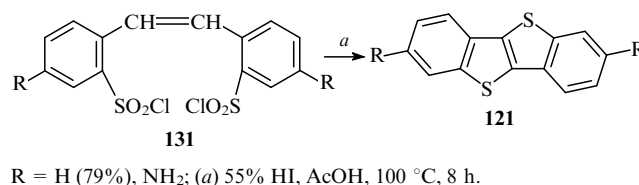


Substituted tetrahydrothieno[3,4-*c*]thiophene (**128a**) and its selenium analogue (**128b**) were synthesised by the reactions of lithium methoxide with γ,γ-dimethylallenyl thio(or seleno)cyanates **129a,b**.<sup>112–114</sup> The multistep mechanism of this reaction involves the formation of bis(dimethylallenyl) chalcogenides **130a,b** as the key intermediates, which undergo successive [3,3]-sigmatropic rearrangement and double Michael addition of a chalcogen-containing group.



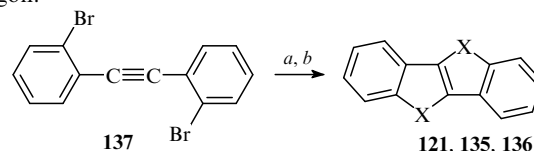
X = S (**a**), Se (**b**).

A new procedure was developed for the synthesis of benzoan-related thienothiophene based on reduction of stilbene-2,2'-disulfochloride (**131**) with concentrated hydroiodic acid in acetic acid.<sup>115–118</sup> This approach is applicable also to the synthesis of 2,7-disubstituted derivatives of thienothiophenes **121** starting from the corresponding 4,4'-disubstituted disulfochlorides.



Diethyl 2,2'-dinitro-(*E*)-stilbene-4,4'-dicarboxylate **132** proved to be a convenient starting compound in the synthesis of diethyl benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene-2,7-dicarboxylate (**133**) and its selenium analogue **134** (Scheme 3).<sup>119</sup>

Sulfur-, selenium- and tellurium-containing heteroaromatic systems **121**, **135** and **136** were prepared by successive treatment of 2,2'-dibromodiphenylacetylene (**137**) with *tert*-butyllithium and chalcogens in anhydrous tetrahydrofuran at –80 °C under argon.<sup>120</sup>

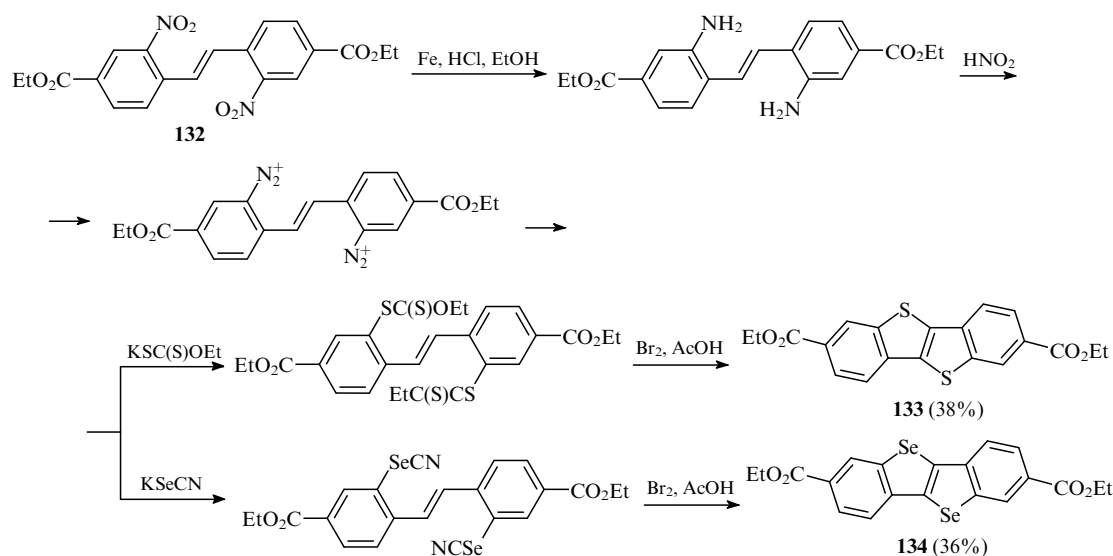


X = S (**121**, 49%), Se (**135**, 52%), Te (**136**, 55%);  
(a) Bu<sup>t</sup>Li, THF, –80 °C, Ar; (b) chalcogen (S, Se or Te).

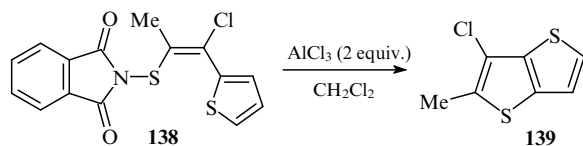
A selenium modification of the Claisen rearrangement of propargylselenochalcogenophenes was employed in the synthesis of fused bicyclic systems, *viz.*, thieno[2,3-*b*]-2*H*-selenopyran, thieno[3,2-*b*]-2*H*-selenopyran, 5-methylselenopheno[2,3-*b*]telluraphene and 5-methylselenopheno[3,2-*b*]thiophene.<sup>121</sup>

The reactions of sulfur with dimethylformamide dimethylacetal<sup>122</sup> and 2,5-dimethylhex-3-yne-2,5-diol<sup>123</sup> give substituted thieno[3,2-*b*]thiophenes.

The reaction of sulfenamide **138** with two equivalents of aluminium chloride produces 3-chloro-2-methylthieno[3,2-*b*]thiophene (**139**) in satisfactory yield.<sup>124</sup>



Scheme 3



Methyl 3-hydroxythieno[2,3-*b*]thiophene-2-carboxylates were also synthesised by cyclisation of substituted methyl 3-hydroxythiophene-2-carboxylates.<sup>125</sup>

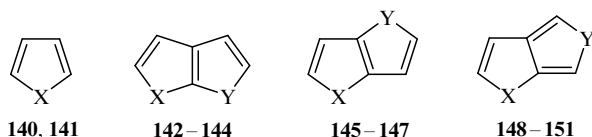
Therefore, the above data demonstrates the diversity of synthetic approaches to thienothiophene derivatives.

### III. Reactivity and chemical transformations

Heteroatoms in the five-membered  $\pi$ -excessive heteroaromatic compounds are responsible for the chemical behaviour of the molecules as a whole. The heteroatoms not only give electrons to form an aromatic  $\pi$ -electron system but also determine the direction of the attack of electrophilic or nucleophilic agents. In fused  $\pi$ -excessive heterocycles containing two or more heteroatoms, the reactivity of compounds and their physical properties are substantially affected by both the mutual arrangement of the heteroatoms and the electronic effects associated with their nature.

#### 1. Reactivity

First studies of the reactivity of thienothiophenes and their analogues by quantum-chemical methods were carried out in the mid-1970s.<sup>2, 5, 126</sup> More recently,<sup>127, 128</sup> the reactivity of thiophene, selenophene, various isomeric thienothiophenes, selenophenothiophenes, selenophenoselenophenes and their various C-protonated forms ( $\sigma$  complexes) in electrophilic substitution reactions was estimated by the semiempirical LCAO SCF MO method for all valence electrons (CNDO/2). The charges on the carbon atoms  $Q_c$  (static index) and the localisation energy  $A^+$  (dynamic index; in the CNDO/2 approximation, this index is determined as  $A^+ = E_{\text{total}}M - E_{\text{total}}MH^+$ , where  $E_{\text{total}}M$  and  $E_{\text{total}}MH^+$  are the total energies of the aromatic molecule and its  $\sigma$  complex with a proton, respectively) were used as the reactivity indices. The method of reactivity indices supplemented by a 'pseudoatom' approach (pseudoatoms simulate an electrophilic agent) provides a correct interpretation of experimental data on electrophilic substitution in fused heteroaromatic systems containing various heteroatoms. In addition, the values of  $Q_c$  and  $A^+$  (relative to position 3 in thiophene) indicate that the direction of electrophilic attack depends on the nature and size of the attacking species. This effect is mainly responsible for the difference in the reactivity of substrates.



The results of calculations made it possible to arrange the relative reactivities of different positions in compounds **140–151** in electrophilic substitution reactions in the following theoretical series: C(4) (**150**) > C(4) (**148**) > C(4) (**151**) > C(4) (**149**) > C(6) (**150**) > C(6) (**148**) > C(6) (**151**) > C(6) (**149**) > C(2) (**146**) > C(2) (**145**) > C(5) (**146**) > C(2) (**147**) > C(2) (**143**) > C(2) (**149**) > C(2) (**142**) > C(2) (**148**) > C(2) (**144**) > C(2) (**151**) > C(5) (**143**) > C(2) (**150**) > C(2) (**140**) > C(2) (**141**) > C(3) (**149**) > C(3) (**143**) > C(3) (**148**) > C(3) (**144**) > C(3) (**151**) > C(3) (**142**) > C(3) (**150**) > C(4) (**143**) > C(3) (**146**) > C(3) (**145**) > C(3) (**147**) > C(6) (**146**) > C(3) (**147**) > C(3) (**140**).<sup>5</sup> This series was confirmed experimentally. For example, the following series of reactivities of different positions in these compounds was obtained in studies of acetylation, formylation and chlorination of thiophene (**140**), thieno[2,3-*b*]thiophene (**142**) and thieno[3,2-*b*]thiophene (**145**): C(2) (**145**) > C(2) (**142**) > C(2) (**140**) > C(3)

(**142**) > C(3) (**145**) > C(3) (**140**).<sup>129</sup> In formylation, position 4 in thieno[3,4-*b*]thiophene (**148**) was found<sup>130</sup> to be more readily subjected to the attack of an electrophilic species compared to position 6.

The detritiation rate was studied for thieno[2,3-*b*]thiophene (**142**), thieno[3,2-*b*]thiophene (**145**), dithieno[2,3-*b*:3',2'-*d*]thiophene (**10**), dithieno[3,2-*b*:2',3'-*d*]thiophene (**108a**) and dithieno[2,3-*d*:2',3'-*d*]thiophene (**123**), which are specially labelled with the <sup>3</sup>H isotope at each position, in trifluoroacetic acid or its mixture with acetic acid.<sup>131, 132</sup> All thiophene systems were demonstrated to be rather active in electrophilic substitution reactions. The reactivity of the corresponding  $\alpha$  and  $\beta$  positions slightly increases in going from thiophene to thienothiophenes and increases to an even larger extent in going from thienothiophenes to dithienothiophenes.

The comparative reactivities in electrophilic substitution of selenopheno[3,2-*b*]thiophene (**143**) and -selenophene (**144**) with respect to thieno[3,2-*b*]thiophene (**142**) were studied by the method of competitive reactions.<sup>133</sup> The reactivity was found to change in the following order: **144** > **143** > **142**. This series agrees well with a higher substitution rate in selenophene compared to thiophene in acetylation, formylation and chlorination reactions.

Competitive metallation of two-component systems, *viz.*, thieno[3,2-*b*]thiophene (**142**) and selenopheno[3,2-*b*]thiophene (**143**), selenophenothiophene **143** and thiophene (**140**), selenophenothiophene **143** and selenophene (**141**), thiophene (**140**) and selenophene (**141**), was investigated.<sup>34</sup> The reactions were carried out with a deficient amount of Bu<sup>n</sup>Li in anhydrous diethyl ether at 25 ± 1 °C followed by hydrolysis with heavy water. Mass-spectrometric analysis of the products demonstrated that the relative reactivities of the compounds increase in the following order: **143** > **142** > **141** > **140**.<sup>34</sup>

The reactivities of thieno[2,3-*b*]thiophene (**142**) and selenopheno[2,3-*b*]thiophene (**143**) were also compared using competitive acetylation of their mixture with thiophene (**140**) or selenophene (**141**) by acetyl chloride in the presence of tin chloride (CHCl<sub>3</sub>, 25 °C).<sup>35</sup> The selenophene rings were found to be more reactive than the thiophene ring.

The above examples demonstrate that the theoretical estimates of the reactivities of the compounds in electrophilic substitution reactions most typical of aromatic systems agree well with the experimental data.

#### 2. Chemical transformations

In the last 20 years, studies of chemical transformation of isomeric thienothiophenes have been aimed primarily at examining the possibilities of using these substrates in the synthesis of new polyannellated heteroaromatic systems and compounds possessing practically useful properties. These compounds can exhibit both electron-withdrawing and electron-donating properties and they were used in the synthesis of numerous charge-transfer complexes. Thienothiophene derivatives have found application as medicines, pesticides, conducting polymers, liquid and clathrate crystals, organic conductors or superconductors, photosensitive receptors, materials for optoelectronics (nonlinear optical chromophores), dyes, *etc.* The most typical reactions of this class of compounds (metallation, condensation and photochemical cyclisations) clearly illustrate their high synthetic potential.

##### a. Metallation

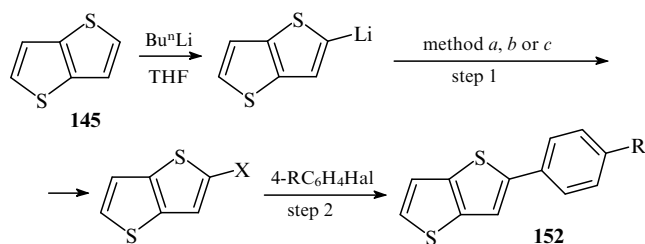
Lithiation (generally, with *n*-butyllithium) is most often and successfully used in the synthesis of various functionalised thienothiophenes. The lithium intermediates thus formed can react with various electrophiles.

For example, thieno[3,2-*b*]thiophene (**142**)<sup>134–141</sup> and its alkyl derivatives<sup>136, 137, 142, 143</sup> are readily metallated with *n*-butyllithium at the  $\alpha$  position, which can be used for the preparation of  $\alpha$ -substituted thienothiophenes. This method was employed to introduce such substituents as Br,<sup>139</sup> I,<sup>134</sup> MgBr,<sup>143</sup> ZnCl, SnBu<sub>3</sub>,



$\text{B}(\text{OH})_2$ ,<sup>135</sup>  $\text{SeMe}$ ,  $\text{TeMe}$ ,<sup>136</sup>  $\text{SR}$  ( $\text{R} = \text{Me}$ ,  $n\text{-C}_{18}\text{H}_{37}$ ),<sup>137</sup>  $\text{SMe}$ ,<sup>141</sup>  $\text{SEt}$ ,<sup>142</sup>  $\text{SO}_2\text{Me}$ ,  $\text{SO}_2\text{NH}_2$ ,<sup>137</sup>  $\text{CHO}$ <sup>140</sup> and  $\text{CO}_2\text{Me}$ .<sup>137</sup>

Lithium derivatives of thieno[3,2-*b*]thiophene (**145**) were used in the synthesis of 2-arylthieno[3,2-*b*]thiophenes **152** through various organometallic (or -boron) intermediates.<sup>135</sup>



$\text{R} = \text{H}$ ,  $\text{NO}_2$ ,  $\text{CN}$ ,  $\text{CO}_2\text{Me}$ ,  $\text{SO}_2\text{Me}$ ;  $\text{Hal} = \text{Br}$ ,  $\text{I}$ .

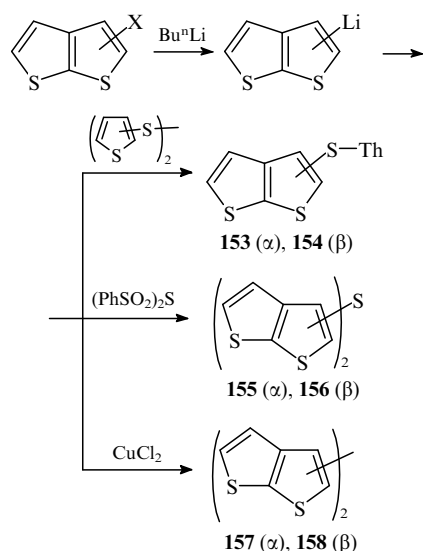
| Method X | Reaction conditions                                      |                                                              | Yields (%) |
|----------|----------------------------------------------------------|--------------------------------------------------------------|------------|
|          | Step 1                                                   | Step 2                                                       |            |
| a        | $\text{ZnCl}$ $\text{ZnCl}_2$ , THF                      | $\text{Pd}(\text{dba})_2$ , $\text{PPh}_3$ , DMF             | 10–85      |
| b        | $\text{B}(\text{OH})_2$ $\text{B}(\text{OBu}^n)_3$ , THF | $\text{Pd}(\text{PPh}_3)_4$ , $\text{Ba}(\text{OH})_2$ , DME | 40–55      |
| c        | $\text{SnBu}_3^a$ $\text{Bu}_3^a\text{SnCl}$ , THF       | $\text{Pd}(\text{PPh}_3)_4$ , dioxane                        | < 60       |

*dba* is dibenzylideneacetone, DME is 1,2-dimethoxyethane.

Metallation of thieno[3,2-*b*]thiophene **145** with two equivalents of  $\text{Bu}^n\text{Li}$  affords the 2,5-dilithium derivative, whose treatment with various reagents [ $\text{CO}_2$ , DMF,  $(\text{MeS})_2$ ,  $(\text{PhS})_2$ ,  $(\text{Me}_3\text{Si})_2$ ,  $(\text{Bu}^t\text{Me}_2\text{Si})_2$ ] gives the corresponding disubstituted thienothiophene.<sup>15, 138, 144</sup>

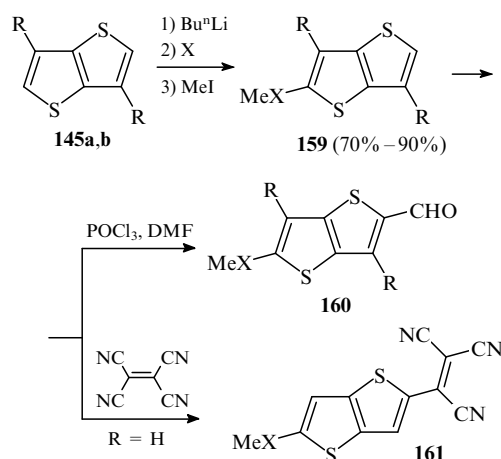
Exchange halogen–lithium reactions provide an approach to thienothiophene sulfides **142** and **145**, which were used in the synthesis of tetrathienocene **6** and pentathienocene **7** (see Section II.1).<sup>7, 145</sup>

Lithium intermediates served as the starting compounds in the synthesis of the corresponding 2( $\alpha$ )- or 3( $\beta$ )-substituted derivatives of thienyl sulfides **153** and **154**, thieno[2,3-*b*]thienyl sulfides **155** and **156** and thieno[2,3-*b*]thienylthieno[2,3-*b*]thiophenes **157** and **158**.<sup>146</sup>



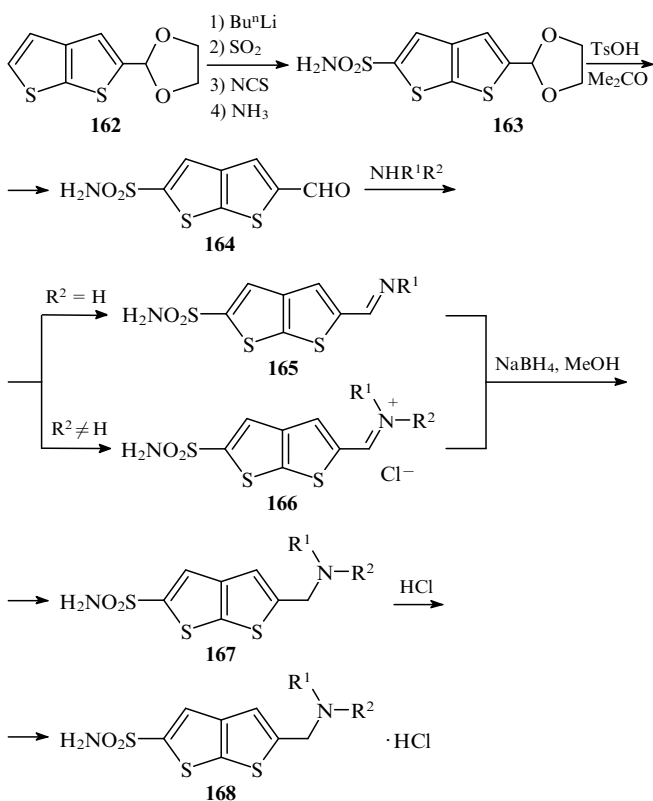
$\text{X} = \text{Br}$ ,  $\text{I}$ .

Lithiation of thieno[3,2-*b*]thiophenes **145a,b** gives 2-lithium derivatives, whose treatment with chalcogens and iodomethane affords chalcogenides **159**.<sup>136</sup> Vilsmeier–Haack formylation of the latter produces aldehydes **160**, whereas the reaction with tetracyanoethylene in DMF affords 5-tricyanovinyl derivatives **161**.



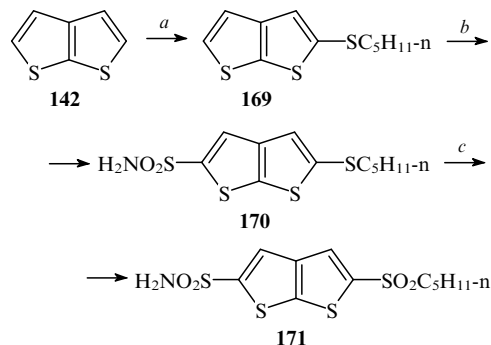
$\text{R} = \text{H}$  (**a**),  $\text{Me}$  (**b**);  $\text{X} = \text{S}$ ,  $\text{Se}$ ,  $\text{Te}$ .

Organolithium derivatives served as intermediates in the synthesis of 5-amino-substituted thieno[2,3-*b*] and -[3,2-*b*]thiophene-2-sulfonamides possessing biological activities. These compounds are carbonic anhydrase inhibitors (CAIs)<sup>36, 147</sup> and non-peptide fibrinogen receptor antagonists.<sup>148</sup> For example, the introduction of the sulfamoyl group into the dioxolane derivative of thieno[2,3-*b*]thiophene **162** can be efficiently performed by metallation with butyllithium at position 5 followed by treatment of the reaction mixture with  $\text{SO}_2$ , *N*-chlorosuccinimide (NCS) and ammonia. The acetal protection in the resulting 5-[1,3]dioxolan-2-ylthieno[2,3-*b*]thiophene-2-sulfonamide **163** was removed<sup>36</sup> by transacetalation giving rise to aldehyde **164** in high yield. The latter reacts with various primary and secondary amines to form imines **165** or immonium salts **166**, respectively, whose reduction with sodium borohydride affords tertiary amines **167**. Transformations of the amines into hydrochlorides **168** produced water-soluble salts, which were tested for biological activities. The same synthetic approach was applied to the synthesis of the corresponding thieno[3,2-*b*]thiophene analogues.



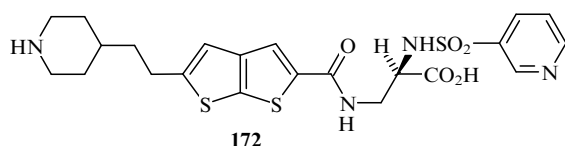
$\text{R}^1, \text{R}^2 = \text{H}$ , Alk.

The reaction of thieno[2,3-*b*]thiophene (**142**) with Bu<sup>n</sup>Li affords a lithium intermediate, whose treatment with elemental sulfur and bromopentane produces sulfide **169**. Regioselective *N*-sulfonation of the latter was successfully carried out by the successive reactions with Bu<sup>n</sup>Li, SO<sub>2</sub> and hydroxylamino-*O*-sulfonic acid. Selective oxidation of sulfide **170** with potassium peroxymonosulfate afforded sulfone **171**.<sup>147</sup>



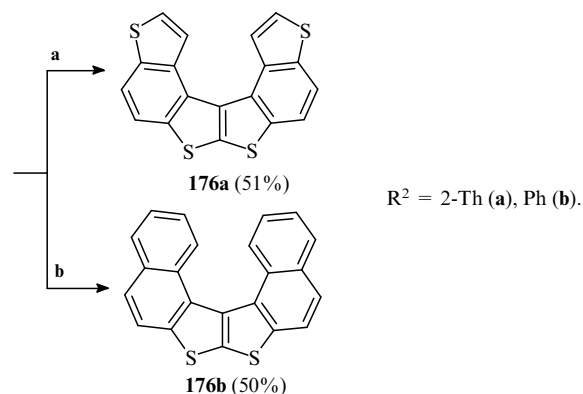
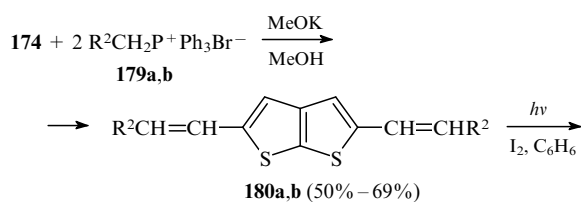
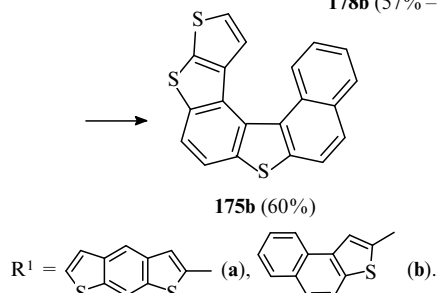
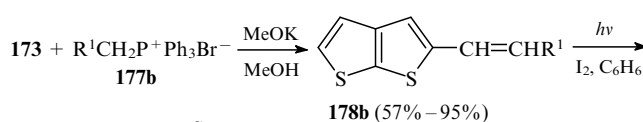
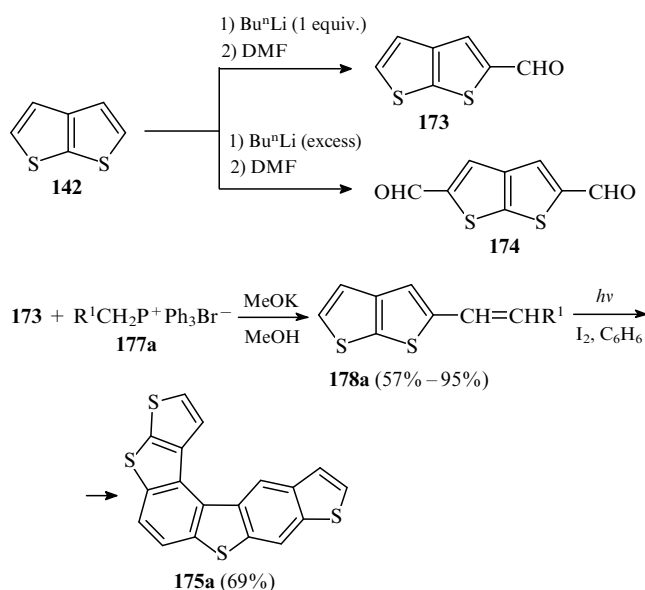
(a) 1) Bu<sup>n</sup>Li, 2) S<sub>8</sub>, n-C<sub>5</sub>H<sub>11</sub>Br; (b) 1) Bu<sup>n</sup>Li, 2) SO<sub>2</sub>, 3) hydroxylamino-*O*-sulfonic acid; (c) K<sub>2</sub>SO<sub>5</sub>.

An analogous approach was employed in the synthesis of sulfonamide **172**, which is a potential non-peptide fibrinogen receptor antagonist.<sup>148</sup>



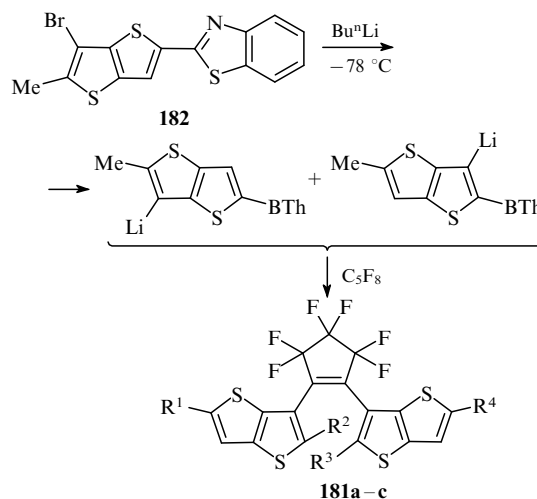
Metallation was involved also as the first step in the synthesis of di-, tri- and tetramers of 3,6-disubstituted thieno[3,2-*b*]thiophene (**145**) and selenopheno[3,2-*b*]selenophene (**147**).<sup>143</sup> These compounds are of practical interest. Many thiophene oligomers exhibit biological activity, which is enhanced upon exposure to visible light.<sup>149</sup>

Metallation of thieno[2,3-*b*]thiophene (**142**) followed by the reactions of the resulting mono- and dilithium derivatives with dimethylformamide afforded aldehydes **173** and **174**, which served as the starting compounds in the synthesis of heterohelicenes **175a,b** and **176a,b**.<sup>150</sup>



The Wittig reaction of aldehyde **173** with phosphonium salts **177a,b** gives alkenes **178a,b**, and the double Wittig reaction of dialdehyde **174** with phosphonium salts **179a,b** affords alkenes **180a,b**. Irradiation of suspensions of alkenes **178a,b** and **180a,b** in benzene in the presence of iodine produces heterohelicenes **175a,b** and **176a,b**.

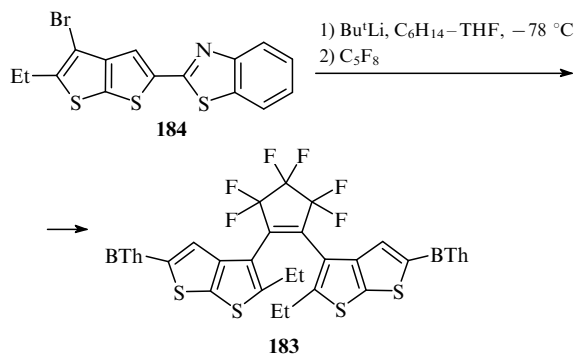
With the aim of synthesising new photochromic dihetaryl-ethenes, viz., 5-substituted 1,2-bis(thieno[3,2-*b*]thiophen-3-yl)perfluorocyclopentenes **181a-c**, 2-(benzothiazol-2-yl)-6-bromo-5-



R<sup>1</sup> = R<sup>4</sup> = BTh, R<sup>2</sup> = R<sup>3</sup> = Me (a); R<sup>1</sup> = R<sup>3</sup> = BTh, R<sup>2</sup> = R<sup>4</sup> = Me (b); R<sup>2</sup> = R<sup>3</sup> = BTh, R<sup>1</sup> = R<sup>4</sup> = Me (c); BTh is benzothiazol-2-yl.

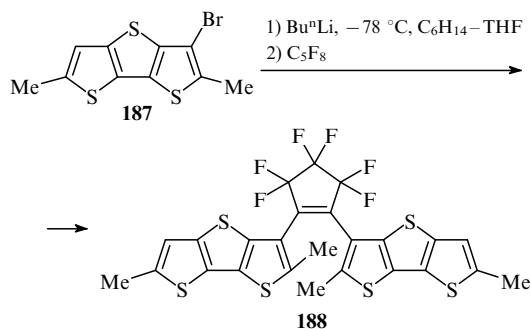
methylthieno[3,2-*b*]thiophene (**182**) was subjected to metallation. A mixture of lithium derivatives produced by this reaction was treated with octafluorocyclopentene ( $C_5F_8$ ).<sup>14, 15</sup>

The thieno[2,3-*b*]thiophene analogue of compound **181**, viz., 1,2-bis{2-ethyl-5-(benzothiazol-2-yl)thieno[2,3-*b*]thiophen-3-yl}-hexafluorocyclopentene (**183**), was synthesised according to an analogous procedure starting from (5-benzothiazol-2-yl)-3-bromo-2-ethylthieno[2,3-*b*]thiophene (**184**).<sup>151</sup>



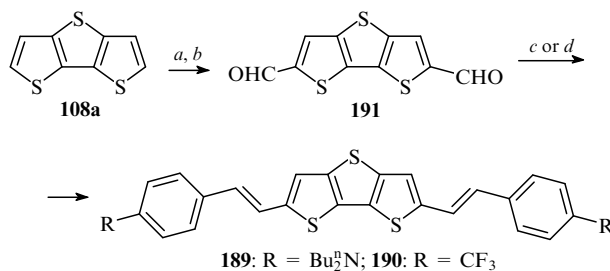
Dithieno[3,2-*b*:2',3-*d'*]thiophene (**108a**) served as a building block in the design of photochromic materials for optical memory. Photochromic compounds **185** and **186** (Scheme 4) were prepared in satisfactory yields by successive transformations involving initial metallation of dithienothiophene **108a** with  $Bu^iLi$  at  $-78\text{ }^\circ C$ .<sup>152</sup>

Photochromic 1,2-bis(2,6-dimethylthieno[3,2-*b*:2',3'-*d'*]thiophen-3-yl)hexafluorocyclopentene (**188**) was synthesised<sup>18</sup> starting from 3-bromo-2,6-dimethylthieno[3,2-*b*:2',3'-*d'*]thiophene (**187**) according to a procedure described in the studies.<sup>14, 15</sup>



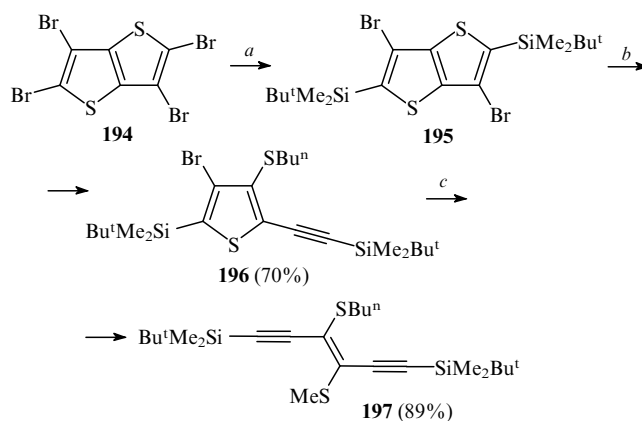
An analogous methodology was employed in the synthesis of new quadrupole photophores **189** and **190**, which have high two-photon excited fluorescence. Conjugated dithienothiophene **108a** was used as the starting compound. The reactions of dialdehyde **191** (see Ref. 153) with phosphonium salt **192** (2.1 equiv.) or

phosphonate **193** (2.2 equiv.) in the presence of phase-transfer catalysts<sup>154</sup> afforded compounds **189** and **190**, respectively, in 80%–90% yields.<sup>155</sup> After crystallisation, these compounds were isolated as pure *E* isomers.



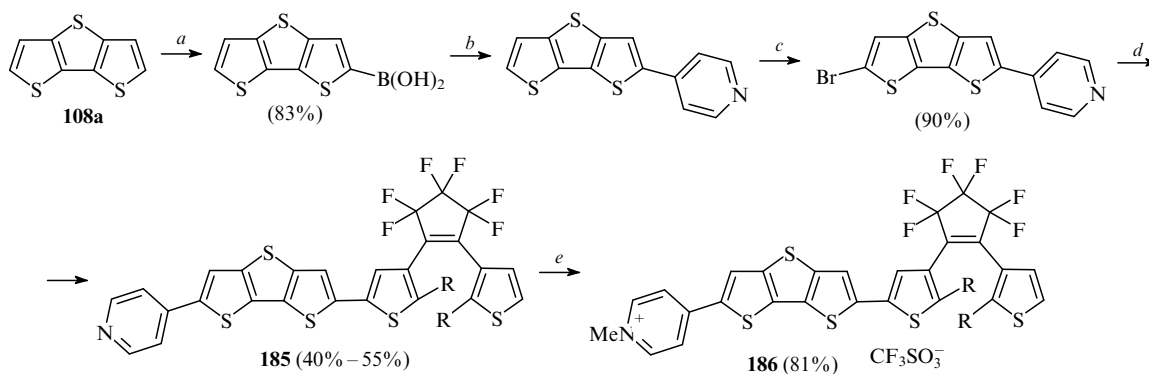
(a)  $Bu^iLi$ , THF,  $-78\text{ }^\circ C$ ; (b) DMF,  $-78\text{ }^\circ C$ ; (c)  $4-Bu_3NC_6H_4CH_2P^+Ph_3I^-$  (**192**),  $Bu^iOK$ ,  $CH_2Cl_2$ ,  $20\text{ }^\circ C$ , 5 h; (d)  $4-F_3CC_6H_4CH_2P(O)(OEt)_2$  (**193**), NaH, THF,  $20\text{ }^\circ C$ , 24 h.

Polyfunctional thiophenes and enediynes were synthesised through the cleavage of the heterocycle in 3-lithiated thieno[2,3-*b*] and -[3,2-*b*]thiophenes, 3,4-dilithiated thieno[2,3-*b*]thiophenes and 3,6-dilithiated thieno[3,2-*b*]thiophenes.<sup>15, 156, 157</sup> For example, tetrabromothieno[3,2-*b*]thiophene (**194**)<sup>158</sup> was successively treated with two equivalents of *n*-butyllithium (THF,  $20\text{ }^\circ C$ ) and two equivalents of  $Bu^iMe_2SiCl$  to prepare dibromide **195**, which was treated with one equivalent of *n*-butyllithium. The corresponding bromothiophene **196** was isolated by flash chromatography on silica gel. Treatment of **196** with  $Bu^iLi$  (1 equiv.) and excess iodomethane afforded enediyne **197**. Both steps of ring opening can be carried out without isolation of intermediates (the so-called tandem process).<sup>157</sup>



(a) 1)  $Bu^iLi$  (2 equiv.), THF,  $20\text{ }^\circ C$ , 2)  $Bu^iMe_2SiCl$  (2 equiv.); (b)  $Bu^iLi$  (1 equiv.),  $-78\text{ }^\circ C$ ; (c)  $Bu^iLi$  (1 equiv.),  $0\text{ }^\circ C$ , MeI.

Scheme 4

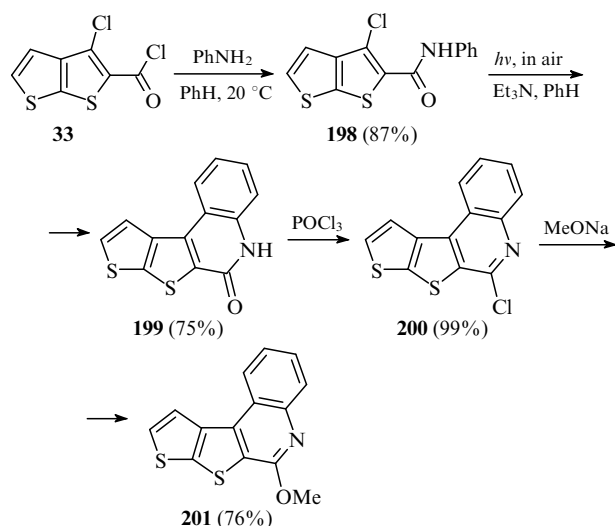


(a) 1)  $Bu^iLi$ , THF  $-78\text{ }^\circ C$ ; 2)  $B(OBu^i)_3$ ; (b) 4-bromopyridine,  $Pd(PPh_3)_4$ ,  $Na_2CO_3$ ,  $H_2O-THF$ ; (c) NBS,  $CHCl_3-AcOH$ ; (d) 1,2-bis[2-hexyl-5-(dihydroxyboryl)thiophen-3-yl]hexafluorocyclopentene,  $Pd(PPh_3)_4$ ,  $Na_2CO_3$ ,  $H_2O-THF$ ; (e)  $CF_3SO_3Me$ ,  $CH_2Cl_2$ ; R = *n*-hexyl; NBS is *N*-bromosuccinimide.

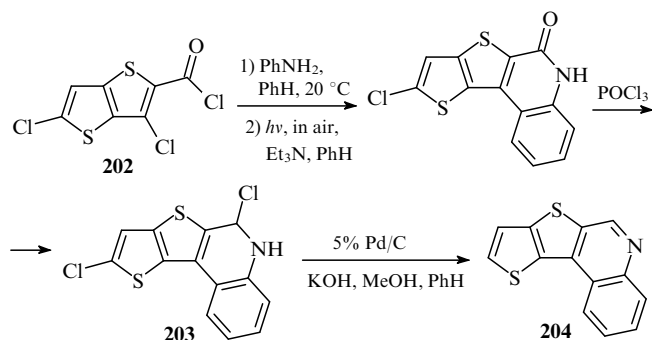
The above reactions exemplify the wide range of applications of metallation of thienothiophenes, which allows one to prepare new derivatives of this class of heterocycles, including those having practically useful properties.

### b. Photocyclisation

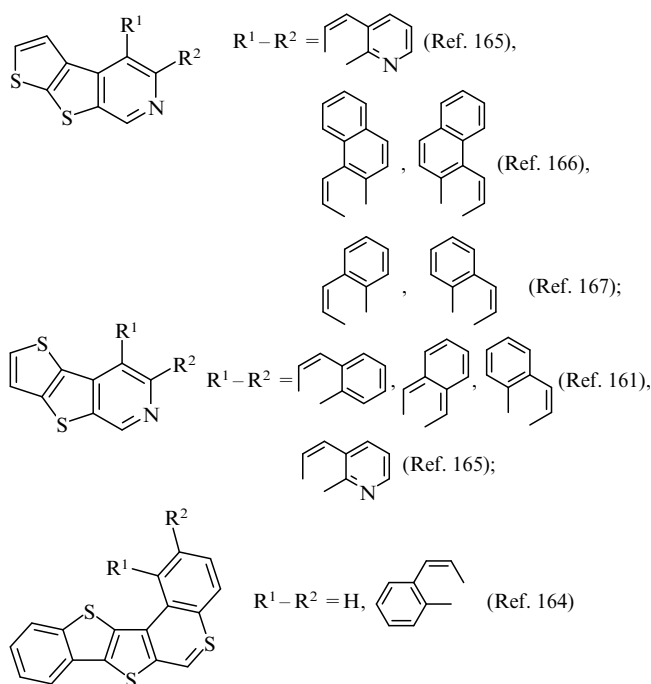
In the last decade, photocyclisation<sup>159</sup> of thienothiophenes and their derivatives (primarily, of amides) has attracted considerable attention as a convenient method for the synthesis of sulfur-containing polyannulated heterocyclic systems.<sup>25,27,160–166</sup> Two examples of the synthesis of such compounds are given below. The reaction of aniline with 3-chlorothieno[2,3-*b*]thiophene-2-carboxylic acid chloride **43** produced *N*-phenylthieno[2,3-*b*]thiophene-2-carboxamide **198**.<sup>24,25</sup> Photocyclisation of the latter in benzene containing a small amount of triethylamine gave thieno[3',2':4,5]-thieno[2,3-*c*]quinolin-2-one (**199**), whose chlorination with POCl<sub>3</sub> afforded 6-chlorothieno[3',2':4,5]thieno[2,3-*c*]quinoline (**200**). The reaction of compound **200** with sodium methoxide produced the corresponding methoxy derivative **201**. All steps of this transformation sequence gave products in good yields.



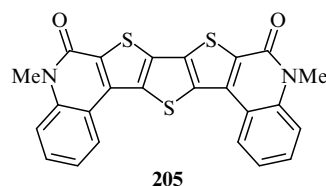
6,9-Dichlorothieno[2',3':4,5]thieno[2,3-*c*]quinoline (**203**) was synthesised from 3,5-dichlorothieno[3,2-*b*]thiophene-2-carboxylic acid chloride (**202**). Catalytic dechlorination of **203** afforded unsubstituted thieno[2',3':4,5]thieno[2,3-*c*]quinoline (**204**).<sup>25</sup>



This procedure was employed to prepare various polyannulated thienothiophene- and benzo[*b*]thiophene-containing systems starting from thieno[2,3-*b*] and -[3,2-*b*]thiophene-2-carboxylic acid chlorides. The structures of these compounds and references to their synthesis are given below.



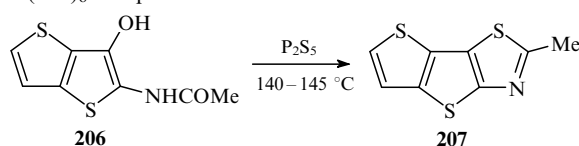
Dithieno[3,2-*b*:2',3'-*d*]thienyl[2'',3''-*c*:2'',3''-*c'*]-5,10-*N,N'*-dimethylquinoline-6,9-dione (**205**) was synthesised by double photochemical dehydrohalogenation of the corresponding thieno[3,2-*b*:2',3'-*d*]thiophene-2,6-dicarboxanilide.<sup>167</sup>



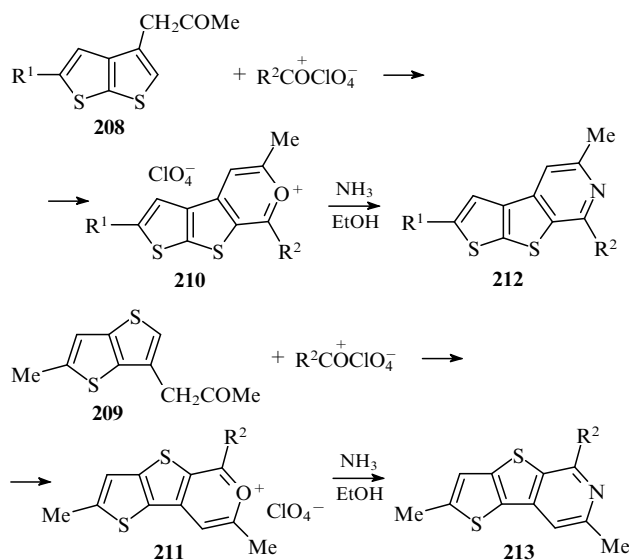
Conjugated thiophene polymers are of interest because of their electrical and optical properties. In this connection, photochemical polymerisation of dithieno[3,2-*b*:2',3'-*d*]thiophene **108a** and dithieno[3,4-*b*:3',4'-*d*]thiophene **11** was studied. Irradiation of solutions containing dithienothiophene and an electron acceptor (for example, *p*-dinitrobenzene, CCl<sub>4</sub>) gives rise to polythienothiophenes with molecular mass of ~10<sup>4</sup>. The radical cation of the starting thienothiophene is efficiently generated by photoinduced electron transfer from the excited state of the monomer to an electron acceptor. The subsequent coupling reaction affords polymers.<sup>168,169</sup>

### c. Fused thienothiophenes and their reactions

To construct additional heterocycles fused to the thienothiophene system, a number of approaches other than the above-mentioned photocyclisations were used. For example, heating of 2-acetyl-amino-3-hydroxythieno[3,2-*b*]thiophene (**206**) in the presence of P<sub>2</sub>S<sub>5</sub> afforded 2-methylthieno[3,2-*b*]thieno[3,2-*d*]thiazole (**207**).<sup>19</sup> Isomeric 2-methylthieno[2,3-*b*]thieno[3,2-*d*]thiazole was prepared by oxidation of 2-thioacetylaminothieno[2,3-*b*]thiophene with K<sub>3</sub>Fe(CN)<sub>6</sub> in aqueous alkali.<sup>170</sup>



Acylation of 3-acetyl-5-alkylthieno[2,3-*b*]thiophenes **208** and 3-acetyl-5-methylthieno[3,2-*b*]thiophenes **209** in a mixture of aliphatic acid anhydride and perchloric acid (actually, acylium perchlorate) was demonstrated<sup>171</sup> to occur at the free  $\alpha$  position followed by cyclisation and formation of perchlorates of tricyclic pyrylium salts **210** and **211** (yields > 80%). The latter are transformed into thieno[2',3':5,4]- (**212**) and -[2',3':4,5]thieno[2,3-*c*]pyridines **213** in yields of higher than 90% by passing ammonia through their suspensions.

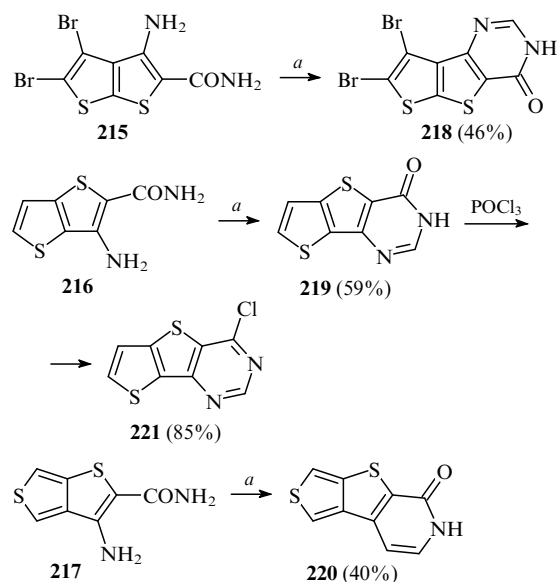


$R^1 = Me, Et; R^2 = Me, Et, Bu^n$ .

Functionalised thieno[2,3-*b*]thiophenes **214** were transformed according to conventional procedures into the following tri- and tetracyclic systems: thienopyrimidines, thieno-1,3-oxazines, bis-(thieno-1,2,3-triazines), dithieno-1,4-oxazepines<sup>38</sup> (presented in Scheme 5) and fused thieno[2,3-*b*]thiophenes containing pyridine, pyrimidine, thiazine, thiazole, oxadiazole, isoxazole, pyrazole,

pyridazine, piperazine, pyrrolpiperazine and other heterocyclic fragments.<sup>172–175</sup>

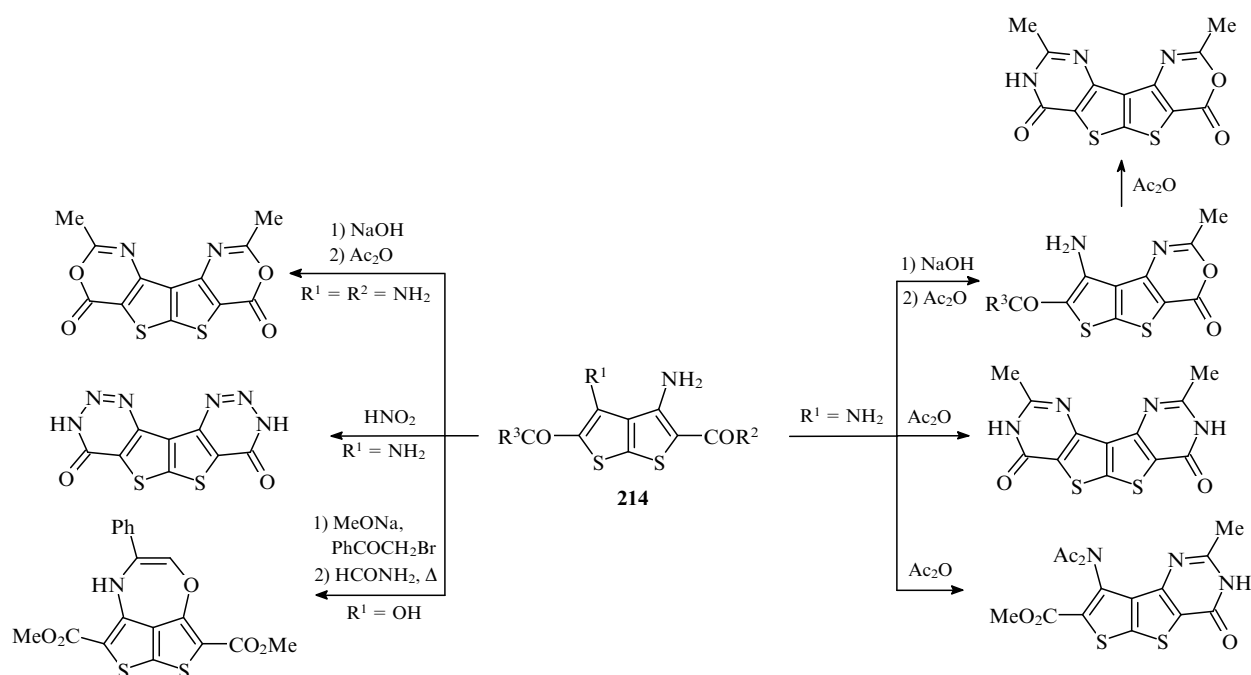
The reactions of thienothiophenes **215**, **216** and **217** containing the amino- and carboxamide groups in the adjacent positions with triethyl orthoformate in boiling acetic anhydride produce thieno[2',3':4,5]- (**218**), thieno[3',2':4,5]- (**219**) and thieno[3',4':4,5]thieno[3,2-*d*]pyrimidin-7(6*H*)-ones (**220**), respectively.<sup>10</sup> The reaction of thienopyrimidine **219** with  $POCl_3$  affords 7-chloro derivative **221**.



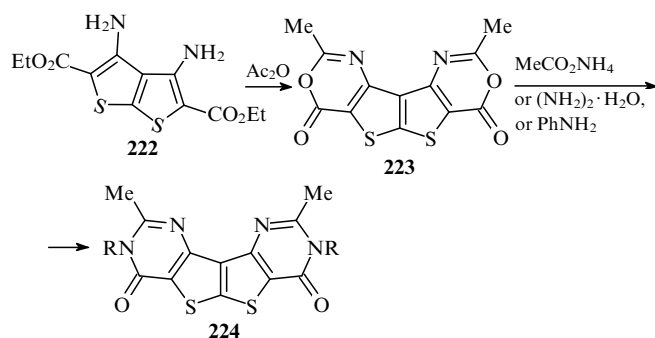
(a)  $CH(OEt)_3, Ac_2O, \Delta, 1.5\ h$ .

Treatment of diethyl 3,4-diaminothieno[2,3-*b*]thiophene-2,5-dicarboxylate (**222**) with acetic anhydride afforded symmetrical tetracyclic derivative **223**, whose reactions with ammonium acetate, hydrazine hydrate or aniline produced its nitrogen analogues **224**.<sup>172</sup>

Scheme 5

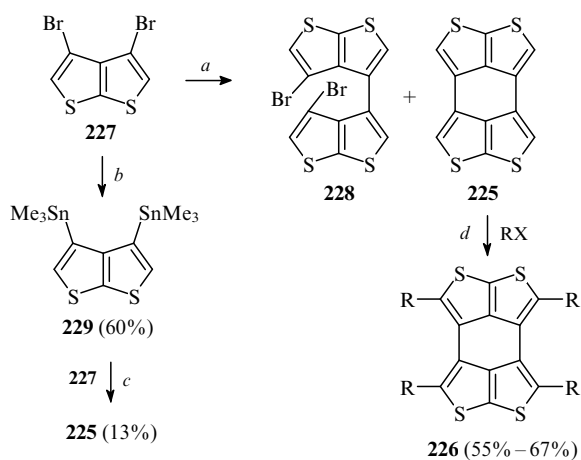


$R^1 = NH_2, OH; R^2 = NH_2, OMe, Ph; R^3 = NH_2, OMe, Ph$ .



R = H, NH<sub>2</sub>, Ph.

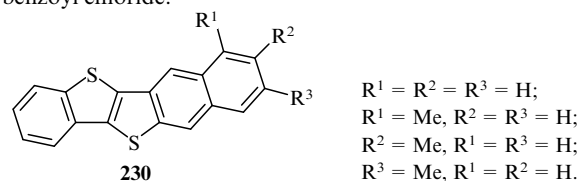
2,3,6,7-Tetrathienobenzene[1,3-*cd*:4,6-*c'd'*]dipentalene (**225**) and its derivatives **226** are new fused polynuclear heteroarenes iso-electronic with perylene. Dipentalene **225** was prepared for the first time by dimerisation of thieno[2,3-*b*]thiophene (**142**).<sup>172</sup> More recently, it was found that catalytic reduction of 3,4-dibromothieno[2,3-*b*]thiophene (**227**) with an excess of activated zinc in the presence of bis(triphenylphosphine)nickel(II) chloride and tetraethylammonium iodide afforded only 4,4'-dibromo-3,3-bis(thieno[2,3-*b*]thiophene) (**228**) (in a maximum yield of 28%).<sup>176</sup> However, the reaction in the presence of a larger amount of the nickel catalyst afforded also dipentalene **225**. Optimisation of the reaction conditions made it possible to increase the yield of the latter to only 14%. An alternative procedure was employed to transform thienothiophene **227** into trimethylstannyl derivative **229**. The reaction of thienothiophene **227** with organotin intermediate **229** in the presence of the palladium triphenylphosphine complex afforded dipentalene **225** (13% yield). Derivatives **226** were prepared by lithiation of dipentalene **225** followed by the reaction with the corresponding alkyl iodide or dialkyl disulfide.<sup>79</sup>



RX = MeI, EtI, (MeS)<sub>2</sub>, (EtS)<sub>2</sub>; R = Me, Et, SMe, SEt;  
 (a) (Ph<sub>3</sub>P)<sub>2</sub>NiCl<sub>2</sub>, Me<sub>4</sub>NI, Et<sub>4</sub>Ni, Zn (excess), PhH, Δ; (b) Bu<sup>n</sup>Li (2 equiv.), Me<sub>3</sub>SnCl (2 equiv.), Et<sub>2</sub>O-TMEDA, -80 °C; (c) (Ph<sub>3</sub>P)<sub>4</sub>Pd, PhMe, 70 °C; (d) LDA, THF, -10 °C; TMEDA is *N,N,N',N'*-tetramethylethylenediamine, LDA is lithium diisopropylamide.

The oxidation potential of heteroarene **225** is equal to that of perylene, and compound **225** forms an analogous complex with iodine having rather high conductivity (0.11 S cm<sup>-1</sup>). However, it appeared that complexes of all derivatives **226** with iodine have low conductivity. In addition, compounds **225** and **226** form charge-transfer complexes with strong electron acceptors, such as 7,7,8,8-tetracyanoquinodimethane (TCNQ), 2,3,5,6-tetrafluoro-7,7,8,8-tetracyanoquinodimethane (TCNQF<sub>4</sub>), 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and 1,1,2,3,4,4-hexacyano-1,3-butadiene (HCB<sub>6</sub>).<sup>79, 176</sup> However, the majority of these π complexes are low-conducting powdered polymers, whereas complexes of tetrakis(methylthio) derivatives **226** (R = SMe) form crystalline radical-cation salts with a conductivity of about 10<sup>-3</sup> S cm<sup>-1</sup>.

Friedel–Crafts condensation of benzo[*b*]thieno[3,2-*b*]thiophene-2-carboxylic acid chloride with *m*- and *p*-xylene affords ketones, which undergo Elbs pyrolysis (420 °C, 15 min) to form pentacyclic derivative **230**.<sup>177</sup> Analogous products were prepared from benzo[*b*]thieno[3,2-*b*]thiophene and (di)methyl homologues of benzoyl chloride.



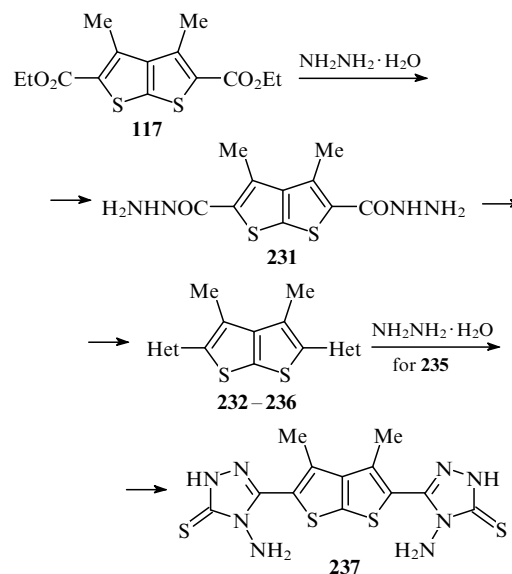
Cyclisation of benzo[*b*]thieno[3,2-*b*]thiophene-2-butyric acid in the presence of P<sub>2</sub>O<sub>5</sub> gives benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene (**121**) in 80% yield.<sup>178</sup>

#### d. Other transformations

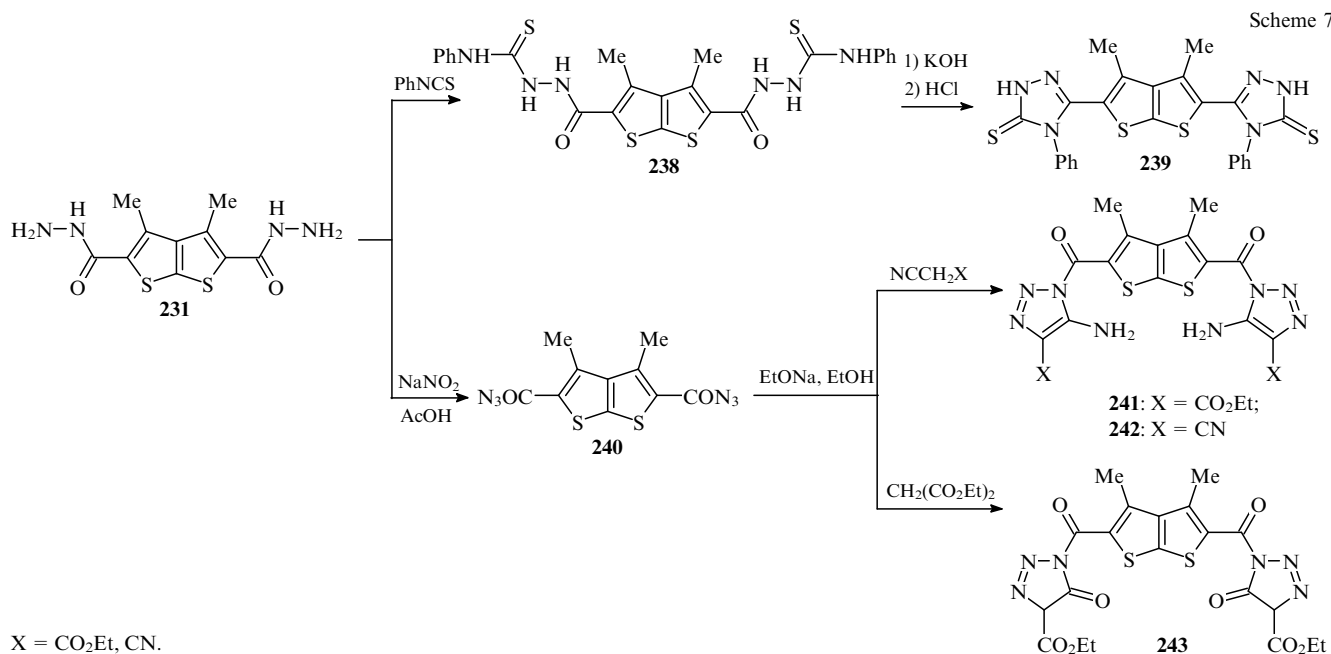
This Section deals with the most interesting reactions of thienothiophenes giving rise to various sulfur-containing heterocyclic systems.

The reaction of diethyl 3,4-dimethylthieno[2,3-*b*]thiophene-2,5-dicarboxylate (**117**, R = Me, EWG = CO<sub>2</sub>Et) with hydrazine hydrate afforded dihydrazide **231**, which was subjected to various transformations (Scheme 6). For example, the reactions with acetylacetone, ethyl acetoacetate or malononitrile<sup>75</sup> are accom-

Scheme 6



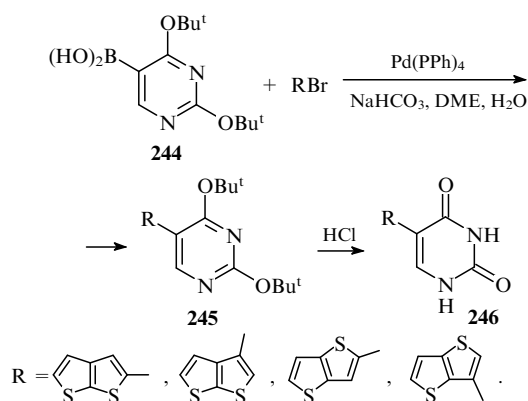
| Compound   | Het | Reaction conditions                                         | Yield (%) |
|------------|-----|-------------------------------------------------------------|-----------|
| <b>232</b> |     | CH <sub>2</sub> Ac <sub>2</sub> , fusion                    | 88        |
| <b>233</b> |     | AcCH <sub>2</sub> CO <sub>2</sub> Et, EtOH, AcOH            | 79        |
| <b>234</b> |     | CH <sub>2</sub> (CN) <sub>2</sub> , EtOH, Pip               | 73        |
| <b>235</b> |     | 1) CS <sub>2</sub> , KOH, 2) HCl                            | 82        |
| <b>236</b> |     | 1) CS <sub>2</sub> , KOH, 2) H <sub>2</sub> SO <sub>4</sub> | 85        |



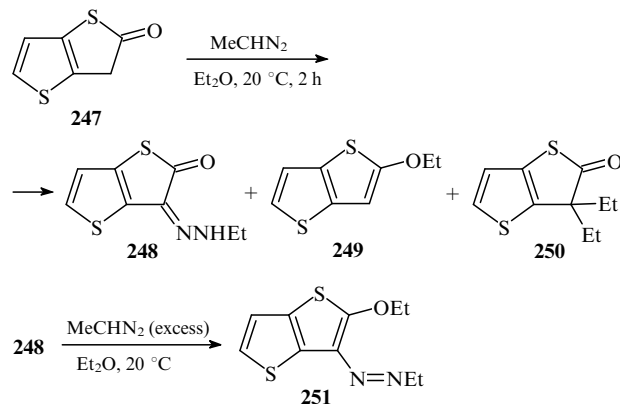
panied by the closure of the exocyclic pyrazole ring to form the corresponding derivatives **232**–**234**. The reaction of dihydrazide **231** with carbon disulfide in the presence of KOH followed by decomposition with dilute HCl or concentrated  $\text{H}_2\text{SO}_4$  produces di(oxadiazole) (**235**) or di(thiadiazole) derivative (**236**). Condensation of di(oxadiazolyl)thienothiophene **235** with hydrazine hydrate affords di(triazolyl)thienothiophene **237** (Scheme 6).

Dihydrazide **231** was also used in the synthesis of thienothiophenes containing triazole substituents. For example, the reaction with phenyl isothiocyanate in ethanol produces di(*N*-phenylthiocarbamoyl)carbohydrazide **238**, whose treatment with KOH followed by acidification affords compound **239**. Diazotisation of dihydrazide **231** with a 10% sodium nitrite solution in acetic acid gives diazide **240**. The reactions of the latter with compounds containing the active methylene group, *viz.*, ethyl cyanoacetate, malononitrile or diethyl malonate, in the presence of sodium ethoxide, yield the corresponding ditriazole derivatives **241**–**243** (Scheme 7).

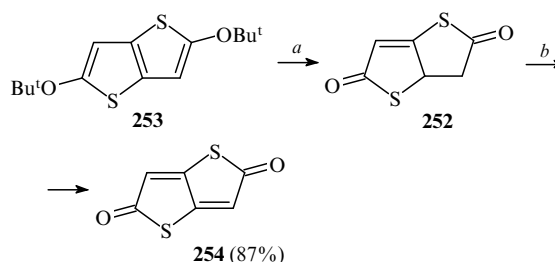
In the presence of zero-valent palladium complexes as the catalyst, 2,4-di-*tert*-butoxypyrimidine-5-boronic acid (**244**) reacts with the bromine derivatives of thieno[2,3-*b*]thiophene (**142**) and thieno[3,2-*b*]thiophene (**145**).<sup>179, 180</sup> This reaction was used to introduce fragments of isomeric thienothiophenes at position 5 of 2,4-di-*tert*-butoxypyrimidine. The resulting compounds **245** were transformed into uracils **246** in quantitative yields.



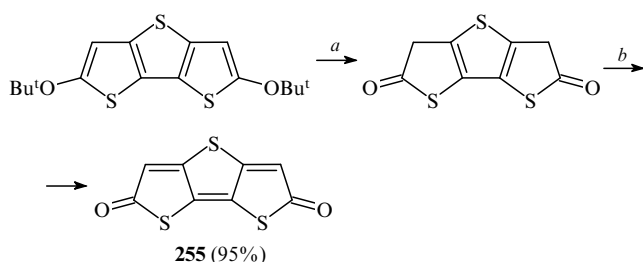
After the reaction of thieno[3,2-*b*]thiophen-2(3*H*)-one (**247**) with diazoethane in diethyl ether, thieno[3,2-*b*]thiophene-2,3-dione 3-ethylhydrazone (**248**), 2-ethoxythieno[3,2-*b*]thiophene (**249**) and 3,3-diethylthieno[3,2-*b*]thiophen-2-one (**250**) were isolated from the reaction mixture.<sup>181</sup> The reaction of hydrazone **248** with diazoethane yielded 2-ethoxy-3-ethylazothieno[3,2-*b*]thiophene (**251**).



Dehydrogenation of dione **252**, which was prepared by treatment of 2,5-di(*tert*-butoxy)thieno[3,2-*b*]thiophene (**253**) with *p*-toluenesulfonic acid, with DDQ in dioxane gave 2,5-dioxothieno[3,2-*b*]thiophene (**254**).<sup>182</sup> 2,6-Dioxothieno[3,2-*b*]thieno[2',3'-*d*]thiophene (**255**) was prepared according to an analogous procedure.

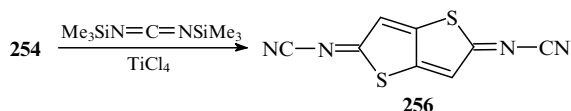




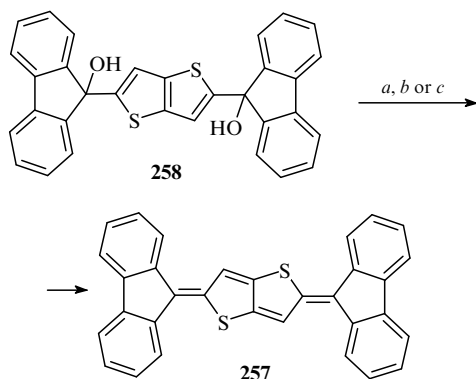


(a) TsOH, PhH,  $\Delta$ , 2 h; (b) DDQ, dioxane,  $\Delta$ , 5 h.

Dicyanodiimide **256** and its various derivatives were synthesised starting from dione **254**. These compounds form high-conducting charge-transfer complexes.<sup>183</sup>

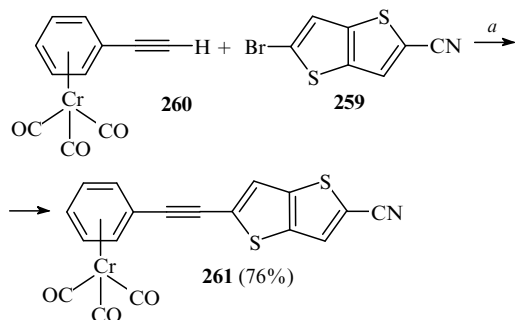


Fluorenylidene derivative **257** was synthesised from diol **258** according to three procedures: by heating without a solvent (35% yield) and by irradiation for 5–10 h in the solid state ( $\sim 10\%$ ) or in a solution in  $\text{CH}_2\text{Cl}_2$  (86%). Irradiation was carried out using a high-pressure mercury lamp through a Pyrex filter.<sup>184</sup>



(a)  $> 200^\circ\text{C}$ ; (b)  $h\nu$ ; (c)  $h\nu$ ,  $\text{CH}_2\text{Cl}_2$ .

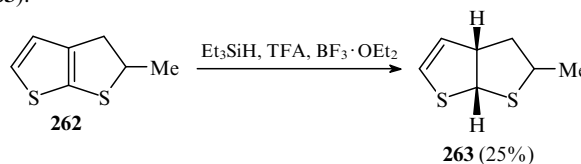
Recently, the first example of Pd-catalysed coupling of bromothiophene **259** with the chromium tricarbonyl complex with phenylacetylene (**260**) giving rise to complex **261** has been published.<sup>185</sup>



(a)  $\text{PdCl}_2(\text{PPh}_3)_2$ , CuI,  $\text{Et}_3\text{N}$ , THF,  $\Delta$ .

Catalytic liquid-phase oxidation of 3-methylthieno[2,3-*b*] and -[3,2-*b*]thiophenes in the presence of cobalt acetate and NaBr in acetic acid ( $90\text{--}110^\circ\text{C}$ ) gave rise to thieno[2,3-*b*]thiophene-2-carboxylic acid (**41**) and the 3-formyl derivative, respectively.<sup>186</sup> The kinetic data provide evidence that electron transfer from the peroxy radical to  $\text{Co}^{2+}$  is the rate-determining step.

Ionic hydrogenation of 2-methyl-2,3-dihydrothieno[2,3-*b*]thiophene (**262**) affords *cis*-2,8-dithiabicyclo[3.3.0]octane (**263**).<sup>187</sup>

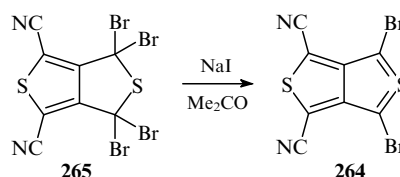


TFA is trifluoroacetic acid.

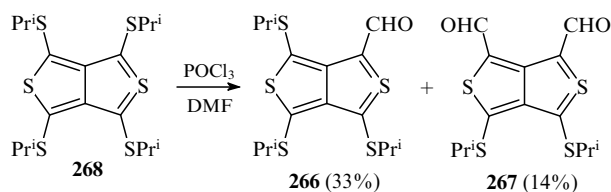
Desulfation of methyl 5,6-dibromo-3-chlorothieno[3,2-*b*]thiophene-2-carboxylate with a Ni–Al melt in a 10% NaOD– $\text{D}_2\text{O}$  solution produced methyl heptanoate containing 96% of deuterium.<sup>188</sup>

As mentioned above, thieno[3,4-*c*]thiophene is very difficult to synthesise compared to all other isomeric thienothiophenes. A few derivatives are known: tetraphenyl-,<sup>189–191</sup> tetrakis(alkylthio)-,<sup>58</sup> tetra(2-thienyl)-,<sup>42</sup> tetrabromo-, 1,3-dibromo-4,6-dicyano-, 1,3-dibromo-4,5-bis(methoxycarbonyl)-,<sup>192</sup> 1,4-bis(*tert*-butylthio)-3,6-diphenyl- and 3,6-di(2-thienyl)thieno[3,4-*c*]thiophenes.<sup>61</sup>

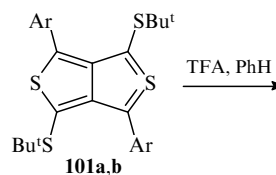
The synthesis of 1,3-dibromo-4,6-dicyanothieno[3,4-*c*]thiophene (**264**) by the reaction of tetrabromide **265** with NaI in acetone is the first example of the synthesis of a stable thieno[3,4-*c*]thiophene derivative.<sup>193</sup>

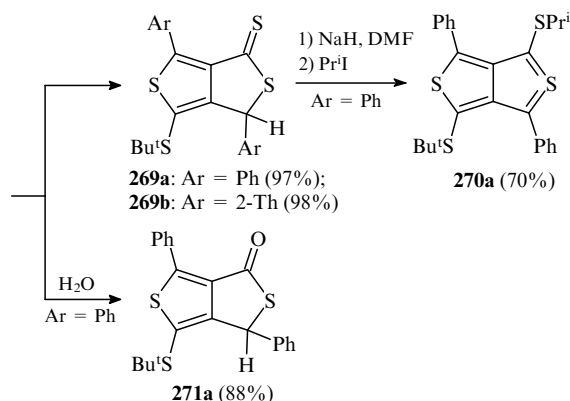


Mono- (**266**) and diformyl derivatives **267**, which were prepared by formylation of 1,3,4,6-tetrakis(isopropylthio)thieno[3,4-*c*]thiophene (**268**) with the Vilsmeier reagent, also proved to be rather stable.<sup>194</sup>



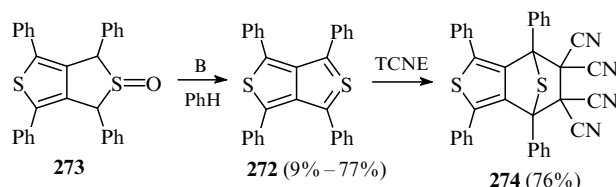
The reactions of thienothiophenes **101a,b** with trifluoroacetic acid are accompanied by protonation of the thienothiophene system, resulting in the  $\text{Bu}^t\text{--S}$  bond cleavage to form the corresponding thieno[3,4-*c*]thiophene-1(3*H*)-thione (**269a,b**).<sup>60, 61</sup> Treatment of thienothiophene **269a** with sodium hydride and isopropyl iodide leads to regeneration of the thieno[3,4-*c*]thiophene system to give 1-(*tert*-butylthio)-3,6-diphenyl-4-(isopropylthio)thieno[3,4-*c*]thiophene (**270a**). The reaction of thienothiophene **101a** with trifluoroacetic acid in the presence of 10 equivalents of water is accompanied by elimination of one sulfur-containing group to form 4-(*tert*-butylthio)-3,6-diphenylthieno[3,4-*c*]thiophene-1(3*H*)-one (**271**).





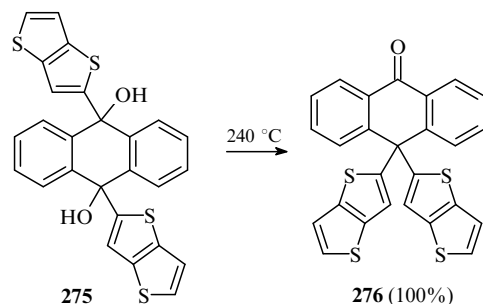
Cycloaddition of thienothiophenes **101a,b** to *N*-phenylmaleimide and dimethyl acetylenedicarboxylate was described in the study.<sup>61</sup>

1,3,4,6-Tetraphenylthieno[3,4-*c*]thiophene (**272**) was derived from a mixture of *cis*- and *trans*-sulfoxides **273** by dehydration with bases [Ba(OH)<sub>2</sub>, MeMgBr, EtMgBr, MeLi, LDA]. Product **272** was isolated either directly or as adduct **274** with tetracyanoethylene (TCNE).<sup>194</sup>

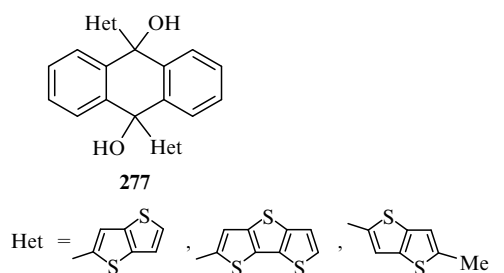


B is a base.

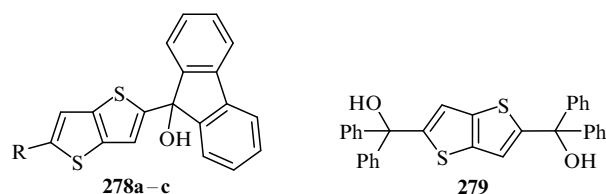
The reactions of thienothiophene derivatives in the absence of a solvent were also described in the literature. For example, the solid-state thermally induced rearrangement of 9,10-dihydroxy-9,10-bis(thieno[3,2-*b*]thiophen-2-yl)-9,10-dihydroanthracene (**275**) occurs at 240 °C and gives 10,10-bis(thieno[3,2-*b*]thiophen-2-yl)anthrone (**276**).<sup>195</sup>



(Thienothienyl)anthracenes **277** were subjected to analogous transformations to prepare the corresponding anthrones.

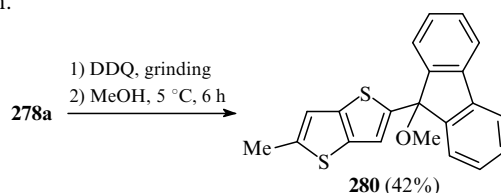


(Hydroxyfluorenyl)thieno[3,2-*b*]thiophenes **278a–c** and their diphenyl analogue **279** were subjected to methanolysis.<sup>196</sup> Substitution of the hydroxy function with the methoxy group requires specific reactions conditions for each substrate.

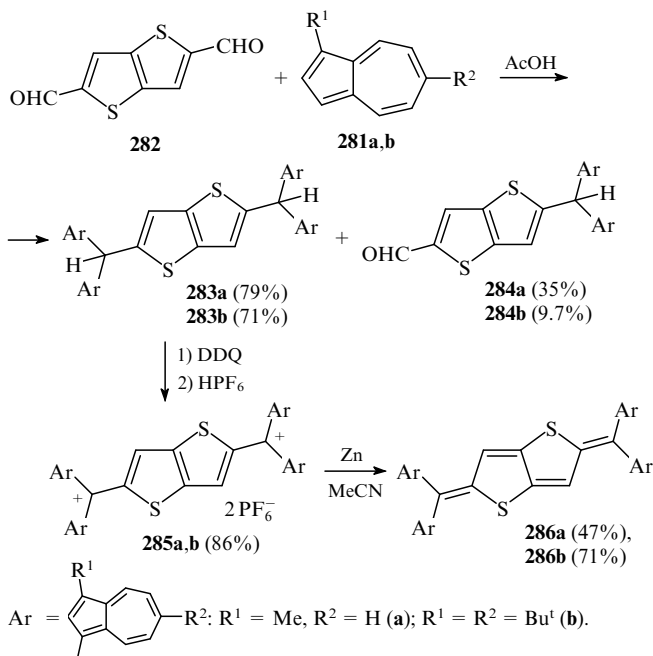


R = Me (**a**), Cl (**b**), 9-hydroxyfluoren-9-yl (**c**).

For example, 2-(9-methoxyfluoren-9-yl)thieno[3,2-*b*]thiophene (**280**) was prepared by careful grinding an equimolar mixture of 5-(9-hydroxyfluoren-9-yl)-2-methylthieno[3,2-*b*]thiophene (**278a**) with DDQ followed by storage of the resulting dark-green powder in methanol at a temperature below 5 °C for 6 h.



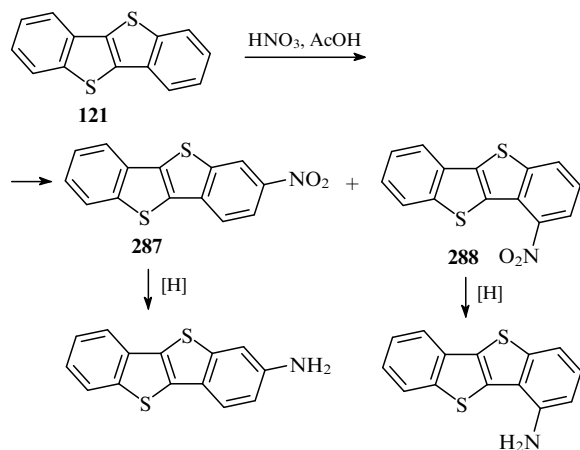
The reaction of 1-methyl- or 1,6-di-*tert*-butylazulenes (**281a,b**) with 2,5-diformylthieno[3,2-*b*]thiophene **282** in acetic acid afforded diazulenyldimethylthieno[3,2-*b*]thiophenes **283a,b** along with products **284a,b** resulting from the reaction at one aldehyde group.<sup>197</sup> The reaction of thienothiophenes **283a,b** with two equivalents of DDQ produced dicationic species, which were isolated as stable hexafluorophosphates **285a,b** by treating the reaction mixture with a 60% HPF<sub>6</sub> aqueous solution. Treatment of salts **285a,b** with zinc powder in acetonitrile afforded 2,5-bis[di(azulenyldimethylene)-2,5-dihydrothieno[3,2-*b*]thiophenes (**286a,b**).



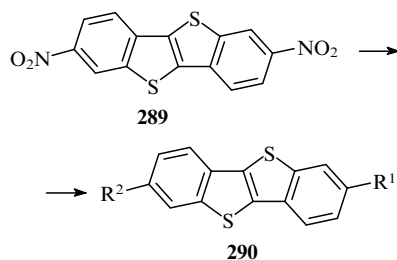
Electrophilic substitution reactions were studied for thienothiophenes annelated with one or two benzene rings. For example, benzo[*b*]thieno[2,3-*b*] and -[3,2-*b*]thiophenes and their 3-methyl derivatives undergo bromination, Vilsmeier–Haack formylation and Friedel–Crafts acylation at position 2. These results agree well with the calculated electron densities.<sup>32, 198–200</sup> If these compounds contain the methyl group at position 2, bromination occurs at position 3, whereas the direction of acylation of 2-methylbenzo[*b*]thieno[2,3-*b*]thiophene depends on the reaction conditions and the reaction produces either a 3- or 6-acetyl

derivative. Bromination of 3-formyl-substituted benzo[*b*]thienothiophenes affords 2-bromo derivatives, whereas the reactions with 2-formyl-substituted derivatives are accompanied by a loss of the formyl group to give, respectively, 2,3-dibromobenzo[*b*]thieno[2,3-*b*]- or 2,6-dibromobenzo[*b*]thieno[3,2-*b*]thiophenes. Nitration of 2-formyl derivatives also leads to the replacement of the formyl group and the formation of 2-nitro derivatives as the major product.<sup>200</sup>

Nitration of benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene **121** containing two fused benzene rings was studied. The reaction of **121** with concentrated nitric acid ( $d = 1.51 \text{ g cm}^{-3}$ ) in acetic acid produced 2- (**287**) and 4-nitro derivatives (**288**), which were reduced to the corresponding amines.<sup>201</sup>



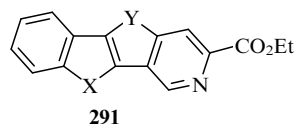
Earlier,<sup>202</sup> it has been reported that nitration of benzothienobenzo[*b*]thiophene **121** with a mixture of nitric and acetic acids led to substitution at the carbon atoms in both rings to give 2,7-dinitrodibenzo[*b*]thieno[3,2-*b*]thiophene **289** in low yield. The latter was transformed according to conventional synthetic procedures into derivatives **290** containing various electron-donating and electron-withdrawing substituents.<sup>116</sup>



$R^1 = R^2 = \text{NH}_2$ ;  $R^1 = \text{NH}_2$ ,  $R^2 = \text{NO}_2$ ;  $R^1 = R^2 = \text{Cl}$ ;  $R^1 = R^2 = \text{Br}$ ;  
 $R^1 = \text{OH}$ ,  $R^2 = \text{Cl}$ ;  $R^1 = \text{NH}_2$ ,  $R^2 = \text{Cl}$ ;  $R^1 = \text{NO}_2$ ,  $R^2 = \text{OH}$ ;  
 $R^1 = \text{OMe}$ ,  $R^2 = \text{NO}_2$ ,  $R^1 = \text{NH}_2$ ,  $R^2 = \text{OMe}$ ;  $R^1 = R^2 = \text{NHAc}$ ;  
 $R^1 = R^2 = \text{NHCOCF}_3$ ;  $R^1 = \text{NO}_2$ ,  $R^2 = \text{NHCOCF}_3$ ;  $R^1 = \text{NHAc}$ ,  
 $R^2 = \text{Cl}$ ;  $R^1 = \text{NHAc}$ ,  $R^2 = \text{OMe}$ .

Nitration of 2-benzoyl- and 4-acetylaminobenzo[*b*]thieno[3,2-*b*]thiophenes with nitric acid occurs predominantly at the *ortho*-position with respect to the substituent to give the nitro derivative, whose deacylation and reduction affords 1,2- and 3,4-diaminobenzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophenes in high yields.<sup>203</sup>

Thermal decomposition of azidoacrylates, which were prepared by condensation of ethyl azidoacetate with heteroaromatic aldehydes, produced a series of the previously unknown fused heteroaromatic analogues of isoellipticine **291**.<sup>204</sup>



X, Y = S, Se.

The above-considered transformation convincingly demonstrate a high synthetic potential of thienothiophene derivatives.

## IV. Molecular structures and physical properties

Theoretical aspects of the structures, reactivities and physico-chemical properties of isomeric thienothiophenes have attracted attention of a wide range of researchers. Earlier investigations of these problems have been covered in reviews<sup>2,205</sup> and other publications (see, for example, Refs 206–212).

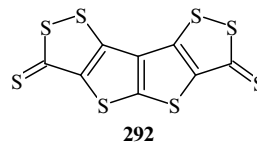
### 1. Structures

In the last 25 years, X-ray diffraction analysis has been particularly widely used (along with other methods) to determine the structures of thienothiophenes. For example, the crystal structures of the following compounds were established by X-ray diffraction: 3,4-dibromothieno[2,3-*b*]thiophene,<sup>79</sup> 2,2,5,5-tetramethyl-2,3,5,6-tetrahydrothieno[3,2-*b*]thiophene-2,6-dione (**127**) [the main chromophoric system of the thioindigo-like dye having the *trans*-(*S*)-*trans*-(*S*)-*trans*-configuration],<sup>111,213</sup> (5-benzoyloxy-methyl)thieno[2,3-*b*]thiophene-5-sulfamide 6,6-dioxide,<sup>147</sup> nitronyl nitroxide and imino nitroxide free radicals bound to isomeric thieno[2,3-*b*]- and -[3,2-*b*]thiophenes,<sup>214</sup> 2,3,5,6-bis(ethylene-dithio)thieno[3,2-*b*]thiophene,<sup>69</sup> 1,2-bis[2-methyl-5-(2-benzothiazolyl)-6-trifluoromethylthieno[3,2-*b*]thiophen-3-yl]hexafluorocyclopentane,<sup>17</sup> 2,5-bis(dicyanomethylene)-2,5-dihydrothieno[3,2-*b*]thiophene<sup>159</sup> and the 3,6-dimethylselenopheno[3,2-*b*]thiophene dimer.<sup>143</sup>

Recently, it has been demonstrated that 2,5-bis(9-hydroxyfluoren-9-yl)thieno[2,3-*b*]- and -[3,2-*b*]thiophenes form crystalline inclusion guest–host complexes with EtOH, Pr<sup>n</sup>OH, Pr<sup>i</sup>OH, DMSO, Me<sub>2</sub>SO and benzene, and the structures of these clathrates were established by X-ray diffraction.<sup>215–223</sup>

The structures of 1,3,4,6-tetraphenylthieno[3,4-*c*]thiophene (**272**),<sup>224</sup> 1,4-bis(*tert*-butylthio)-3,6-diphenylthieno[3,4-*c*]thiophene, 4-(*tert*-butylthio)-3,6-diphenylthieno[3,4-*c*]thiophene-1(3*H*)-thione and 4-(*tert*-butylthio)-3,6-diphenylthieno[3,4-*c*]thiophen-1(3*H*)-one<sup>61</sup> were also characterised by X-ray diffraction.

Study of the crystal structure of sulfur-containing heterocyclic compound **292**, which was prepared by the reaction of diethyl dihydroxythieno[2,3-*b*]thiophene-2,5-dicarboxylate with Lawesson's reagent in the presence of sulfur, revealed the presence of a three-dimensional S–S interaction.<sup>225</sup>



The  $\pi$ -electron systems of thiophene, isomeric thienothiophenes and other fused sulfur-containing compounds (58 compounds, including those annelated with the benzene and naphthalene rings) were considered from the viewpoint of the degree of contribution of the sulfur atom to the ability of the probable resonance structures to include the hydrocarbon portion of the molecule.<sup>226</sup>

Bicyclic conjugated systems consisting only of five-membered heterocycles were studied theoretically. The authors used the topological resonance energy (TRE) as a new aromaticity index,<sup>227</sup> which correctly predicts the aromatic behaviour of all groups of isomeric heteroaromatic systems, including thienothio-

phenes. These isomers are referred to as positional isomers, because they formally differ only in the position of  $\sigma$ -bivalent heteroatoms and can be considered as a special group in accordance with the mode of their annelation. The calculated TREs agree well with the experimental values.<sup>227, 228</sup>

To study the effect of the nature of the heteroatom on the aromatic system, the photoelectron spectra of thieno[2,3-*b*]thiophene (**142**), thieno[3,2-*b*]thiophene (**145**),<sup>229</sup> thieno[2,3-*b*]selenophene (**143**), selenopheno[3,2-*b*]selenophene (**147**), thieno[2,3-*b*]pyrrole, selenopheno[2,3-*b*]pyrrole, pyrrolo[2,3-*b*]pyrrole and selenopheno[3,2-*b*]pyrrole<sup>230</sup> were measured and analysed. The replacement of the sulfur atom with selenium causes slight changes in all characteristics in accordance with the simple excitation theory. The replacement of the sulfur or selenium atom with the NH group influences the  $\pi$ -electron system. In this case, an increase in the resonance integral of the bonds including the heteroatom is compensated by a strong destabilising inductive effect due to N–H bond polarity. The efficient electronegativity of the NH group was found to differ only slightly from that of the sulfur atom.<sup>230</sup>

Thieno[3,2-*b*]thiophene (**145**), thieno[3,2-*b*]thieno[2',3'-*d*]thiophene (**108a**), thieno[2'',3'':4',5']thieno[2',3'-*d*]thieno[3,2-*b*]thiophene (**6**) and dithieno[2,3-*d*:2',3'-*d'*]thieno[3,2-*b*:4,5-*b'*]thiophene (**7**) were studied by gas-phase and solid-state photoelectron spectroscopy.<sup>145</sup> For tetrathienocene **6**, the ionisation energy for the gas phase (7.22 eV) differs substantially from that for the solid state (4.86 eV), resulting in an increase in the polarisation energy by 2.36 eV, which is larger than the calculated value (1.83 eV). This phenomenon was interpreted in terms of intramolecular orbital interactions for the solid state of polythienothiophene **6**. This interaction is not observed for lower homologues (thienothiophenes **145** and **108a**).

Recently, among isomeric thienothiophenes, thieno[3,4-*c*]thiophenes have attracted most attention from both the theoretical and spectroscopic points of view as  $10\pi$ -electron heterocycles having a non-classical structure.<sup>61, 224, 231–239</sup> Examination of the photoelectron and UV-Vis absorption spectra of 1,3,4,6-tetraphenylthieno[3,4-*c*]thiophene (**240**)<sup>236</sup> confirmed the singlet aromatic ground state of the molecule predicted by quantum-chemical calculations<sup>224</sup> (by the MINDO/3 method without allowance for d-orbital interactions).

In the  $\pi$ -electron approximation of the MO LCAO SCF method, a procedure was developed on the basis of the Longuet–Higgins model to account for the d orbitals of the sulfur atoms. The chemical shifts in the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, the lowest singlet–singlet and singlet–triplet transitions and the dipole moments of a series of sulfur-containing heterocyclic systems, including thieno[2,3-*b*]thiophene (**142**), thieno[3,2-*b*]thiophene (**145**) and thieno[3,4-*c*]thiophene, were calculated.<sup>240</sup> These results are in agreement with experimental data.

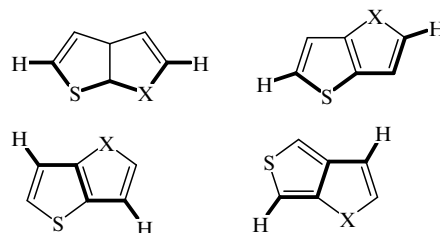
The multiplicity of the ground state, p-stability ('aromaticity'), the order and energy of the electron-excited and ionic states of thieno[3,4-*c*]thiophene were studied.<sup>235</sup> In particular, this compound was demonstrated to have 'aromaticity' analogous to that of thiophene, but it is much less stable due to a specific structure of its highest occupied molecular orbital.

## 2. NMR spectra

NMR spectroscopy along with and combined with other physicochemical methods is rather widely used to study the chemical structures of thienothiophenes and their heteroanalogs. In the study,<sup>241</sup> CNDO/2 calculations were carried out for selenophene and [2,3-*b*]-, [3,2-*b*]- and [3,4-*b*]-annelated thienoselenophenes **143**, **144**, **146** and **149–151**. Correlations between the calculated electron density and experimental  $^{77}\text{Se}$  NMR chemical shifts in the spectra of these compounds were revealed. The chemical shifts were demonstrated to depend substantially on both the total and  $\pi$ -electron density on the selenium atom.

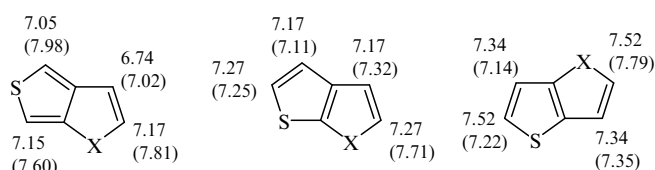
The  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{77}\text{Se}$  NMR spectra of selenopheno[2,3-*c*]thiophene (**149**),<sup>242</sup> selenopheno[2,3-*b*]selenophene (**144**),<sup>243</sup> selenopheno[3,2-*b*]selenophene (**146**),<sup>244</sup> selenopheno[3,4-*b*]selenophene (**151**)<sup>245</sup> and a series of 2-substituted selenopheno[2,3-*b*]selenophenes<sup>246</sup> and -[3,2-*b*]selenophenes<sup>247</sup> were measured and analysed.

The  $^1\text{H}$  NMR spectra of isomeric thienothiophenes, selenophenothiophenes and their derivatives<sup>130, 248, 249</sup> revealed long-range spin–spin coupling through five and six bonds located in a 'direct zigzag' system. This phenomenon is analogous to that observed in a series of other bicyclic systems including sulfur, nitrogen and oxygen atoms [see, for example, Ref. 250].



X = S, Se.

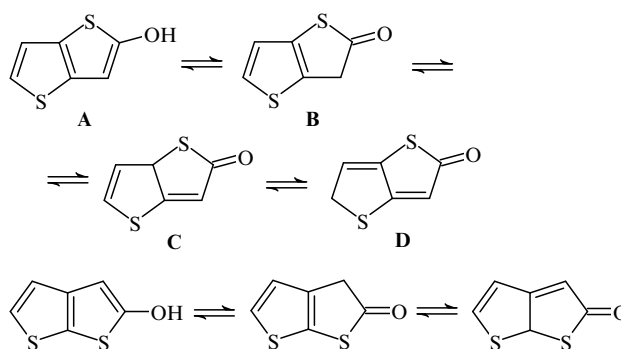
It was also concluded that the signals for the  $\alpha$ - and  $\beta$ -protons of isomeric thieno- and selenophenothiophenes are characteristic of different modes of fusion of heterocyclic rings.<sup>205</sup> The chemical shifts of annelated thiophenes with X = S are given below (the values for X = Se are given in parentheses).

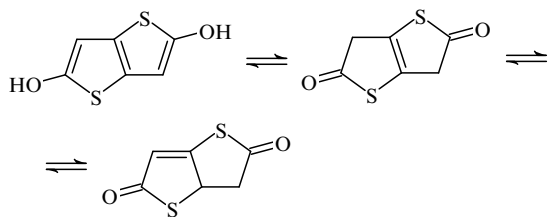


X = S, Se.

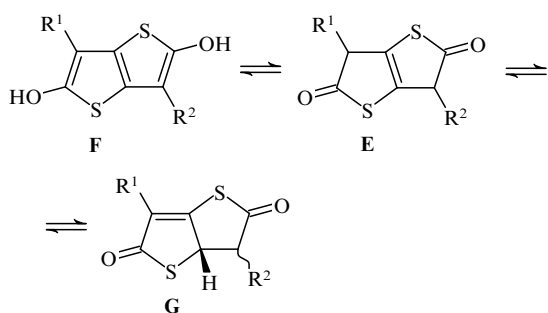
The spectra of isomeric selenophenothiophenes are characterised also by spin–spin coupling between the  $^{77}\text{Se}$  atom (spin 1/2) and protons of the selenophene fragment<sup>249</sup> analogous to that observed in selenides of the thiophene series.<sup>251</sup>

Tautomerism of 2-hydroxythieno[2,3-*b*]- and -[3,2-*b*]thiophenes, 2,5-dihydroxythieno[3,2-*b*]thiophene and their alkyl- and aryl-substituted derivatives was also examined by NMR spectroscopy.<sup>252, 253</sup> These compounds were demonstrated to occur predominantly as thiolactones rather than in the hydroxy form. For the thieno[2,3-*b*]thiophene system, this equilibrium is completely shifted to thieno[2,3-*b*]thiophen-2(3*H*)-ones, whereas the forms **B** and **D** were found for [3,2-*b*]-fused systems. The effect of the nature and positions of the substituents on the tautomeric equilibrium was discussed.





Alkyl- and aryl-substituted 2,5-dihydroxythieno[3,2-*b*]thiophenes appeared to occur exclusively as dithiolactones. In no case was the hydroxy form of these compounds was detected.<sup>253</sup> The results of NMR spectroscopy demonstrated that 2,3-dihydrothieno[3,2-*b*]thiophene-2,5-dione (**E**) is a favourable structure. The tautomer **F** was detected only for the unsubstituted compound. However, this tautomer is readily transformed into the tautomer **E**. For 6-substituted compounds, two stereoisomers of the form **G** are observed; these stereoisomers have opposite configurations at the C(6) atom.

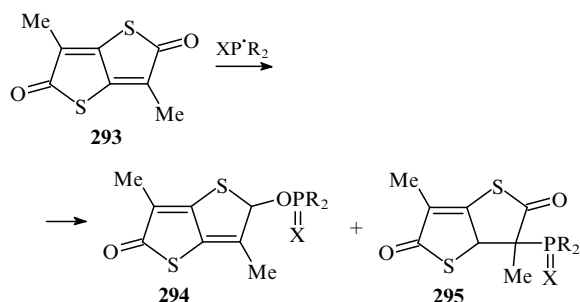


$R^1 = \text{H, Me, Bu}^t, \text{Ph}$ ;  $R^2 = \text{H, Me, Ph}$ .

The effects of the nature and positions of the substituents on stability of tautomeric forms were discussed.

### 3. ESR spectra

The reactions of the diphenylphosphoryl ( $\text{OP}^*\text{Ph}_2$ ) and diethoxyphosphoryl [ $\text{OP}^*(\text{OEt})_2$ ] radicals with 3,6-dimethylthieno[3,2-*b*]thiophene-2,5-dione (**293**) were studied by ESR spectroscopy.<sup>254</sup> Both reactions produce the oxygen-containing (**294**) and cyclic (**295**) adducts. The hyperfine coupling constants of the former adducts are close to those of analogous oxygen-containing adducts of Group IVB organometallic radicals.<sup>255</sup> The attack can occur on the carbon atoms at positions 3, 6 or 4, 5 of the ring. In the former case, the structure of the adduct is similar to that of the substituted allylic system, and the ESR spectra would be expected to show methyl splitting with the constant of  $\sim 10$  Hz. The reactions of dione **293** with the  $\text{SP}^*\text{Et}_2$  and  $\text{P}^*\text{Ph}_2$  radicals afforded predominantly derivatives **294**, although the ESR signals of cyclic adduct **295**, which was generated simultaneously with **294**, were recorded.



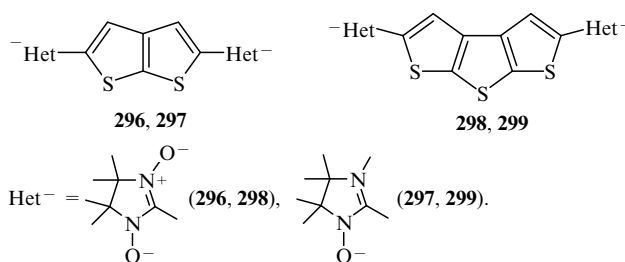
$\text{X} = \text{O}$ :  $\text{R} = \text{Ph, OEt}$ ;  $\text{X} = \text{S}$ ,  $\text{R} = \text{Et}$ ;  $\text{X}$  is absent,  $\text{R} = \text{Ph}$ .

The hyperfine coupling constants for paramagnetic adducts of the  $\text{M}^*\text{R}_3$  ( $\text{M} = \text{Si, Ge, Sn}$ ) radicals with dithienyl and bis(thieno[2,3-*b*]- and -[3,2-*b*]thienyl) ketones were measured and compared with those of the diarylhydroxymethyl radicals. These

results were confirmed by INDO calculations and indicate that the  $2p_z$  orbital is involved in the  $\text{O}-\text{M}$  bond in dithienyl derivatives.<sup>256</sup>

Complexation of dibenzo-18-crown-6 ether with 3,6-dimethylthieno[3,2-*b*]thiophene-2,5-dione **293**,<sup>257</sup> homolytic aromatic silylation of 2-cyanothieno[2,3-*b*]- and -[3,2-*b*]thiophenes,<sup>258</sup> addition of silyl radicals to 3,6-dimethylthieno[3,2-*b*]thiophene-2,5-dione and 5-benzylidene-3,6-dimethylthieno[3,2-*b*]thiophene-2-one<sup>259</sup> and the conformational behaviour of the dithieno[3,2-*b*:2',3'-*d*]thiophene-2,6-dicarbaldehyde radical anions<sup>260</sup> were studied by ESR spectroscopy.

Diradical species **296–299**, in which two nitronyl nitroxide ( $\text{ONC}=\text{NO}$ ) or imino nitroxide ( $\text{NCNO}$ ) radical centres are bound to the thieno[2,3-*b*]thiophene and thieno[2,3-*b*]thieno[3',2'-*d*]thiophene chromophores, were investigated. Their intramolecular exchange coupling in frozen solutions and the magnetic sensitivity at low temperatures were examined by ESR spectroscopy.<sup>261, 262</sup>



The ESR spectra of mononitronyl nitroxide and imino nitroxide free radicals bound to isomeric thieno[3,2-*b*]thiophenes (**145**) and -[2,3-*b*]thiophenes (**142**) were measured in toluene at room temperature.<sup>212</sup>

### 4. UV spectra

The nature and properties of the ground and first low-lying excited states of the thieno[3,2-*b*]thiophene (**145**) molecule were investigated in a series of spectroscopic studies.<sup>263–268</sup>

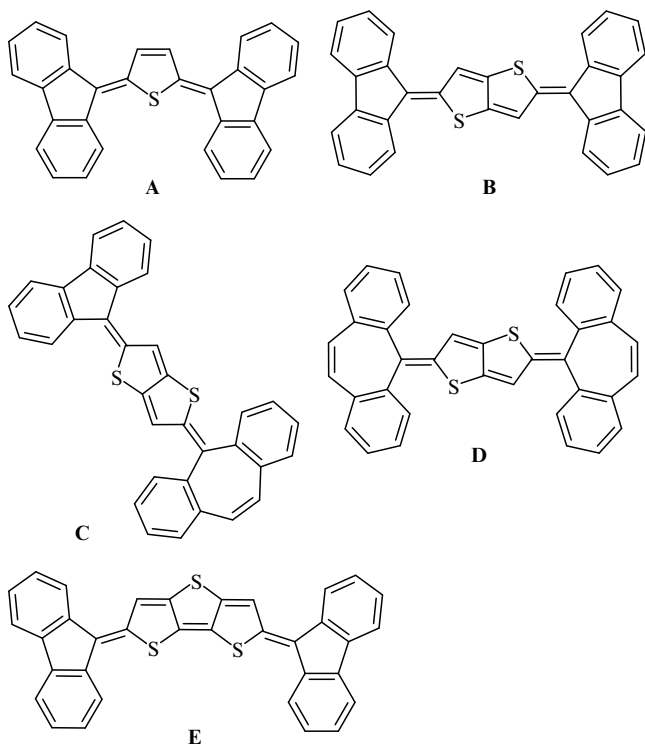
The first UV spectrum of thienothiophene **145** in the gas phase was recorded in 1956.<sup>263</sup> However, some details of the spectrum have remained uninterpreted because of the complicated spectral pattern. Only 20 years later, complete spectroscopic study, including IR and UV-Vis spectroscopy, of this compound was carried out both in the gas phase and in the crystalline state.<sup>269</sup> Two systems of intense absorption bands at  $36\,000\text{--}40\,000\text{ cm}^{-1}$  were assigned to two electron transitions in the excited state, whereas a very weak band observed in the spectrum of the crystal at  $34\,394\text{ cm}^{-1}$  was assigned to a singlet–triplet transition caused by spin–orbit coupling. Calculations by the LCAO method with the STO/3G basis set<sup>270</sup> confirmed the assignment of the electron transitions.

The possibility of using the liquid-crystal linear dichroism (LCLD) technique for the assignment of electron transitions was exemplified by two models of chromophores with high (phenylthiol) and low (thienothiophene **145**) symmetry.<sup>271</sup> The LCLD spectrum of the thienothiophene chromophore revealed a new band, which has not been observed earlier, and confirmed the theoretical results.<sup>270</sup>

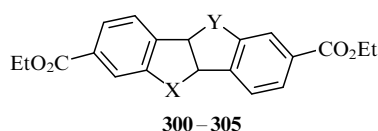
The thieno[3,2-*b*]thiophene (**145**), selenopheno[3,2-*b*]thiophene (**146**) and selenopheno[3,2-*b*]selenophene (**151**) charge-transfer complexes based on tetracyanoethylene (TCNE) were studied by UV and IR spectroscopy. The absorption spectra recorded in  $\text{CCl}_4$  and  $\text{CH}_2\text{Cl}_2$  show numerous charge-transfer bands.<sup>272</sup> A comparison with photoelectron spectra of other donors demonstrated that these bands appear due to transitions from two different occupied orbitals of the donor to unoccupied orbitals of the acceptor. The calculated ionisation potentials of the donors are consistent with the photoelectron spectroscopic data.

The quinoid compounds **A**, **B** and **E** have similar UV spectra, although the absorption maximum is shifted to longer wave-

lengths by approximately 50 nm with increasing number of thiophene rings.<sup>182</sup> The observed absorption maxima agree with the values calculated by the Pariser–Parr–Pople (PPP) method with allowance for restricted configuration interactions. For the **B–C–D** series, the long-wavelength band is shifted to higher frequencies in going from the first to the last compound, in spite of an increase in  $\pi$ -conjugation in this series of compounds. This may be a consequence of steric interactions between the phenyl fragment and the quinoid thienothiophene system, resulting in a deviation of the seven-membered ring from the plane. The discrepancy between the observed and calculated electron transitions for the long-wavelength band in the compounds **C** and **D** also confirms a non-planar structure of the total  $\pi$ -system of these molecules.



The UV spectra of 3,6-dimethylthieno[3,2-*b*]thiophene, 3,6-dimethylselenopheno[3,2-*b*]selenophene, their dimers, trimers and tetramers,<sup>143</sup> 2,2,5,5-tetramethylthieno[3,2-*b*]thiophene-3,6-dione,<sup>111,211</sup> and derivatives of benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene **121**<sup>115</sup> and compounds **300–305**<sup>119</sup> were measured and analysed.



X = Y = NMe (**300**); X = Y = S (**301**); X = Y = Se (**302**); X = NMe, Y = S (**303**); X = NMe, Y = Se (**304**); X = S, Y = Se (**305**).

The strongest absorption maximum in the UV-Vis spectra of compounds **300–305** is observed between 331 nm (for **301**) and 354 nm (for **300**); the longest-wavelength absorption is most intense, and the maximum is observed between 367 nm (for **301**) and 426 nm (for **300**). All compounds, except for **302**, show fluorescence: compound **300** shows strong fluorescence, whereas compounds **301** and **305** exhibit relatively weak fluorescence due, apparently, to the effect of the heavy atom.

The UV spectra of a homologous thienocene series show a shift of the long-wavelength band to the red region characterised by a good linear correlation with the number of the thiophene rings. A comparison of the UV spectra of heterohelicenes **175a,b**

and **176a,b**<sup>273–275</sup> with the spectra of benzohelicenes<sup>274,275</sup> demonstrated that the longest-wavelength band ( $\alpha$  band) is shifted to higher frequencies (by approximately 30 nm), whereas the positions of the second and third bands ( $\rho$  and  $\beta$  bands, respectively) are only slightly different.

The twist angles of the phenyl ring relative to the plane of the bicyclic fragment in 2-phenylthieno(or selenopheno)[2,3-*b*]thiophenes, -furans and analogous *N*-methylpyrroles were determined from absorption spectra and data on molecular refraction.<sup>276</sup>

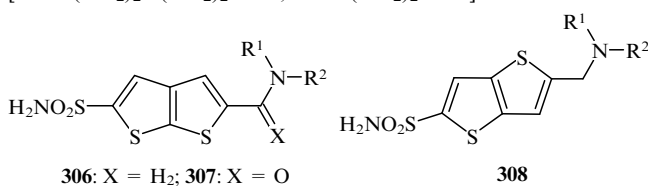
## V. Fields of application

Earlier, the practical use of thienothiophenes has been limited primarily to the preparation of polymethine dyes, transition metal complexes,<sup>2</sup> as well as the synthesis of *N*-(aminoalkyl)thieno[3,2-*b*]thiophene-2-carboxamide derivatives, which were proposed as antidepressants and antitumor agents,<sup>277</sup> and the synthesis of benzo[*b*]thienobenzo[*b*]thiophenes, which are used as pesticides.<sup>200,278</sup> In recent years, the field of applications of these compound has been substantially extended due to the synthesis of numerous derivatives of this class of compounds. The introduction of pharmacophoric substituents into thienothiophene molecules and the use of these compounds in the synthesis of annelated systems gave rise to new types of biological activities. The discovery of unusual optical, electrical and complexation properties made it possible to prepare new materials for modern technology.

### 1. Biological activity

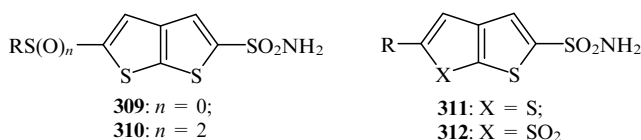
Since many thiophene-containing compounds, including annelated compounds, exhibit biological activities,<sup>279–282</sup> the structure–activity relationships for this series of heterocycles have attracted considerable attention. Studies are aimed both at using thienothiophenes as building blocks and searching for new types of biological activity of fused systems containing various central fragments.<sup>38,81</sup>

For example, 5-substituted thieno[2,3-*b*]thiophene-2-sulfonamides **306–312** were synthesised and proposed as glaucoma medicines.<sup>36,147,283–289</sup> In the cited studies, the substituents at position 5 were varied to increase solubility in water and achieve  $pK_a$  minimising binding of the iris pigment. The best results were obtained in tests of compound **306** [ $R^1 = (CH_2)_2O(CH_2)_2OMe$ ,  $R^2 = (CH_2)_2OMe$ ].<sup>36</sup>



$R^1 =$  Me,  $(CH_2)_2OH$ ,  $(CH_2)_2CH(OH)CH_2OH$ ,  $(CH_2)_2NMe_2$ ,  $(CH_2)_2S(O)Me$ ,  $(CH_2)_2O(CH_2)_2OMe$ ,  $(CH_2)_2N(CH_2CH_2)_2O$ ,  $(CH_2)_2N(CH_2CH_2)_2S$ ;

$R^2 =$  H, Me  $(CH_2)_2OH$ ,  $(CH_2)_2OMe$ .

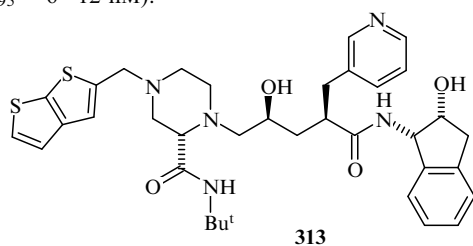


R =  $n$ -C<sub>5</sub>H<sub>11</sub>,  $(CH_2)_3OH$ ,  $(CH_2)_3N(CH_2CH_2)_2O$ .

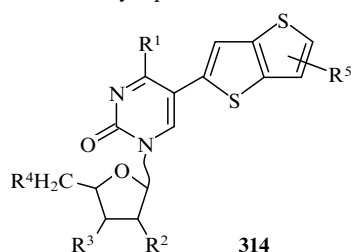
The results of pharmacological studies of the potential non-peptide fibrinogen receptor antagonist, *viz.*, thieno[2,3-*b*]thiophene-based compound **172**, were reported.<sup>148,290</sup>

A series of thieno[2,3-*b*]thiophene-based HIV protease inhibitors were synthesised and tested.<sup>291,292</sup> At low concentrations, these inhibitors are efficient against HIV, and some of them provide a satisfactory plasma level in animals upon peroral administration. Among compounds of this series, compound **313**

proved to be the most promising ( $IC_{50} = 0.12$  nM and  $IC_{95} = 6-12$  nM).<sup>291</sup>



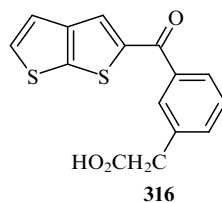
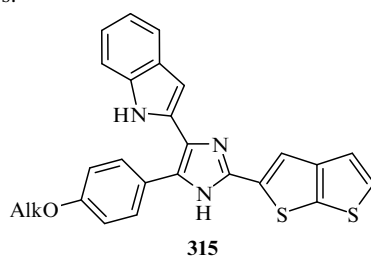
Pyrimidine nucleosides **314** containing the thieno[3,2-*b*]thiophene substituent hold promise against HIV and hepatitis B and were covered by a patent.<sup>293</sup>



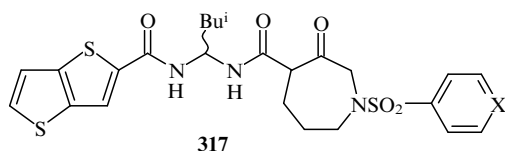
$R^1 = OH, NH_2$ ;  $R^2 = H, F, OH, OMe$ ;  $R^3 = H, F, OH$ ;  
 $R^4 = OH, (CH_2)_nP(O)(OMe)_2$ ;  $R^5 = H, C_1-C_{10}-Alk$ ;  $n = 0, 1$ .

2-(Thienothiethylglycyl)cephalosporin<sup>294, 295</sup> and 2-(thienothiethylphenyl)carbapenam derivatives<sup>296</sup> possess antibacterial properties.

Patents covered procedures for the preparation of 4(5)-(3-indolyl)imidazoles **315**, which are useful for treatment of central nervous system function disorders, cerebrovascular dementia, senile dementia and memory or learning disorder,<sup>297</sup> the synthesis of thieno[2,3-*b*]thienyl-containing carboxylic acids **316** and their derivatives used as analgetics, inflammation and thrombosis inhibitors<sup>298, 299</sup> and the synthesis of thieno[3,2-*b*]thiophene-2-carboxamides used as cyclooxygenase and lipoxygenase inhibitors.<sup>300</sup>

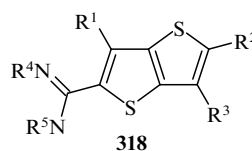


Thieno[3,2-*b*]thiophene-2-carboxamides **317**, which were prepared as mixtures of diastereomers and separated by high-performance liquid chromatography, were covered by patents as cysteine protease inhibitors.<sup>301-305</sup>



$X = N, N^+ - O^-$ .

Amidines of the thieno[3,2-*b*]thiophene series **318** were covered by patents as urokinase inhibitors.<sup>306</sup>



$R^1 = H, NH_2, Hal$ ;  $R^2, R^3 = H, Hal, HO, NH_2, NO_2$ ;  
 $R^4, R^5 = H, C_1-C_6-Alk$ .

Thieno[2,3-*b*] and -[3,2-*b*]thiophene-2-carboxylic acids and their benzo[*b*]annelated analogues were synthesised and their lipid-reducing properties were investigated.<sup>307</sup> A number of hydrazides and sulfonamides of the thienothiophene series were covered by patents as pesticides.<sup>308, 309</sup>

It was found that the smells given off by heated food include those of compounds formed by the reaction of thienothiophene-containing 4-hydroxy-5-methyl-3(2*H*)-furanones with cysteine or  $H_2S$ .<sup>310</sup> Thieno[3,2-*b*]thiophene derivatives were used in combinatorial synthesis to compile chemical libraries with the aim of examining the biological action of these compounds.<sup>311</sup>

## 2. Other areas of practical applications

Sulfur-containing heteroaromatic compounds, particularly, fused compounds having an extensive conjugated system can be used as building blocks for preparing organic conductors,<sup>312-315</sup> magnetic<sup>316</sup> and photosensitive receptors,<sup>317</sup> materials for optoelectronics,<sup>318, 319</sup> *etc.* These compounds most often belong to charge-transfer complexes.<sup>320-322</sup> A rational combination of conducting polymers<sup>323</sup> and magnetic materials<sup>324, 325</sup> requires the presence of precursors containing functional groups, which can enhance  $\pi$ -conjugation in the system as a result of condensation.

### a. Complexation properties of isomeric thienothiophenes

Isomeric thienothiophenes and their derivatives are of considerable interest as electron donors or acceptors for the design of new types of charge-transfer complexes and as ligands coordinating metal ions. As mentioned above (see Section IV.4), charge-transfer complexes of some five-membered fused heteroaromatic systems with tetracyanoethylene were studied by UV and IR spectroscopy and their relative stabilities were discussed using the association constants and enthalpies of formation.<sup>272</sup>

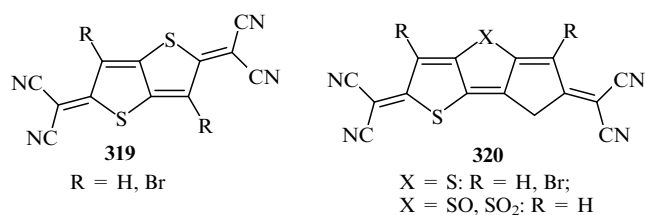
Thieno[2,3-*b*]thiophene and -[3,2-*b*]thiophene containing two 9-hydroxyfluoren-9-yl groups as substituents form charge-transfer complexes with 1,2,4,5-tetracyanobenzene (TCNB), which show fluorescence in the solid state.<sup>222, 326</sup> Benzo[*b*]thieno[3,2-*b*]thiophene forms charge-transfer complexes with various organic acceptors.<sup>327</sup>

In recent years, dithienothiophenes have attracted considerable attention because these compounds have three various types of  $\pi$ -conjugation, which play a decisive role in the donor ability of these compounds.<sup>7-9, 157, 215, 218, 328-333</sup> Two higher homologues of fused polythiophenes, *viz.*, thienocenes **6** and **7**, which are isoelectronic with chrysene and picene, respectively, but contain many fewer peripheral hydrogen atoms, were also used as precursors of organic conductors.<sup>7, 145, 315</sup>

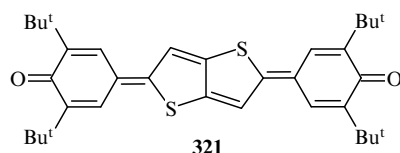
As mentioned above (see Section III.2.c, and Ref. 334), 2,3,6,7-tetrathiabenz[1,3-*cd*:4,6-*c'd'*]dipentalene (**225**) and its derivatives **226** form charge-transfer complexes with strong electron acceptors (TCNQ, TCNQF<sub>4</sub>, DDQ and HCBd), most of which have a low conductivity.

New fused thienothiophene, *viz.*, 2,3:5,6-bis(ethylenedithio)-thieno[3,2-*b*]thiophene (**112**), was used to prepare conducting organic salts.<sup>69</sup>

Examples of the use of 2,5-bis(dicyanomethylene)-2,5-dihydrothieno[3,2-*b*]thiophenes (**319**) and -2,6-dihydrothieno[3,2-*b*:2',3'-*d'*]thiophenes **320** as electron acceptors were reported, and the resulting charge-transfer complexes have a very high (up to metallic) conductivity.<sup>157</sup>



2,5-Bis(3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-2-ylidene)-2,5-dihydro-1,4-dithiapentalene (**321**) is also a promising electron acceptor for the formation of complexes.<sup>335</sup>



Dinuclear complexes of Group VIB (Cr, Mo, W)<sup>336, 337</sup> and Group VIII (Pt)<sup>338</sup> metal ions with 3,6-dimethylthieno[3,2-*b*]- and dithieno[3,2-*b*:2',3']thiophene as ligands were synthesised and studied.

#### b. Thienothiophenes as liquid and clathrate crystals

In the last 15 years, the liquid-crystalline properties of azomethines, azines, vinylenes and hexatrienes containing the thiophene or thieno[3,2-*b*]thiophene fragment were examined. Their thermal and optical properties were compared with those of analogous compounds of the benzene series.<sup>144, 339</sup> Taking into account particular characteristics, these compounds were proposed as materials for various purposes of modern technology.

Certain thieno[2,3-*b*]- and -[3,2-*b*]thiophene derivatives can be used in liquid-crystalline mixtures for electrooptical switches and evaluation devices.<sup>340–342</sup>

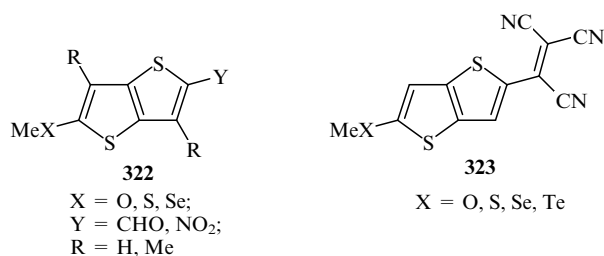
Benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene-2,7-dicarboxylate derivatives exhibit properties of smectic liquid crystals, whose stability depends on the length and nature of terminal chains. Samples of these liquid crystals show pronounced photoconducting behaviour.<sup>343</sup>

Liquid-crystal linear dichroism of the thieno[3,2-*b*]thiophene molecule has been examined.<sup>271</sup>

Recently,<sup>7, 145, 182, 215–223, 344–347</sup> a series of new compounds possessing host-type complexation properties, for example, 2,5-bis(9-hydroxyfluoren-9-yl)thieno[3,2-*b*]thiophene (**278c**), were introduced into crystals of complexes. Such compounds are referred to as 'clathrate crystals'.<sup>348</sup>

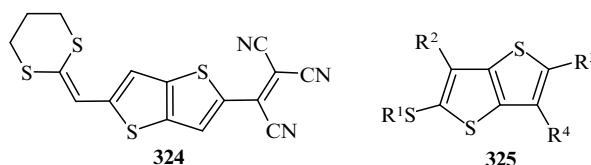
#### c. Materials for nonlinear optics

The recently discovered physical and chemical properties of thieno- and dithienothiophenes make it possible to use these fused heteroaromatic compounds for the design of new nonlinear optical materials. For example, the following two conjugated chromophoric charge-transfer systems were synthesised:<sup>136</sup> thieno[3,2-*b*]thiophenes **322**, which contain simultaneously electron-donating and electron-withdrawing substituents, and trinitriles **323**, which are heteroaromatic chromophores due to formation of charge-transfer complexes. The first hyperpolarisability ( $\beta$ ) of these compounds was determined by electric-field-induced second-harmonic (EFISH) generation; the replacement of the oxygen atom with sulfur leads to a substantial increase in  $\beta$ , which remains unchanged in going to other chalcogens (Se or Te).



2-(1,3-Dithian-2-ylidenemethyl)-5-(tricyanovinyl)thieno[3,2-*b*]thiophene (**324**) was used to prepare nonlinear optical polymers.<sup>349</sup>

Substituted thioethers of thieno[3,2-*b*]thiophenes **325** possess analogous optical properties. The procedure for their preparation was covered by a patent.<sup>350</sup>

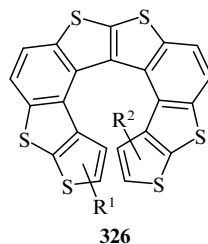


R<sup>1</sup> = C<sub>1</sub>–C<sub>22</sub>-Alk, CH = C(CN)<sub>2</sub>; R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> = H, Me;  
R<sup>2</sup> = H, R<sup>3</sup> = NO<sub>2</sub>, R<sup>4</sup> = CN, NO<sub>2</sub>.

Thienothiophene-containing chromophores bearing the TCNQ group as an acceptor are as thermally stable as analogous chromophores containing the strong tricyanovinyl substituent but they are characterised by a substantially larger second-order optical nonlinearity.<sup>351</sup>

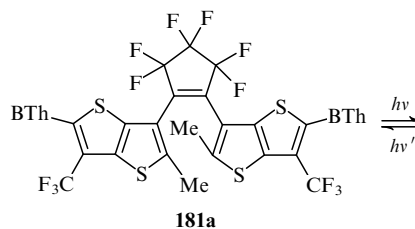
Many thieno[3,2-*b*]thiophene derivatives are important synthons for the design of new functional materials possessing chromophoric, conducting or nonlinear optical properties.<sup>134, 137, 182, 183, 350, 352, 353</sup>

Materials containing hexathiaoctahelicene derivatives **326**, which show high third-harmonic generation and are resistant to thermal and optical laser action, were constructed.<sup>354</sup>

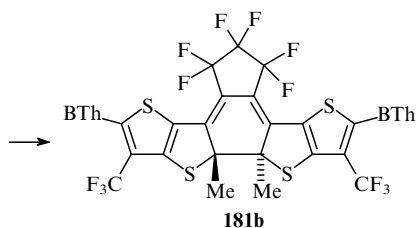


R<sup>1</sup>, R<sup>2</sup> = H, C<sub>1</sub>–C<sub>6</sub>-Alk, C<sub>1</sub>–C<sub>6</sub>-OAlk, OH, NO<sub>2</sub>, CN, CHO, Hal.

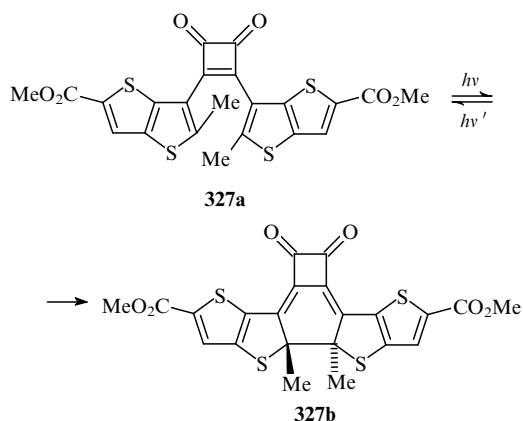
Photochromic compounds **181** were synthesised on the basis of benzothiazole derivatives of thieno[3,2-*b*]thiophene (see Section III.2). Their open (colourless, **181a**) and cyclic (coloured, **181b**) forms have high thermal stability, which makes it possible to perform repeated direct and reverse photoinduced transitions **181a**  $\rightleftharpoons$  **181b** with retention of the structure.<sup>14, 15</sup>



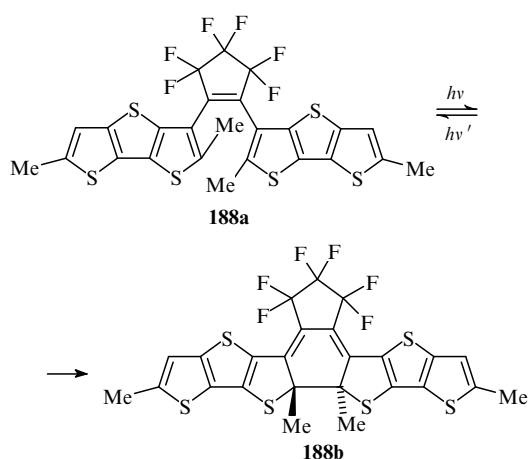




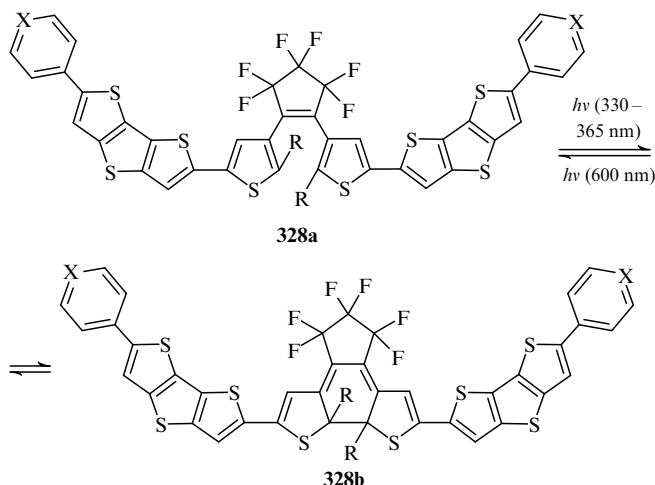
Analogous cyclobutenedione derivatives of thieno[3,2-*b*]thiophene **327** were synthesised in continuing studies of the use of thienothiophenes for the design of new photochromic materials.<sup>355, 356</sup> Under UV irradiation ( $\lambda = 313$  nm), compound **327** forms thermally stable (in the dark) cyclic form **327b**, which is again transformed into open form **327a** under irradiation with visible light ( $\lambda = 578$  nm).



The photochromic characteristics of 1,2-bis(2,6-dimethyldithieno[3,2-*b*:2',3'-*d*]thiophen-3-yl)hexafluorocyclopent-1-ene (**188**) were studied in an acetonitrile solution.<sup>18</sup> The photocyclisation **188a**  $\rightarrow$  **188b** was carried out under UV irradiation at  $\lambda = 313$  nm, and the reverse reaction was performed under irradiation at  $\lambda = 578$  nm. The long-wavelength absorption maxima for open form **188a** and cyclic form **188b** are 290 and 612 nm, respectively, which are comparable with the corresponding characteristics of benzothiazole derivatives.<sup>14, 15</sup>



Compounds **328a, b**, which have an extensive conjugation between two fused dithienothiophene fragments, were synthesised in the study.<sup>152</sup> High thermal stability, fatigue strength, sensitivity to the diode laser wavelength, nearly quantitatively reversible interconversion and, particularly, ability to perform nondestructive data reading give a real possibility to use these compounds as photoswitching elements in practice.



R = *n*-C<sub>6</sub>H<sub>13</sub>; X = N or MeN<sup>+</sup>(CF<sub>3</sub>SO<sub>3</sub>)<sup>-</sup>.

New quadrupolar photophores **189** and **190**, which contain fragments exhibiting very high two-photon absorption and simultaneously have high quantum yield, were synthesised.<sup>155</sup> Other dithienothiophene-containing nonlinear-optical chromophores were also prepared and have found use as optical relays of a new type.<sup>153</sup>

Benzo[*b*]annulated thieno[3,2-*b*]thiophenes were covered by patents as organic photoconductors<sup>357</sup> and fluorescent bleaching agents.<sup>358</sup>

#### d. Conjugated polymers

In recent years, the number of publications on photochemical and electrochemical polymerisation of thienothiophenes and their polyannulated analogues has been increased sharply. These compounds form conjugated polymers possessing unique properties. Since this field of thienothiophene chemistry is beyond the scope of the present review, only the references to such studies are given.<sup>7, 143, 167, 169, 347, 359–381</sup>

Studies of copolymerisation of a new class of highly efficient optical chromophores with thieno- and dithienothiophenes as linking units led to the design of conducting polymers.<sup>169, 353, 382–391</sup> Poly(thieno[3,4-*b*]thiophenes), which are stable conducting polymers, have attracted particular attention. These compounds were prepared by electrochemical polymerisation of thieno[3,4-*b*]thiophene and its derivatives. These polymers hold promise, in particular, as new materials for electrochromic devices.<sup>392–405</sup>

A new class of silicon-containing copolymers were synthesised by the Heck reaction of distyrylsilane monomers with thiophene and thieno[3,2-*b*]thiophene derivatives, their luminescence properties were studied, and these polymers were demonstrated to be promising electroluminescent materials.<sup>406, 407</sup>

The electropolymerisation kinetics of 3,6-dimethylthieno[3,2-*b*]thiophene was studied by cyclic voltammetry, chronoamperometry and chronopotentiometry on glassy carbon in the presence of a 0.1 M LiClO<sub>4</sub> solution.<sup>408</sup>

#### 3. Dyes

A few publications were devoted to the use of thienothiophene derivatives for the design of new dyeing materials. For example, diazotisation of aminothiophene derivatives afforded disperse azo dyes for colouring synthetic or polyester fibres.<sup>409–411</sup> Thieno[3,2-*b*]thienylidenebis(benzoquinones) were covered by a patent as dyes for optical recording devices.<sup>412</sup>

New electro- and photoactive multifunctional dyes were designed on the basis of dithienothiophenes.<sup>413–415</sup> The pigment properties of 2,2,5,5-tetramethyl-2,3,5,6-tetrahydrothieno[3,2-*b*]thiophene (**127**) were compared with those of analogous compounds containing the thioindigoid fragment, and thienothiophene **127** was demonstrated to belong to indigoid dyes.<sup>113, 213</sup>

Compounds of the thieno[2,3-*b*]thiophene (**142**), thieno[3,2-*b*]thiophene (**145**), dithieno[3,2-*b*:2',3'-*d*]thiophene (**108a**) and thieno[2',3':4,5]thieno[2',3'-*d*]thieno[3,2-*b*]thiophene (**6**) series were also covered by a patent as components (in amounts of 0.01%–0.8%) for the preparation of nonaqueous electrolyte solutions.<sup>416</sup>

## VI. Conclusion

In the chemistry of heterocyclic compounds, the end of the 20th century was marked by a growing interest in fused systems, as evidenced, in particular, by a snowballing increase in the number of publications in this field of chemistry. Analysis of the data published in the literature in the last 25 years demonstrates that the theoretical, synthetic, physicochemical and, particularly, practical aspects of the chemistry of thienothiophenes and their analogues attract growing attention of researchers working in different fields.

The range of practical applications of isomeric thienothiophene derivatives and their O-, N-, S-, Se-, Te-containing and fused analogues is very wide, from real prospects for the design of new medicines (due to a wide spectrum of pharmacological activities) to the design of the previously unknown liquid and clathrate crystals, charge-transfer complexes (organic conductors, magnetic and photosensitive receptors), electroconducting polymers, new nonlinear optical materials necessary for informational technologies, dyes, *etc.*<sup>417</sup>

The further development of the chemistry of fused chalcogen-containing heterocycles will be, apparently, associated with the introduction of various pharmacophoric groups at different positions of the molecules with the aim of preparing new efficient medicines and also with the use of these heterocycles as building blocks for the design of new highly conjugated heterocyclic systems as promising technological materials of the 21st century.

I hope that the present review will be not only helpful to researchers dealing with the chemistry of heterocyclic compounds but also will attract attention of researchers working in other fields of science, such as pharmacology, technology, optoelectronics, *etc.*

I thank Professor M M Krayushkin, who has successfully combined the development of methods for the synthesis of the previously unknown thienothiophene derivatives and the use of these compounds for the design of new photochromic materials in his recent studies (see, for example, Ref. 417), for the idea to write this review and help in analysing published data.

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# Structures and properties of spatially distorted porphyrins

O A Golubchikov, S G Pukhovskaya, E M Kuvshinova

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**Abstract.** The published data on the structures and properties of porphyrins with distorted aromatic macrocycles are generalised and analysed. Data on the crystal structures, spectra and kinetics of formation and dissociation of their coordination derivatives are summarised. It is demonstrated that the distortion of the planar structure of the tetrapyrrole core is one of the most efficient means of controlling spectral, physicochemical and coordination properties of these compounds. The bibliography includes 95 references.

## I. Introduction

That the tetrapyrrole rings of porphyrins ( $H_2P$ ) are non-planar was demonstrated for the first time more than 30 years ago based on the data from X-ray diffraction analysis.<sup>1–4</sup> Generalisation of X-ray diffraction data has led Hoard<sup>5</sup> to conclude that the non-planarity of porphyrins and their metal derivatives (MP) is their common feature. Yet another important conclusion was that the size of the coordination centre of the porphyrin core is limited due to its cyclic structure. Radial distortion of the macrocycle is a minimum where the radius of the central cavity is  $\sim 200$  pm. Any change in the size of the coordination cavity brings about distortion of the planar structure of the porphyrin macrocycle. These pioneering studies have formed the basis of conformational description of porphyrins.

In 1971, Hambright<sup>6</sup> proposed a mechanism of coordination of porphyrins by metal cations; its key idea was high deformability of the porphyrin macrocycle. Presumably, the Hambright mechanism is inapplicable for non-aqueous solutions;<sup>7</sup> however, distortion of the porphyrin core is obviously one of the most efficient mechanisms of controlling physicochemical, coordination and catalytic properties of porphyrins.

Distortion of porphyrin molecules (here, we imply distortion of the planar structures of their tetrapyrrole cores) can be achieved in various ways, *e.g.*, by introducing a large number of peripheral

substituents or short spacers that form bridges between the *meso*- or  $\beta$ -positions or by protonation, *N*-alkylation or *N*-arylation of the coordination centre. Metalloporphyrins also contain distorted macrocycles; the role of complex-forming agents is played by bulky and some highly charged cations. The main emphasis in this review will be laid on the porphyrins distorted due to peripheral substitution.

In the 1990's, Smith *et al.*<sup>8</sup> synthesised and characterised a large series of porphyrins containing up to 12 peripheral substituents as well as *N*-alkyl derivatives and porphyrins containing bulky *meso*-substituents inducing deformation of the tetrapyrrole core. The methods for the synthesis of this type of compounds have been reviewed.<sup>9</sup>

Analysis of NMR spectra revealed that in the majority of cases the structural parameters of such porphyrins are not changed on going from the crystalline state to solution, *i.e.*, distortion of polysubstituted porphyrins is a result of steric strains in the porphyrin molecules due to intramolecular interactions rather than intermolecular forces in crystals. If direct methods, *e.g.*, X-ray diffraction analysis or NMR, cannot be used, the structure of porphyrins can be deduced from calculations by molecular mechanics methods (MM), which reflect adequately their molecular geometry provided that competent approaches are used.

## II. Structural characteristics

Conformational flexibility of porphyrins can be exemplified by structurally simple compounds, such as tetraphenylporphine (**1**), octaethylporphine (**2**) and their nickel complexes (NiP). These compounds were obtained in the crystalline state with both planar and non-planar structures of their cores.<sup>1,2,10–14</sup> The X-ray diffraction data summarised in Table 1 suggest that in the tetragonal modifications the mean deviation of the C and N atoms of the porphyrin skeleton from the mean-square plane passing through 24 atoms ( $\Delta_{24}$ ) is  $\sim 20$  pm. The *meso*-carbon atoms ( $C_{ms}$ ) are at the largest distance from this plane (50 pm).<sup>1,10</sup>

Coordination of porphyrins by the  $d^8$ -nickel cation, which has a small radius in the low-spin state, leads to further distortion of the core and formation of a non-planar ruffled conformation where the pyrrole rings are tilted about the axes  $C_\alpha - C_\alpha$  eventually resulting in a significant displacement of the  $C_{ms}$  atoms. Two crystalline forms, *viz.*, the planar triclinic<sup>11</sup> and the highly ruffled tetragonal<sup>10</sup> forms of NiP (**2**), were first detected. Yet another planar triclinic modification of NiP (**2**) was described later.<sup>14</sup> The deviations of the carbon and nitrogen atoms from the mean planes of the macrocycles of NiP (**1**) and NiP (**2**) are shown in Fig. 1.

**O A Golubchikov, E M Kuvshinova** Ivanovo State University of Chemistry and Technology, prosp. F Engelsa 7, 153460 Ivanovo, Russian Federation. Fax (7-0932) 41 79 95, tel. (7-0932) 32 73 78, e-mail: golubch@isuct.ru (O A Golubchikov), tel. (7-0932) 33 25 43 (E M Kuvshinova)

**S G Pukhovskaya** Institute of Solution Chemistry, Russian Academy of Sciences, ul. Akademicheskaya 1, 153045 Ivanovo, Russian Federation. Fax (7-0932) 33 62 37, tel. (7-0932) 33 69 90, e-mail: puhovskaya@isuct.ru (S G Pukhovskaya)

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**Table 1.** Structural characteristics of tetraphenylporphine (**1**), octaethylporphine (**2**) and their nickel complexes.

| A. Bond lengths /pm              |          |                 |                             |                          |                            |                      |      |
|----------------------------------|----------|-----------------|-----------------------------|--------------------------|----------------------------|----------------------|------|
| Porphyrin                        | M–N      | N–C $_{\alpha}$ | C $_{\alpha}$ –C $_{\beta}$ | C $_{\alpha}$ –C $_{ms}$ | C $_{\beta}$ –C $_{\beta}$ | C $_{ms}$ –C $_{Ph}$ | Ref. |
| H <sub>2</sub> P (1), tetragonal | —        | 135.0(7)        | 143.8(8)                    | 140.3(7)                 | 136.2(9)                   | 151.4                | 1    |
| H <sub>2</sub> P (1), triclinic  | —        | 137.2           | 144.2                       | 140.0                    | 135.1                      | 150.3                | 2    |
| H <sub>2</sub> P (2)             | —        | 136.6(2)        | 145.1(2)                    | 139.2(2)                 | 136.8(2)                   | —                    | 12   |
| NiP (1)                          | 193.1(2) | 137.7(3)        | 142.9(3)                    | 138.2(4)                 | 134.0(4)                   | 149.9(3)             | 13   |
| NiP (2), tetragonal              | 192.9(3) | 138.6(2)        | 144.9(5)                    | 137.2(2)                 | 136.2(2)                   | —                    | 10   |
| NiP (2), triclinic               | 195.8(2) | 137.6(4)        | 144.3(3)                    | 137.1(4)                 | 134.6(2)                   | —                    | 11   |

| B. Bond angles /deg                   |         |                   |                            |                               |                                |                                         |                                           |                                        |      |
|---------------------------------------|---------|-------------------|----------------------------|-------------------------------|--------------------------------|-----------------------------------------|-------------------------------------------|----------------------------------------|------|
| Porphyrin                             | N–M–N   | M–N–C $_{\alpha}$ | N–C $_{\alpha}$ –C $_{ms}$ | N–C $_{\alpha}$ –C $_{\beta}$ | C $_{\alpha}$ –N–C $_{\alpha}$ | C $_{\alpha}$ –C $_{ms}$ –C $_{\alpha}$ | C $_{\alpha}$ –C $_{\beta}$ –C $_{\beta}$ | C $_{ms}$ –C $_{\alpha}$ –C $_{\beta}$ | Ref. |
| H <sub>2</sub> P (1), tetra-<br>gonal | —       | —                 | 126.0(5)                   | 107.5(4)                      | 108.9(4)                       | 125.2(5)                                | 106.9(5)                                  | 125.1(5)                               | 1    |
| H <sub>2</sub> P (1), triclinic       | —       | —                 | 126.2                      | 108.8                         | 107.7                          | 125.6                                   | 107.5                                     | 124.9                                  | 2    |
| H <sub>2</sub> P (2)                  | —       | —                 | 125.1(1)                   | 109.4(1)                      | 107.7(1)                       | 127.6(1)                                | 106.8(1)                                  | 125.7(1)                               | 12   |
| NiP (1)                               | 90.0    | 127.5(2)          | 125.5(2)                   | 110.4(2)                      | 104.9(2)                       | 120.0(2)                                | 107.1(2)                                  | 123.9(2)                               | 13   |
| NiP (2), tetra-<br>gonal              | 90.0    | 127.4(2)          | 124.0(2)                   | 110.6(2)                      | 105.1(3)                       | 124.1(2)                                | 106.8(3)                                  | 125.0(2)                               | 10   |
| NiP (2), triclinic                    | 90.2(1) | 128.0(2)          | 124.4(3)                   | 111.6(3)                      | 103.9(2)                       | 125.1(3)                                | 106.5(3)                                  | 124.1(3)                               | 11   |

| C. Inclination of the pyrrole and phenyl fragments relative to, and deviation of the atoms from, the mean plane of the macrocycle. |                  |                |                                                                  |             |            |                 |                     |                    |    |      |
|------------------------------------------------------------------------------------------------------------------------------------|------------------|----------------|------------------------------------------------------------------|-------------|------------|-----------------|---------------------|--------------------|----|------|
| Porphyrin                                                                                                                          | Inclination /deg |                | Deviation of the atoms from the mean plane of the macrocycle /pm |             |            |                 |                     |                    |    | Ref. |
|                                                                                                                                    | $\varphi_{pyr}$  | $\varphi_{Ar}$ | $R$ (see <sup>a</sup> )                                          | $\Delta 24$ | $\Delta N$ | $\Delta C_{ms}$ | $\Delta C_{\alpha}$ | $\Delta C_{\beta}$ |    |      |
| H <sub>2</sub> P (1), tetragonal                                                                                                   | 11.5             | 78.5           | 205.4                                                            | 19          | 4          | 38              | 21                  | 14                 | 1  |      |
| H <sub>2</sub> P (1), triclinic                                                                                                    | 7.5              | 60.0           | 206                                                              | 5           | 0          | 4               | 2                   | 3                  | 2  |      |
| H <sub>2</sub> P (2)                                                                                                               | 1.7              | —              | 206.2                                                            | 2           | 0          | 4               | 2                   | 8                  | 12 |      |
| NiP (1)                                                                                                                            | 14.4             | 78.7           | 193.1                                                            | 22          | 1          | 45              | 26                  | 18                 | 13 |      |
| NiP (2), tetragonal                                                                                                                | 16.4             | —              | 192.9                                                            | 26          | 1          | 51              | 30                  | 27                 | 10 |      |
| NiP (2), triclinic                                                                                                                 | 1.7              | —              | 195.8                                                            | 2           | 0          | 3               | 7                   | 6                  | 11 |      |

<sup>a</sup> Hereinafter,  $R$  is the radius of the coordination plane of the porphyrin core.

Octasubstituted tetraphenylporphines containing alkyl, cycloalkyl groups and halogens in the β-positions are studied in most detail in comparison with other porphyrins distorted due to the presence of a large number of peripheral substituents. The structural characteristics of β-octaethyl-*meso*-tetraphenylpor-

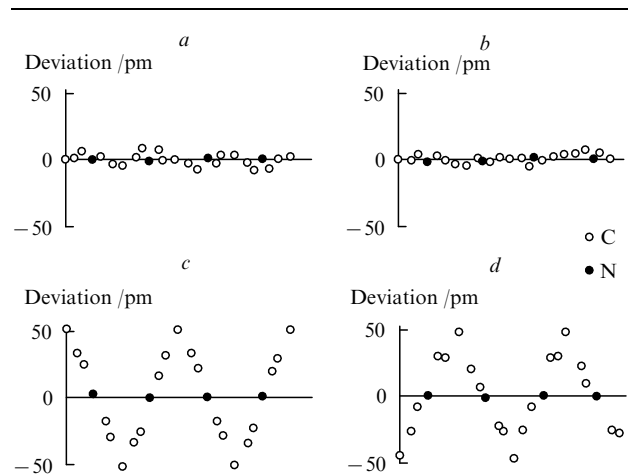


**Figure 1.** Deviations of carbon and nitrogen atoms from the mean plane passing through 24 atoms of the tetrapyrrole macrocycle in nickel complexes of octaethylporphine and tetraphenylporphine. (a) NiP (**2**) triclinic,<sup>11</sup> (b) NiP (**2**) triclinic,<sup>14</sup> (c) NiP (**2**) tetragonal,<sup>10</sup> (d) NiP (**1**).<sup>13</sup>

phine (**3**) and its complexes obtained by X-ray diffraction analysis and MM are listed in Table 2.<sup>15–19</sup>

The macrocyclic core of β-octaethyl-*meso*-tetraphenylporphine and its coordination compound has a symmetric saddle shape. A characteristic feature of this conformation is that two opposite pyrrole cores are raised above the mean plane of the molecule, while the other two are depressed as a result of the van der Waals repulsions of the *meso*-phenyl and alkyl groups; such *meso*-carbon atoms are coplanar with the macrocycle. This type of deformation is also characteristic of octamethyl analogues, *e.g.*, CuP (**3**) (see Ref. 16) and zinc β-octamethyl-*meso*-tetraphenylporphine pyridinate Zn(Py)P (**4**)<sup>†</sup> (see Ref. 19). Both complexes possess substantially distorted macrocycles, the differences between the methyl and ethyl derivatives being insignificant (Fig. 2).

The deviation of C<sub>β</sub>-atoms owing to sequential up-and-down displacement of the pyrrole rings relative to the mean-square plane (the torsion angle is ~30°) reaches 109–115 pm. Compared to tetraphenylporphin, the *meso*-phenyl rings of its β-octaalkyl-substituted derivatives are rotated by a smaller angle relative to the mean plane of the macrocycle (43–46°); however, this does not result in any significant decrease in the lengths of the C<sub>ms</sub>–C<sub>Ph</sub> bonds. Such a structural type is characteristic of all tetraphenylporphine derivatives containing methyl, ethyl, propyl and cycloalkyl substituents in the β-positions. It is noteworthy

<sup>†</sup> Coordinated acido- and molecular ligands are indicated in parentheses after the metal cation; crystallisation molecules of the solvent stand after a dot. For example: Zn(Py)P (**1**) · 2 MeOH.

**Table 2.** Structural characteristics of  $\beta$ -octaethyl-*meso*-tetraphenylporphine (**3**) and its metallocomplexes.

| A. Bond lengths /pm                                                                                                                |                   |                    |                                                                  |                                  |                                  |                                                 |                                                |                                                 |                 |      |
|------------------------------------------------------------------------------------------------------------------------------------|-------------------|--------------------|------------------------------------------------------------------|----------------------------------|----------------------------------|-------------------------------------------------|------------------------------------------------|-------------------------------------------------|-----------------|------|
| Porphyrin                                                                                                                          | M–L <sub>ax</sub> | M–N                | N–C <sub>α</sub>                                                 | C <sub>α</sub> –C <sub>β</sub>   | C <sub>α</sub> –C <sub>ms</sub>  | C <sub>β</sub> –C <sub>β</sub>                  | C <sub>ms</sub> –C <sub>Ph</sub>               | Ref.                                            |                 |      |
| H <sub>2</sub> P (3)                                                                                                               | —                 | —                  | 136.8                                                            | 145.1                            | 140.7                            | 137.7                                           | —                                              | 15                                              |                 |      |
| Fe(Cl)P (3)                                                                                                                        | 224.2(2)          | 203.1(5)           | 138.6(7)                                                         | 144.9(9)                         | 140.5(8)                         | 136.0(9)                                        | 152.4(8)                                       | 16                                              |                 |      |
| CoP (3)                                                                                                                            | —                 | 192.9(3)           | 138.2(6)                                                         | 145.7(7)                         | 140.2(7)                         | 136.2(7)                                        | —                                              | 16                                              |                 |      |
| NiP (3)                                                                                                                            | —                 | 190.6(2)           | 138.1(2)                                                         | 145.1(3)                         | 139.5(2)                         | 136.5(5)                                        | 149.1(1)                                       | 17                                              |                 |      |
| CuP (3)                                                                                                                            | —                 | 197.3(4)           | 137.9(6)                                                         | 145.5(7)                         | 140.3(7)                         | 136.7(7)                                        | 149.3(7)                                       | 18                                              |                 |      |
| CuP (3) · 2 CH <sub>2</sub> Cl <sub>2</sub>                                                                                        | —                 | 197.7(5)           | 137.8(8)                                                         | 145.8(8)                         | 140.4(8)                         | 136.8(8)                                        | —                                              | 16                                              |                 |      |
| CuP (3) (see <sup>a</sup> )                                                                                                        | —                 | 197.4(3)           | 138.3(6)                                                         | 144.4(6)                         | 140.7(6)                         | 136.7(7)                                        | 149.0(7)                                       | 18                                              |                 |      |
| Zn(MeOH)P (3)                                                                                                                      | 222.6(5)          | 206.3(5)           | 137.1(2)                                                         | 146.1(2)                         | 141.6(3)                         | 137.0(7)                                        | —                                              | 19                                              |                 |      |
| B. Bond angles /deg                                                                                                                |                   |                    |                                                                  |                                  |                                  |                                                 |                                                |                                                 |                 |      |
| Porphyrin                                                                                                                          | N–M–N             | M–N–C <sub>α</sub> | N–C <sub>α</sub> –C <sub>ms</sub>                                | N–C <sub>α</sub> –C <sub>β</sub> | C <sub>α</sub> –N–C <sub>α</sub> | C <sub>α</sub> –C <sub>ms</sub> –C <sub>α</sub> | C <sub>α</sub> –C <sub>β</sub> –C <sub>β</sub> | C <sub>ms</sub> –C <sub>α</sub> –C <sub>β</sub> | Ref.            |      |
| H <sub>2</sub> P (3)                                                                                                               | —                 | —                  | 122.4                                                            | 108.7                            | 108.6                            | 123.8                                           | 106.9                                          | 128.8                                           | 15              |      |
| Fe(Cl)P (3)                                                                                                                        | 87.1(2)           | 122.8(4)           | 121.5(5)                                                         | 109.4(5)                         | 106.2(1)                         | 123.0(5)                                        | 107.2(5)                                       | 128.8(5)                                        | 16              |      |
| CoP (3)                                                                                                                            | 90.5(2)           | 125.6(3)           | 121.7(4)                                                         | 110.0(4)                         | 105.6(4)                         | 122.2(5)                                        | 106.7(4)                                       | 127.9(5)                                        | 16              |      |
| NiP (3)                                                                                                                            | 90.6(2)           | 125.3(2)           | 121.3(2)                                                         | 109.8(1)                         | 105.9(2)                         | 121.4(1)                                        | 106.8(1)                                       | 128.3(1)                                        | 17              |      |
| CuP (3)                                                                                                                            | 90.3(2)           | 124.5(3)           | 121.8(4)                                                         | 109.5(4)                         | 106.7(4)                         | 123.2(4)                                        | 106.8(4)                                       | 128.4(5)                                        | 18              |      |
| CuP (3) · 2 CH <sub>2</sub> Cl <sub>2</sub>                                                                                        | 90.3(2)           | 124.7(4)           | 122.0(4)                                                         | 109.6(4)                         | 106.6(5)                         | 123.4(5)                                        | 107.0(5)                                       | 128.1(5)                                        | 16              |      |
| CuP (3) (see <sup>a</sup> )                                                                                                        | 89.9(2)           | 121.2(4)           | 119.8(4)                                                         | 110.5(4)                         | 105.3(4)                         | 121.1(3)                                        | 106.7(4)                                       | 129.5(4)                                        | 18              |      |
| Zn(MeOH)P (3)                                                                                                                      | 89.4(4)           | 122.9(6)           | 122.4(2)                                                         | 109.2(3)                         | 107.7(4)                         | 124.4(4)                                        | 106.8(2)                                       | 128.2(2)                                        | 19              |      |
| C. Inclination of the pyrrole and phenyl fragments relative to, and deviation of the atoms from, the mean plane of the macrocycle. |                   |                    |                                                                  |                                  |                                  |                                                 |                                                |                                                 |                 |      |
| Porphyrin                                                                                                                          | Inclination /deg  |                    | Deviation of the atoms from the mean plane of the macrocycle /pm |                                  |                                  |                                                 |                                                |                                                 |                 | Ref. |
|                                                                                                                                    | φ <sub>pyr</sub>  | φ <sub>Ar</sub>    | R                                                                | Δ24                              | ΔM                               | ΔN                                              | ΔC <sub>ms</sub>                               | ΔC <sub>α</sub>                                 | ΔC <sub>β</sub> |      |
| H <sub>2</sub> P (3)                                                                                                               | 31.2              | 43.2               | 205.1                                                            | 54                               | —                                | 7                                               | 3                                              | 42                                              | 117             | 15   |
| Fe(Cl)P (3)                                                                                                                        | 29.8              | 44.9               | 197.6                                                            | 58                               | 47                               | 11                                              | 19                                             | 44                                              | 115             | 16   |
| CoP (3)                                                                                                                            | 27.5              | 46.1               | 192.0                                                            | 58                               | 1                                | 18                                              | 5                                              | 47                                              | 117             | 16   |
| NiP (3)                                                                                                                            | 29.4              | 43.4               | 190.6                                                            | 62                               | 1                                | 19                                              | 3                                              | 52                                              | 124             | 17   |
| CuP (3)                                                                                                                            | 28.2              | 45.6               | 197.3                                                            | 57                               | 0                                | 14                                              | 5                                              | 45                                              | 115             | 18   |
| CuP (3) · 2 CH <sub>2</sub> Cl <sub>2</sub>                                                                                        | 27.4              | 46.9               | 197.3                                                            | 55                               | 0                                | 14                                              | 4                                              | 44                                              | 112             | 16   |
| CuP (3) (see <sup>a</sup> )                                                                                                        | 37.3              | 33.1               | 197.2                                                            | 66                               | 9                                | 4                                               | 20                                             | 49                                              | 135             | 18   |
| Zn(MeOH)P (3)                                                                                                                      | 28.4              | 46.1               | 206.3                                                            | 51                               | 22                               | 6                                               | 4                                              | 39                                              | 109             | 19   |

<sup>a</sup> The radical cation form of the copper complex with perchlorate as a counterion.

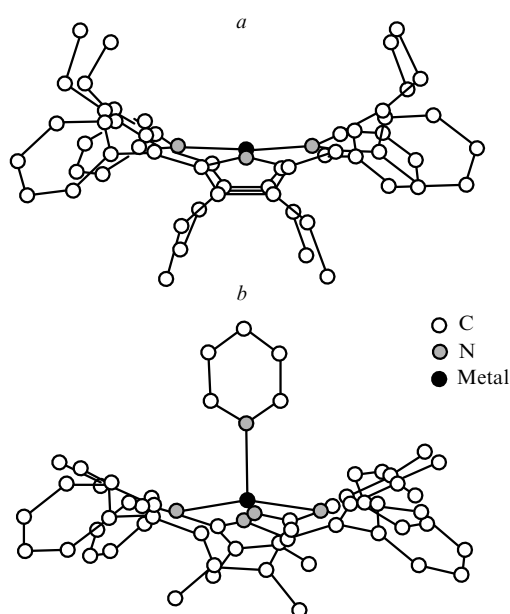


**Figure 2.** Structures of the copper complex of  $\beta$ -octaethyl-*meso*-tetraphenylporphine (**a**)<sup>16</sup> and zinc  $\beta$ -octamethyl-*meso*-tetraphenylporphine pyridinate (**b**)<sup>19</sup>.

that the saddle conformation of the  $\beta$ -octamethyl-*meso*-tetraphenylporphine (**4**) macrocycle is slightly ruffled (Fig. 3).

The shapes of the tetrapyrrole macrocycles of distorted porphyrins are rather diverse (Fig. 4).<sup>20</sup> In addition to the aforementioned saddle and ruffled structures, two wavelike, dome-shaped and propeller conformations are also known. In the majority of cases, the shape of the tetrapyrrole core of a distorted porphyrin can be described by one of the above-mentioned types or their combination.

Dodecasubstituted porphyrins and their planar analogues differ in the angles between the same type of bonds (see Tables 1 and 2). The increase in the  $\text{C}_{\text{ms}}-\text{C}_{\alpha}-\text{C}_{\beta}$  angles and the decrease in the  $\text{N}-\text{C}_{\alpha}-\text{C}_{\text{ms}}$  and  $\text{M}-\text{N}-\text{C}_{\alpha}$  angles in the distorted porphyrins by 3–4° in comparison with planar porphyrins are the most significant. This peculiarity is characteristic of all metalloporphyrins **3** (see Tables 1 and 2). Using nickel complexes of highly substituted porphyrins as an example, it was shown<sup>4</sup> that these parameters correlate with the degree of the non-planarity of the macrocycle.

Studies of the structure of Zn(Py)P (**4**) revealed<sup>19</sup> that the conformation of the macrocycle depends on the axial ligands. The displacement of the  $\text{C}_{\beta}$  atoms of the pyrrole rings close to the axial ligand is less pronounced (90 pm) than that of the opposite  $\text{C}_{\beta}$  atoms of the pyrrole cores (120 pm).

In the case of dodecasubstituted porphyrin complexes with 3d-metals, the degree of non-planarity of the tetrapyrrole macro-

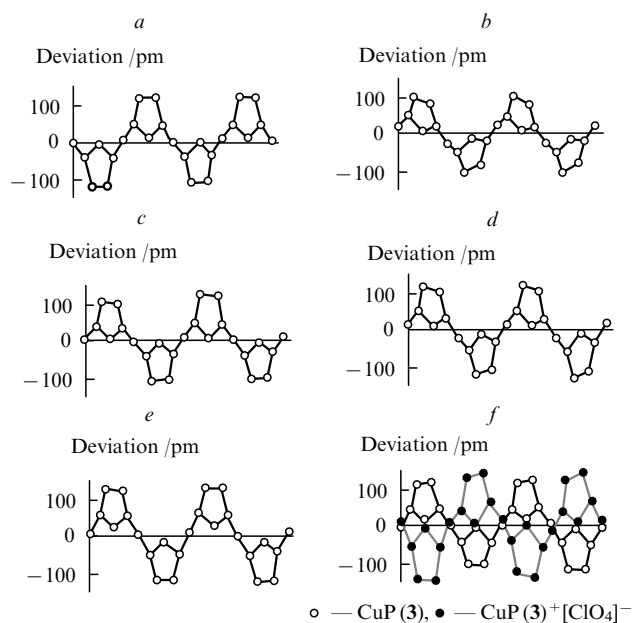


**Figure 3.** Deviations of carbon and nitrogen atoms in dodecasubstituted porphyrins and metalloporphyrins from the mean plane of the macrocycle.

(a)  $\text{H}_2\text{P}(3)$ , (b)  $\text{H}_2\text{P}(4)$ , (c)  $\text{ZnP}(4) \cdot \text{MeOH}$ , (d)  $\text{Fe}(\text{Cl})\text{P}(3)$ , (e)  $\text{NiP}(3)$ , (f)  $\text{CuP}(3)$  and its radical-cation form.<sup>15</sup>

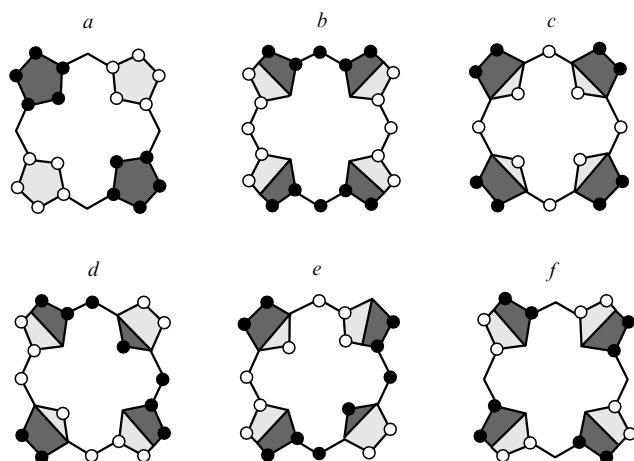


**Figure 4.** Typical conformations of non-planar porphyrins.

(a) saddle-shaped, (b) ruffled, (c) dome-shaped, (d, e) wave-shaped, (f) propeller-shaped. The unshaded fragments lie above the mean plane of the macrocycle, the dark fragments lie under it.<sup>20</sup>

cycle depends on the size of the complex-forming atom (see Table 2). Judging from the displacement of N,  $\text{C}_\alpha$  and  $\text{C}_\beta$  atoms relative to the mean plane of the macrocycle, the distortion of the macrocycle decreases with an increase in the size of the metal cation in the series from  $\text{Ni}^{2+}$  (69 pm) to  $\text{Zn}^{2+}$  (74 pm). In this case, the lengths of the  $\text{M}-\text{N}$  and  $\text{C}_\alpha-\text{C}_{ms}$  bonds increase, while those of the  $\text{N}-\text{C}_\alpha$  bonds decrease; the angles between the  $\text{M}-\text{N}-\text{C}_\alpha$  bonds decrease, while those between the  $\text{C}_\alpha-\text{N}-\text{C}_\alpha$  and  $\text{C}_\alpha-\text{C}_{ms}-\text{C}_\alpha$  bonds increase. The changes in other structural parameters of metalloporphyrins on going from the smallest to the largest metal atom are insignificant and do not exceed  $1^\circ$ . It is of note that complexes of spatially distorted porphyrins with cations the sizes of which differ substantially from those of 3d-metals have not been investigated yet.

Similarly, the geometry of the complexes of the non-strained planar porphyrins **1** and **2** with 3d-metal cations depends on the sizes of these cations. The sizes of the coordination cavities of porphyrins decrease with an increase in the degree of distortion of the tetrapyrrole core. In turn, coordination of porphyrins by small cations results in further distortion of the macrocycle (Fig. 5).<sup>16</sup> It should be kept in mind, however, that coordination of porphyrins by cations having very large sizes, e.g.,  $\text{Pt}(\text{II})$ ,<sup>21</sup>  $\text{In}(\text{III})$ ,<sup>22</sup> or  $\text{Tl}(\text{III})$ ,<sup>23</sup> also results in the distortion of the tetrapyrrole cores of metalloporphyrins. According to spectral measurements and calculations, distortions of polysubstituted porphyrins are retained on going from the crystalline state to solution.<sup>24–32</sup>

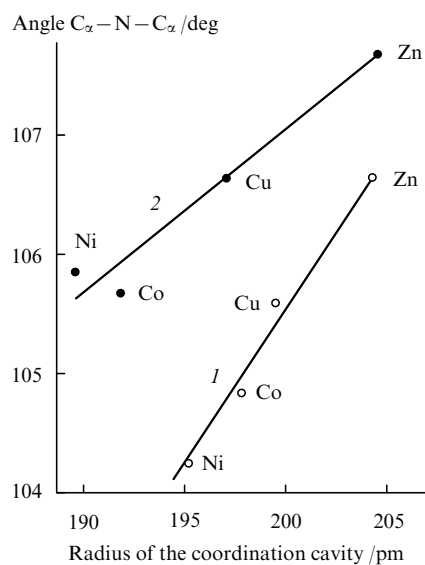


**Figure 5.** Relationship between the radius of the coordination cavity and the bond angle  $\text{C}_\alpha-\text{N}-\text{C}_\alpha$  of octaethylporphyrine (**1**) and  $\beta$ -octaethyl-*meso*-tetraphenylporphyrine (**2**) complexes.<sup>16</sup>

Porphyrins halogenated in the  $\beta$ -positions constitute a large group of spatially distorted dodecasubstituted compounds. The tetrapyrrole cores in copper<sup>33</sup> and nickel<sup>33,34</sup> complexes of  $\beta$ -octabromo-*meso*-tetrakis(pentafluorophenyl)porphine (**5**) and  $\beta$ -octabromo-*meso*-tetramesitylporphine (**6**) and its nickel complex have a saddle conformation. The average distances of the  $\text{C}_{ms}$ ,  $\text{C}_\beta$  and Br atoms from the plane formed by four nitrogen atoms for the copper and nickel complexes of porphyrin **5** are 16.3, 112 and 199 pm and 18.7, 118 and 205 pm, respectively.<sup>33</sup> Very short contacts  $\text{Br}-\text{Br}$  and  $\text{Br}-\text{C}(1)_{\text{Ph}}$  were observed; the sums of the van der Waals radii of these pairs of atoms exceed the real distances between them by  $\sim 45$  pm. However, the lengths of the  $\text{C}-\text{N}$  and  $\text{C}-\text{C}$  bonds in the  $\beta$ -halogenated complexes are virtually the same as those of metalloporphyrins devoid of steric strains. Some structural characteristics of copper and nickel complexes of the porphyrin **5** are listed in Table 3. In these complexes, one of the two bromine atoms in each pair occupying the  $\beta$ -position of the pyrrole ring is more remote from the mean plane of the macrocycle than the other atom. Bulky *ortho*-substituents in the benzene rings of porphyrins **5** and **6** and the neighbouring halogen  $\beta$ -atoms form cavities on both sides of the porphyrin core (Fig. 6).<sup>34</sup> This restricts spatial arrangements of the ligands additionally coordinated by metalloporphyrins<sup>26,28,29,35</sup> and can be directly related to high and specific catalytic activity of polyhalogenated porphyrin complexes with iron(III) in oxidation processes.<sup>36–43</sup>

Dodecaarylporphine derivatives pertain to the class of porphyrins with the most strongly distorted macrocycle. Dodecaphenylporphine (**7**) has a saddle conformation with two highly asymmetric pairs of pyrrole rings in crystals with rhombohedral

**Table 3.** Bond lengths and bond angles in copper and nickel complexes of  $\beta$ -octabromo-*meso*-tetrakis(pentafluorophenyl)porphine.<sup>33</sup>

| Bond               | Bond length /pm |                | Bond angle                       | Angle magnitude /deg |                |
|--------------------|-----------------|----------------|----------------------------------|----------------------|----------------|
|                    | for<br>NiP (5)  | for<br>CuP (5) |                                  | for<br>NiP (5)       | for<br>CuP (5) |
| M–N <sub>1</sub>   | 190.2(4)        | 196.9(6)       | N <sub>2</sub> –M–N <sub>1</sub> | 90.5(2)              | 90.1           |
| M–N <sub>2</sub>   | 190.4(4)        | 197.7(6)       | N <sub>3</sub> –M–N <sub>1</sub> | 168.4(2)             | 171.0          |
| M–N <sub>3</sub>   | 189.8(4)        | 197.1(6)       | N <sub>4</sub> –M–N <sub>1</sub> | 90.8(2)              | 91.2           |
| M–N <sub>4</sub>   | 190.6(4)        | 196.8(6)       | N <sub>3</sub> –M–N <sub>2</sub> | 90.3(2)              | 89.9           |
| Br–C <sub>2</sub>  | 185.8(6)        | 188.4(7)       | N <sub>4</sub> –M–N <sub>2</sub> | 168.5(2)             | 171.5          |
| Br–C <sub>3</sub>  | 187.2(6)        | 188.7(8)       | N <sub>4</sub> –M–N <sub>3</sub> | 90.8(2)              | 90.2           |
| Br–C <sub>7</sub>  | 186.3(6)        | 187.4(8)       |                                  |                      |                |
| Br–C <sub>8</sub>  | 187.1(6)        | 186.7(8)       |                                  |                      |                |
| Br–C <sub>12</sub> | 188.0(6)        | 185.6(8)       |                                  |                      |                |
| Br–C <sub>13</sub> | 186.1(6)        | 188.2(8)       |                                  |                      |                |
| Br–C <sub>17</sub> | 187.0(6)        | 188.5(8)       |                                  |                      |                |
| Br–C <sub>18</sub> | 187.1(6)        | 187.0(8)       |                                  |                      |                |

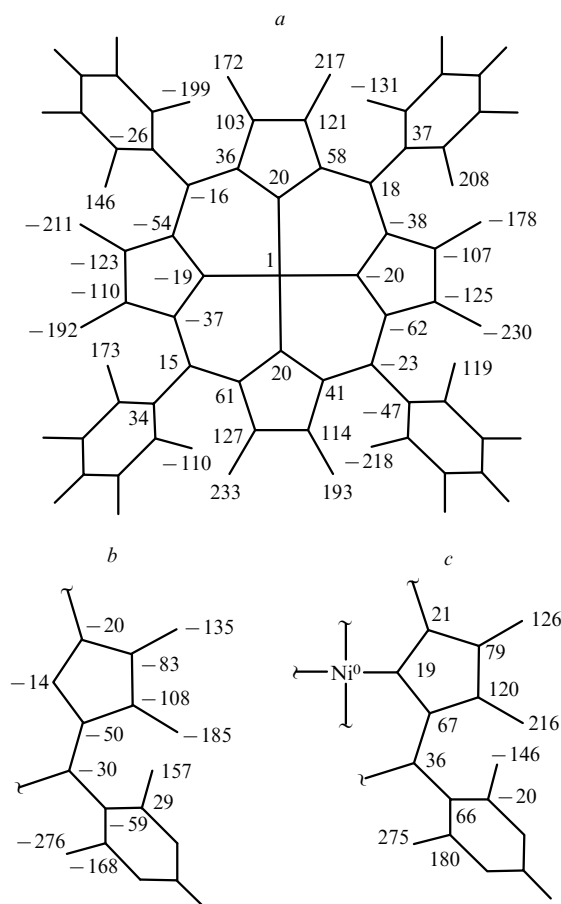


**Figure 6.** Deviations of atoms (pm) from the mean plane of the tetrapyrrole macrocycle in a nickel complex of  $\beta$ -octabromo-*meso*-tetraakis(pentafluorophenyl)porphine (*a*),  $\beta$ -octabromo-*meso*-tetramesitylporphine (*b*) and its nickel complex (*c*).<sup>34</sup>

modification (Figs. 7 and 8 *a*).<sup>44</sup> Analysis of intra- and intermolecular interactions revealed<sup>44</sup> that the distortion of the macrocycle in this modification is due to the intramolecular repulsion of the phenyl substituents rather than to the crystal packing effects. Later, two new crystalline forms of dodecaphenylporphine, *viz.*, the triclinic form<sup>45</sup> [ $\text{H}_2\text{P}$  (**7**)  $\cdot 2 \text{ EtOH} \cdot 2 \text{ CH}_2\text{Cl}_2$ ] with a configuration similar to that described above (Fig. 8 *b*) and a much more symmetric rhombohedral conformation [ $\text{H}_2\text{P}$  (**7**)  $\cdot 3 \text{ H}_2\text{O}$ ], were found.<sup>46</sup> The latter has a saddle shape; its  $\text{C}_\beta$  atoms are displaced

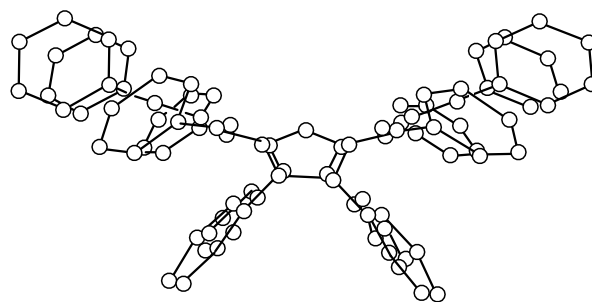


**Figure 7.** Structure of dodecaphenylporphine of rhombohedral crystals of  $\text{H}_2\text{P}$  (7)  $\cdot$  3  $\text{CH}_2\text{Cl}_2$  (the hydrogen atoms are not shown).<sup>44</sup>

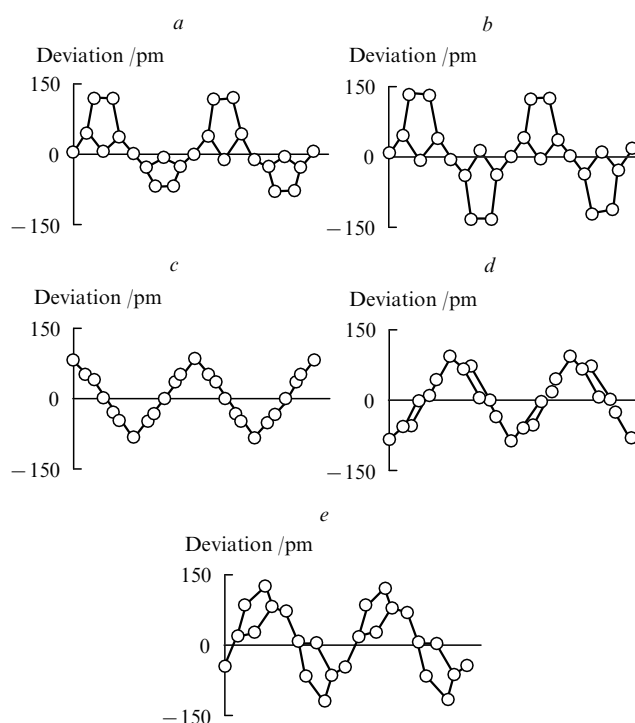


**Figure 8.** Deviations of carbon and nitrogen atoms in different crystalline modifications of dodecaphenylporphine and its nickel complex from the mean plane passing through 24 atoms of the tetrapyrrole macrocycle.<sup>44–46</sup>

(a)  $\text{H}_2\text{P}(\mathbf{7}) \cdot 3 \text{CH}_2\text{Cl}_2$  rhombohedral, (b)  $\text{H}_2\text{P}(\mathbf{7}) \cdot 2 \text{CH}_2\text{Cl}_2 \cdot 2 \text{EtOH}$  triclinic, (c)  $\text{NiP}(\mathbf{7}) \cdot 5.8 \text{C}_6\text{H}_{12} \cdot 0.9 \text{CHCl}_3$  cubic, (d)  $\text{NiP}(\mathbf{7}) \cdot 3.5 \text{CHCl}_3$  rhombohedral and  $\text{NiP}(\mathbf{7}) \cdot 1.5 \text{H}_2\text{O}$ . (e)  $\text{NiP}(\mathbf{7})$  rhombohedral.

by 132 pm relative to the mean plane of the tetrapyrrole core,<sup>46</sup> which markedly exceeds the corresponding parameter for  $\beta$ -octaethyl-*meso*-tetraphenylporphine H<sub>2</sub>P (**3**) (117 pm).<sup>15</sup> Some structural characteristics of the porphyrin **7** and its complexes are listed in Table 4; it can be seen that the macrocycle of the dodecaphenyl-substituted porphyrin is more flexible than that of octaalkyltetraphenyl derivatives. For example, four crystalline forms of NiP (**7**) differing notably from one another have been established. The cubic form has a purely ruffled configuration; its *C<sub>ms</sub>* atoms are displaced relative to the mean plane of the macrocycle by 86 pm (Fig. 8 *c*).<sup>45</sup> The rhombohedral modification of a solvate containing 3.5 molecules of CHCl<sub>3</sub>, albeit also ruffled, has an entirely different shape (Fig. 8 *d*). In this case, two C <sub>$\beta$</sub>  atoms in each pyrrole ring are displaced asymmetrically by 70 and 10 pm, while the deviation of the *meso*-atoms projecting from the mean plane of the macrocycle is as large as before.<sup>46</sup> Yet another crystal solvate, *viz.*, NiP (**7**)·1.5H<sub>2</sub>O, described in<sup>46</sup> has a similar conformation. And, finally, the fourth crystal modification,

**Table 4.** Structural characteristics of dodecaphenylporphine and its complexes.<sup>44–46</sup>

| Porphyrin                                                             | Bond length<br>M–N /pm | $\varphi_{\text{pyr}}$ /deg | $\varphi_{\text{ms (Ar)}}$ /deg | $\Delta 24$ /pm | $\Delta M$ /pm | $\Delta N$ /pm | $\Delta C_{\text{ms}}$ /pm | $\Delta C_{\beta}$ /pm |
|-----------------------------------------------------------------------|------------------------|-----------------------------|---------------------------------|-----------------|----------------|----------------|----------------------------|------------------------|
| H <sub>2</sub> P (7) · 3 CH <sub>2</sub> Cl <sub>2</sub>              | —                      | 18.0; 33.6                  | 43.8                            | —               | —              | 14; 1          | 0                          | 78; 120                |
| H <sub>2</sub> P (7) · 3 H <sub>2</sub> O                             | —                      | —                           | —                               | 60              | —              | 7              | 5                          | 132                    |
| H <sub>2</sub> P (7) · 2 EtOH · 2 CH <sub>2</sub> Cl <sub>2</sub>     | —                      | 40.9                        | 22.0                            | 60              | —              | 10             | 7                          | 132                    |
| NiP (7) · 5.8 C <sub>6</sub> H <sub>12</sub> · 0.9 CHCl <sub>3</sub>  | 190.9                  | 22.8                        | 89.1                            | 43              | 0              | 1              | 86                         | 36                     |
| Ni (7)                                                                | 188.5                  | —                           | —                               | 60              | 6              | 13             | 60                         | 76; 133                |
| NiP (7) · 3.5 CHCl <sub>3</sub> and<br>NiP (7) · 1.5 H <sub>2</sub> O | 189.4                  | —                           | —                               | 45              | 2              | 4              | 92                         | 70; 10                 |
| ZnP (7)                                                               | 203.7                  | —                           | 48                              | 46              | 7              | 10             | 1                          | 96                     |

which corresponds to the non-solvated form of the tetrapyrrole macrocycle represents a combination of ruffled and saddle conformations with a shift of the *meso*-carbon atoms from the mean plane by 60 pm and a non-symmetric shift of the C<sub>β</sub> atoms by 76 and 133 pm (Fig. 8e).<sup>46</sup>

Tetraphenylporphine derivatives containing from two to six ethyl groups in the β-positions were synthesised and characterised by X-ray diffraction.<sup>47</sup> The structural characteristics of 2,3-diethyl- (8), 2,3,7,8-tetraethyl- (9), 2,3,12,13-tetraethyl- (10) and 2,3,7,8,12,13-hexaethyl-5,10,15,20-tetraphenylporphine (11) and their nickel(II), copper(II) and zinc(II) complexes are listed in Table 5. For the sake of comparison, the corresponding parameters for tetraphenylporphine (1) and octaethyltetraphenylporphine (3) are also given. As expected, the degree of distortion of the tetrapyrrole macrocycle increases with an increase in the number of peripheral substituents. Of two tetraethyltetraphenyl-

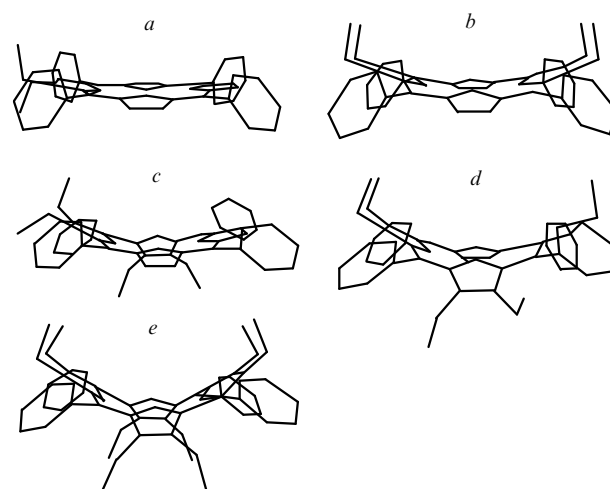
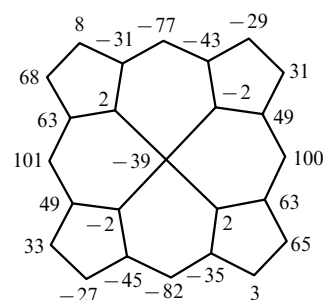
porphine derivatives, the non-symmetrical isomer 9 is distorted to a much greater degree than the symmetrical isomer 10. All porphyrins of this series have a saddle conformation of the macrocyclic core (Fig. 9).

The planar structure of the macrocycle extended along the axis C(5)–C(15) is retained in the molecules of symmetrical 2,3,5,7,8,12,13,15,17,18-decaalkylporphyrins and 5,15-diaryl-β-octaalkylporphyrins.<sup>48,49</sup> At the same time, copper and nickel complexes of these porphyrins are subject to extraplanar distortion: their tetrapyrrole macrocycles are folded along the axis C(5)–C(15) and have a gable roof conformation.<sup>49–52</sup> Non-symmetrical 5,10-di- and 5,10,15-trisubstituted porphyrins are highly distorted.<sup>49</sup> The conformations of their macrocycles represent a combination of ruffled and saddle-like distortions.

Macrocycles of porphyrins containing only four substituents can also be distorted. Zinc *meso*-tetra-*tert*-butylporphine pyridinate (12) has a strongly ruffled aromatic core (Fig. 10).<sup>53,54</sup> Nickel

**Table 5.** Structural characteristics of tetraphenylporphine and its β-ethyl derivatives.

| Compound                        | $\Delta 24$<br>/pm | $\Delta C_{\beta}$<br>/pm | $\Delta C_{\text{ms}}$<br>/pm | $\varphi_{\text{pyr}}$<br>/deg | $R$<br>/pm | $\Delta M$<br>/pm | Ref. |
|---------------------------------|--------------------|---------------------------|-------------------------------|--------------------------------|------------|-------------------|------|
| H <sub>2</sub> P (1) triclinic  | 5                  | 6                         | 4                             | 4.0                            | 206        | —                 | 2    |
| H <sub>2</sub> P (1) tetragonal | 19                 | 14                        | 38                            | 11.9                           | 205.4      | —                 | 1    |
| H <sub>2</sub> P (8)            | 10                 | 19                        | 5                             | 4.3                            | 206.4      | —                 | 47   |
| H <sub>2</sub> P (10)           | 29                 | 61                        | 4                             | 15.0                           | 205.7      | —                 | 47   |
| H <sub>2</sub> P (9)            | 38                 | 76                        | 12                            | 20.4                           | 207.0      | —                 | 47   |
| H <sub>2</sub> P (11)           | 46                 | 95                        | 6                             | 24.0                           | 204.9      | —                 | 47   |
| H <sub>2</sub> P (3)            | 54                 | 117                       | 3                             | 31.2                           | 205.1      | —                 | 15   |
| NiP (8)                         | 45                 | 82                        | 28                            | 21.0                           | 192.3(6)   | 0                 | 47   |
| NiP (10)                        | 39                 | 32                        | 79                            | 25.7                           | 189.3(6)   | 3                 | 47   |
|                                 | 46                 | 61                        | 68                            | 26.1                           | 189.3(6)   | 0                 | 47   |
| NiP (9)                         | 49                 | 89                        | 20                            | 20.8                           | 192.3(4)   | 1                 | 47   |
| Ni (11)                         | 53                 | 100                       | 16                            | 23.4                           | 192.1(3)   | 1                 | 47   |
| Ni (3)                          | 62                 | 125                       | 3                             | 29.4                           | 190.6(2)   | 1                 | 17   |
| Cu (1)                          | 21                 | 16                        | 42                            | 13.4                           | 198.1(7)   | 0                 | 5    |
| CuP (8)                         | 32                 | 58                        | 16                            | 13.9                           | 199.0(3)   | 5                 | 47   |
|                                 | 26                 | 52                        | 7                             | 12.2                           | 199.9(3)   | 2                 | 47   |
| CuP (10)                        | 40                 | 73                        | 23                            | 18.1                           | 198.4(4)   | 2                 | 47   |
| CuP (9)                         | 44                 | 83                        | 17                            | 19.8                           | 197.5(5)   | 2                 | 47   |
| CuP (11)                        | 49                 | 95                        | 13                            | 23.0                           | 198.0(5)   | 2                 | 47   |
| CuP (3)                         | 55                 | 113                       | 4                             | 27.4                           | 197.7(5)   | 0                 | 18   |
| ZnP (1) · H <sub>2</sub> O      | 1                  | 0                         | 0                             | 0                              | 205.0(3)   | 17                | 5    |
| ZnP (1) triclinic               | 5                  | 21                        | 15                            | 6.5                            | 203.7(3)   | 0                 | 5    |
| ZnP (8) · MeOH                  | 6                  | 12                        | 2                             | 3.1                            | 206.2(5)   | 21                | 47   |
| ZnP (8) · (β-pic) <sup>a</sup>  | 18                 | 25                        | 17                            | 9.3                            | 206.8(4)   | 32                | 47   |
| ZnP (10) · Py                   | 28                 | 54                        | 20                            | 15.0                           | 207.1(3)   | 31                | 47   |
| ZnP (9) · Py                    | 33                 | 63                        | 18                            | 16.9                           | 207.0(3)   | 32                | 47   |
| ZnP (11)                        | 45                 | 84                        | 12                            | 22.5                           | 202.8(4)   | 7                 | 47   |
| ZnP (11) · Py                   | 43                 | 89                        | 6                             | 22.4                           | 206.9(3)   | 35                | 47   |
| ZnP (3) · MeOH                  | 50                 | 109                       | 4                             | 28.4                           | 206.3(5)   | 22                | 19   |

<sup>a</sup> β-pic is β-picoline.**Figure 9.** Structures of ethyltetraphenylporphine derivatives: (a) H<sub>2</sub>P (8), (b) H<sub>2</sub>P (10), (c) H<sub>2</sub>P (9), (d) H<sub>2</sub>P (11), (e) H<sub>2</sub>P (3).<sup>47</sup>**Figure 10.** Deviation of the atoms (pm) from the mean plane of the macrocycle of Zn(Py)P (12).<sup>53,54</sup>

*meso*-tetraisopropylporphine manifests saddle-like distortion of the macrocycle.<sup>53</sup>

It is noteworthy that introduction of substituents into *meso*-positions brings about stronger deformation of the tetrapyrrole core of porphyrins in comparison with  $\beta$ -substitution.

### III. Physicochemical properties

Distortion of the planar structure of the tetrapyrrole core strongly affects the spectral characteristics of porphyrins. The  $^1\text{H}$  NMR spectra of octamethylporphine (**13**) and its *meso*-phenyl derivatives, *viz.*, 5-phenyl- (**14**), 5,15-diphenyl- (**15**), 5,10-diphenyl- (**16**), 5,10,15-triphenyl- (**17**) and 5,10,15,20-tetraphenyl-2,3,7,8,12,13,17,18-octamethylporphine (**4**), have been analysed.<sup>55</sup> Symmetrical compounds of this series have extremely low solubility in neutral and basic solvents; therefore, their  $^1\text{H}$  NMR spectra were recorded for solutions in deuteriochloroform with 0.5% trifluoroacetic acid. In this medium, porphyrins are easily soluble and exist in the protonated form.

As expected, the  $^1\text{H}$  NMR spectrum of porphyrin **13** contained only three singlet peaks corresponding to the protons in the *meso*-positions, of the methyl and NH groups (Table 6). The  $^1\text{H}$  NMR spectrum becomes more complicated on going to the monophenyl derivative **14** as can be evidenced from the splitting of the signals corresponding to the  $\beta$ -methyl groups and the appearance of peaks at  $\delta \sim 8$  corresponding to protons of the phenyl substituents. The results of MM calculations of the porphyrin **14** structure (Fig. 11) suggest that the methyl groups in positions 3 and 7 lie in the region of the anisotropic shielding by the ring current of the phenyl nucleus. The signals for the protons of these methyl groups at  $\delta \sim 2.3$  resonate and thus are upfield shifted by  $\sim 1.4$  ppm in comparison with the corresponding signals in the  $^1\text{H}$  NMR spectrum of octamethylporphine (**13**). The upfield shift of the signals by  $\sim 0.5$  ppm was also observed for the neighbouring 2,8-groups and even for the 12,18-methyl groups. Obviously, these shifts cannot be only due to the anisotropic effect of the ring

current of the phenyl residue. More probably, in this case two effects operate, *viz.*, the negative inductive effect of the phenyl group and the effect of deformation of the porphyrin macrocycle. Introduction of the phenyl group decreases the strength of the ring current owing to the porphyrin macrocycle as can be judged from the upfield shift of the signals for the *meso*-protons and the downfield shift of the central NH group protons. Both signals are split into two components, the splitting being large for the NH groups (by 1.2 ppm) and small for the *meso*-protons (by 0.13 ppm). Judging from the integral intensity, the signal at  $\delta$  10.37 corresponds to the hydrogen atom in position 15, whereas the signal at  $\delta$  10.50 corresponds to the protons at the C(10) and C(20) atoms. This suggests that the splitting is due to the negative inductive effect of the phenyl substituent.

MM calculations of two diphenyloctamethylporphine derivatives have shown that the tetrapyrrole core of the symmetrical isomer **15** is distorted to a much lesser degree than that of its 5,10-substituted analogue **16** (Fig. 12). The  $^1\text{H}$  NMR spectrum of porphyrin **15** (Table 6, Fig. 13a) contains one singlet for the protons of the NH groups ( $\delta -3.07$ ), two singlets for the methyl groups ( $\delta$  2.27 and 3.26), a multiplet for the *meta*- and *para*-protons of the phenyl substituents ( $\delta$  7.94–7.97), a doublet for the *ortho*-protons ( $\delta$  8.23) and a singlet for the *meso*-protons ( $\delta$  10.34). A comparison of average values of the chemical shifts of the *meso*-protons of monophenyl- (**14**) and 5,15-diphenyloctamethylporphine derivatives (**15**) revealed that the strength of the ring current induced by the aromatic macrocycle of diphenylporphyrin is reduced. A similar conclusion can be derived from a comparison of positions of the protons of the NH groups in the  $^1\text{H}$  NMR spectra of these porphyrins. Thus, introduction of the second phenyl substituent confers additional strain on the structure of the porphyrin macrocycle.

The  $^1\text{H}$  NMR spectrum of the non-symmetrical porphyrin **16** is even more complicated (see Table 6 and Fig. 13b). The protons of the central NH groups appear as three peaks at  $\delta -3.84$  (24-H),  $-2.23$  (21, 23-H) and  $-1.31$  (22-H); their assignment was based on the measurements of their integral intensities. The assignment of the protons of the methyl groups, which give four signals with the same integral intensities, was carried out taking account of the deshielding effect of the phenyl substituents on the neighbouring methyl groups:  $\delta$  1.81 — 7, 8-Me,  $\delta$  2.22 — 3, 12-Me,  $\delta$  3.23 — 2, 13-Me and  $\delta$  3.51 — 17, 18-Me. The *meso*-protons of the non-symmetrical porphyrin **16** resonate as a singlet at  $\delta$  9.99 and are shifted upfield in comparison with the symmetrical isomer **15**. At the same time, the protons of the NH groups of the porphyrin **16** are shifted downfield in comparison with compound **15**. The  $^1\text{H}$  NMR spectrum of the neutral form of compound **16** recorded

**Table 6.**  $^1\text{H}$  NMR spectra of octamethylporphine and its *meso*-phenyl derivatives in  $\text{CDCl}_3$  with 0.5%  $\text{CF}_3\text{CO}_2\text{H}$ .<sup>55</sup>

| Porphyrin | $\delta$       |                         |                                   |           |
|-----------|----------------|-------------------------|-----------------------------------|-----------|
|           | <i>meso</i> -H | Me                      | Ph                                | NH        |
| <b>13</b> | 10.45, s       | 3.70, s                 | —                                 | —4.45, s  |
| <b>14</b> | 10.50, s;      | 3.70, s (13, 17-Me);    | 8.22, m ( <i>o</i> -H);           | —2.99, s; |
|           | 10.37, s       | 3.26, s (2,8,12,18-Me); | 7.96, m ( <i>m</i> , <i>p</i> -H) | —4.21, s  |
| <b>15</b> | 10.34, s       | 2.27, s (3,7-Me)        | —                                 | —         |
| <b>16</b> | 9.99, s        | 3.26, s (2,8,12,18-Me); | 8.22, d ( <i>o</i> -H);           | —3.07, s  |
|           |                | 2.27, s (3,7,13,17-Me)  | 7.95, m ( <i>m</i> , <i>p</i> -H) | —         |
|           |                | 3.51, s (17,18-Me);     | 8.32, m ( <i>o</i> -H);           | —1.31, s; |
|           |                | 3.23, s (2,13-Me);      | 7.95, m ( <i>m</i> , <i>p</i> -H) | —2.23, s; |
| <b>17</b> | 9.79, s        | 2.22, s (3,12-Me);      | —                                 | —3.84, s  |
|           |                | 1.81, s (7,8-Me)        | —                                 | —         |
|           |                | 3.13, s (2,18-Me);      | 7.98, m ( <i>o</i> -H);           | —1.26, s; |
|           |                | 2.24, s (3,17-Me);      | 7.94, m ( <i>m</i> , <i>p</i> -H) | —2.47, s  |
| <b>4</b>  | —              | 1.84, s                 | —                                 | —         |
|           |                | (7,8,12,13-Me)          | —                                 | —         |
| <b>4</b>  | —              | 1.84, s                 | 8.35, m ( <i>o</i> -H);           | —1.14, s  |
|           |                | —                       | 7.93, m ( <i>m</i> , <i>p</i> -H) | —         |

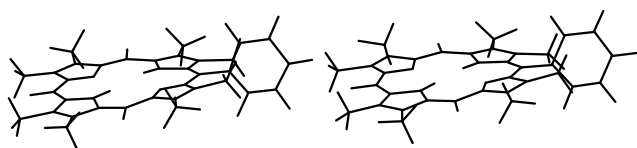


**Figure 11.** A stereo image of the structure of 5-phenyloctamethylporphine (**14**) optimised by the molecular mechanics method (force field MM+).<sup>55</sup>

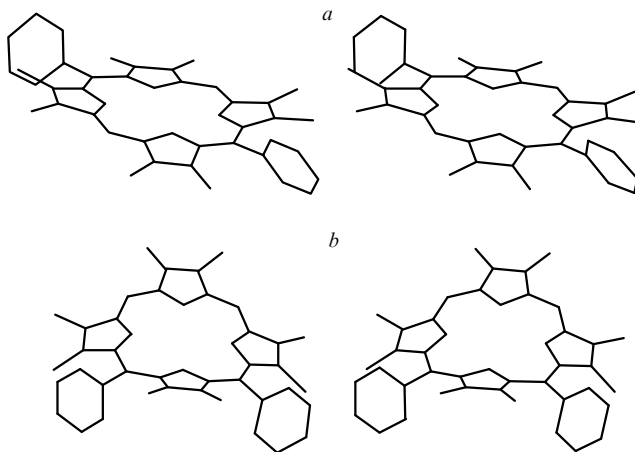


**Figure 12.** Stereo images of the structures of diphenyl derivatives of octamethylporphines **15** (a) and **16** (b) optimised by the molecular mechanics method.<sup>55</sup>

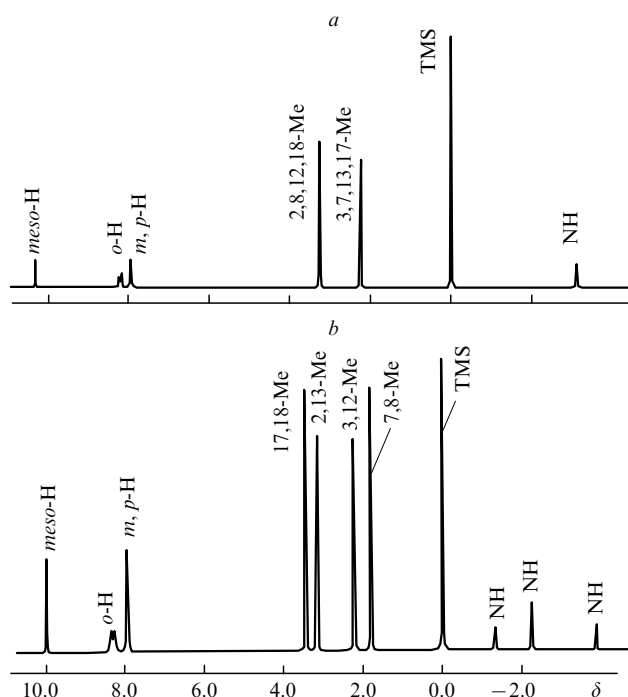


**Figure 13.**  $^1\text{H}$  NMR spectra of 5,15-diphenyl-2,3,7,8,12,13,17,18-octamethylporphyrine (a) and 5,10-diphenyl-2,3,7,8,12,13,17,18-octamethylporphyrine (b) in  $\text{CDCl}_3$  with 0.5%  $\text{CF}_3\text{CO}_2\text{H}$ .<sup>55</sup> TMS is tetramethylsilane.

in deuteriochloroform at room temperature differs from that of the protonated porphyrin in the absence of the signals for the protons of the NH groups. Apparently, these peaks can be detected at lower temperatures. Other characteristics of the  $^1\text{H}$  NMR spectra of protonated and non-protonated porphyrins are similar.

The  $^1\text{H}$  NMR spectrum of the neutral form of porphyrin **17**, like that of compound **16**, does not contain signals corresponding to the protons of the NH groups; the latter appear upon protonation of the porphyrin at  $\delta -2.47$  and  $-1.26$  (see Table 6 and Fig. 14). In the region of positive values of the chemical shifts, the  $^1\text{H}$  NMR spectra of the neutral and protonated forms are virtually the same. Upon protonation, the signals of the protons of the methyl groups are shifted downfield by 0.04–0.13 ppm, while those of the *meso*-protons are shifted by 0.2 ppm.

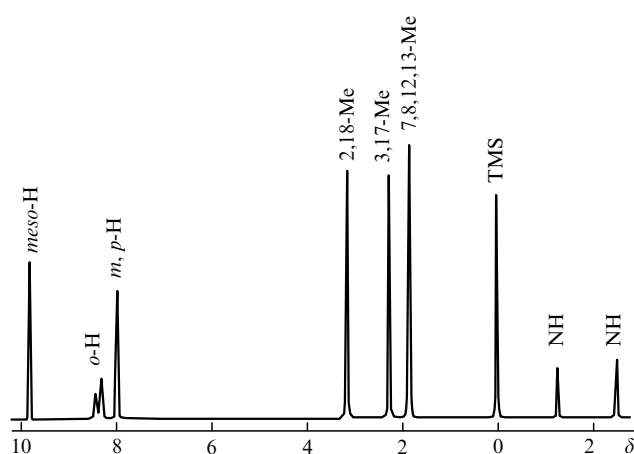


**Figure 14.**  $^1\text{H}$  NMR spectrum of 5,10,15-triphenyl- $\beta$ -octamethylporphyrine in  $\text{CDCl}_3$  with 0.5%  $\text{CF}_3\text{CO}_2\text{H}$ .<sup>55</sup>

Steric repulsion of the phenyl and methyl substituents in the porphyrin **4** results in the saddle-shaped conformation of the macrocycle. In its  $^1\text{H}$  NMR spectrum, this is manifested as a downfield shift of the signals for the protons corresponding to the NH groups and the appearance of a singlet at  $\delta -1.14$ . In addition, the  $^1\text{H}$  NMR spectrum of the porphyrin **4** contains a singlet corresponding to the protons of the methyl groups at  $\delta 1.84$  and two multiplets corresponding to the *ortho*- ( $\delta 8.35$ ), *meta*- and *para*-protons ( $\delta 7.93$ ).

Analysis of the data listed in Table 6 suggests that the signals for the protons of the NH groups are gradually shifted downfield with an increase in the number of the phenyl substituents in the *meso*-positions of octamethylporphyrine. The signals for the *meso*-proton are shifted in the opposite direction in the same series. This suggests that the strength of the ring current decreases, while the degree of distortion of the porphyrin macrocycle increases in the following series of substituted octamethylporphyrines: unsubstituted < 5-phenyl- < 5,15-diphenyl- < 5,10-diphenyl- < 5,10,15-triphenyl- < tetraphenyl-octamethylporphyrine.

A series of *meso*-phenyloctaethylporphyrine derivatives, viz., 5-phenyl- (**18**), 5,15-diphenyl- (**19**), 5,10-diphenyl- (**20**), 5,10,15-triphenyl- (**21**) and 5,10,15,20-tetraphenyl-2,3,7,8,12,13,17,18-octaethylporphyrine (**3**), have been investigated.<sup>56</sup> The structures of these porphyrins were calculated using the semiempirical quantum-chemical method (PM3).

The results of optimisation of the structure of the monophenyl octaethylporphyrine derivative (**18**) by molecular mechanics methods (force field MM+) and PM3 (Fig. 15) are qualitatively similar, although the MM method predicts a somewhat larger deformation of the planar structure of the macrocycle. What is essential, is that the introduction of even one aryl substituent in the *meso*-position of a  $\beta$ -octaalkylporphyrine results in the distortion of its planar structure. The results of calculations of the structures of *meso*-phenyloctaethylporphyrine derivatives are shown in Fig. 16; the  $^1\text{H}$  NMR spectra of porphyrins **3** and **18–21** are presented in Table 7.

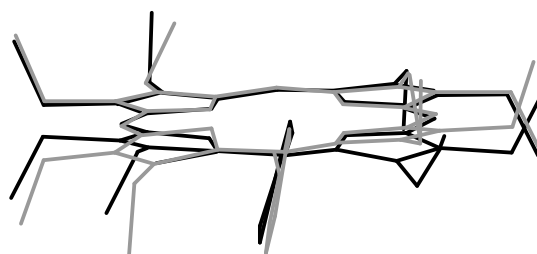


**Figure 15.** Structure of porphyrin **18** optimised using the MM (black coloured) and PM3 (grey coloured) methods.<sup>56</sup>

As expected, the simplest  $^1\text{H}$  NMR spectrum was observed for  $\beta$ -octaethylporphyrine (**2**). This contains four signals: a singlet for the *meso*-proton ( $\delta 10.10$ ), a quartet ( $\delta 4.11$ ) and a triplet ( $\delta 1.92$ ) corresponding to the protons of the methyl and methylene groups and a singlet ( $\delta -3.75$ ) corresponding to the protons of the NH groups.

Introduction of a phenyl group into the *meso*-position of the macrocycle results in the complication of the  $^1\text{H}$  NMR spectrum of the porphyrin **18** manifested in the appearance of additional signals for the protons of the phenyl substituent. Splitting of these signals is due to the anisotropic effect of the ring current of the macrocycle. The intensity of the magnetic field induced by this current diminishes the effect of an external magnetic field on the *ortho*-protons which are deshielded more strongly ( $\delta 8.21$ ) than the *meta*- and *para*-protons ( $\delta 7.66$  and  $7.79$ , respectively). The signals of the ethyl groups adjacent to the benzene ring form a separate group as a result of anisotropic shielding by the phenyl substituent and are shifted upfield ( $\delta 2.78$  and  $1.18$ ) in comparison with the more remote ethyl groups ( $\delta 4.12$  and  $1.89$ ). The signals



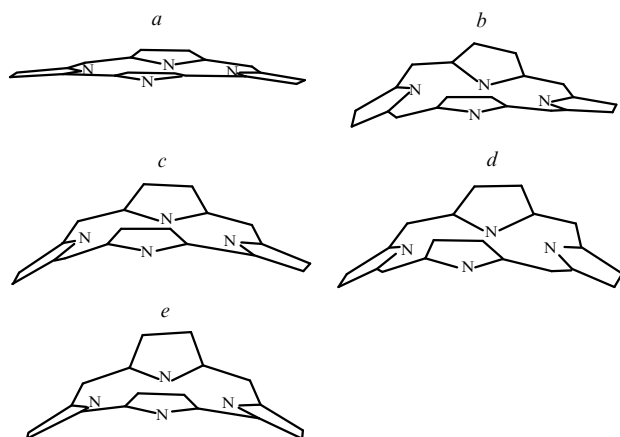


**Figure 16.** Structures of the tetrapyrrole cores of *meso*-phenyl derivatives of 2,3,7,8,12,13,17,18-octaethylporphyrin: H<sub>2</sub>P(**19**) (a), H<sub>2</sub>P(**20**) (b), H<sub>2</sub>P(**21**) (c), H<sub>2</sub>P(**3**) (d) and dodecaphenylporphyrine H<sub>2</sub>P(**7**) (e) calculated using the PM3 method.<sup>56</sup>

**Table 7.** <sup>1</sup>H NMR spectra of octaethylporphine, its *meso*-phenyl derivatives and dodecaphenylporphyrine in CDCl<sub>3</sub> (hexamethyldisilane as an internal standard).<sup>56</sup>

| Por-<br>phyr-<br>in | $\delta$             | <i>meso</i> -H    |                  | Et                                                                              | NH                    |
|---------------------|----------------------|-------------------|------------------|---------------------------------------------------------------------------------|-----------------------|
|                     |                      | Ph<br><i>o</i> -H | <i>m, p</i> -H   |                                                                                 |                       |
| <b>2</b>            | 10.10, s             | —                 | —                | 4.11, q; 1.92, t                                                                | −3.75, s              |
| <b>18</b>           | 10.18, s;<br>9.93, s | 8.21, d           | 7.79, d; 7.66, t | 4.12, q; 1.89, t;<br>2.78, q; 1.18, t                                           | −3.02, s;<br>−3.15, s |
| <b>19</b>           | 10.23, s             | 8.21, d           | 7.78, d; 7.67, t | 4.09, q; 1.89, t;<br>2.79, q; 1.18, t                                           | −2.08, s              |
| <b>20</b>           | 9.63, s              | 8.30, d           | 7.75, d; 7.67, t | 3.92, q; 1.80, t;<br>3.80, q; 1.57, t;<br>2.65, q; 0.63, t;<br>2.25, q; 0.44, t | −2.72,<br>br.s        |
| <b>21</b>           | 9.45, s              | 8.32, m           | 7.71, m          | 3.75, q; 1.56, t;<br>2.70, q; 0.72, t;<br>2.25, m; 0.46, t;<br>0.37, t          | −2.09, s              |
| <b>3</b>            | —                    | 8.36, m           | 7.71, m          | 2.52, br.s;<br>0.47, br.s                                                       | —                     |
| <b>7</b>            | —                    | 8.02, m; 7.06, m  | —                | —                                                                               | −0.85, s              |

of the protons in the *meso*-positions and in the NH groups are split into two components, *viz.*,  $\delta$  10.18, 9.93 and −3.02, −3.15, respectively. The fact that the signals of peripheral *meso*- and intracyclic NH group protons come closer suggests a decrease in the strength of the ring current of the macrocycle upon introduction of a *meso*-phenyl substituent into the octaethylporphine molecule.

Diphenyl- $\beta$ -octaethylporphine derivatives have a strongly distorted macrocycle, the distortion of the 5,15-substituted isomer **19** is much less pronounced than that of its non-symmetrical analogue **20** (see Fig. 16). The <sup>1</sup>H NMR spectra of these compounds manifest a downfield shift of the signals for the protons of the NH groups to  $\delta$  −2.08 (for the symmetrical isomer **19**) and to  $\delta$  −2.72 (for the 5,10-substituted analogue **20**). Special mention should be made of a significant broadening of the signals for the protons of the NH groups in the <sup>1</sup>H NMR spectrum of the porphyrin **20**.

The signals for the *meso*-protons of the porphyrin **19** are present at  $\delta$  10.23 and are slightly shifted downfield in comparison with the corresponding signals in the <sup>1</sup>H NMR spectrum of compound **18**. At the same time, the signals for the *meso*-protons

in the <sup>1</sup>H NMR spectrum of the porphyrin **20** are shifted noticeably upfield ( $\delta$  9.63).

The signals for the *meta*- and *para*-protons of the *meso*-phenyl groups in the <sup>1</sup>H NMR spectra of compounds **19** and **20** do not change their positions relative to the corresponding signals in the <sup>1</sup>H NMR spectrum of the porphyrin **18**. A noticeable shift of the signals for the *ortho*-protons of the phenyl groups of the non-symmetrical isomer **20** can be attributed to the effect of steric factors. The phenyl rings of the more strongly distorted porphyrin **20** cannot any longer be perpendicular to the plane of the macrocycle and are rotated relative to the framework of the molecule. As a result, the *ortho*-protons of the phenyl substituents that are close to the macrocycle are exposed to the stronger deshielding effect of the ring current of the porphyrin as a result of which their signals are shifted downfield ( $\delta$  8.30).

An analogous trend for the signals of the protons of the NH groups and the protons in the *meso*-positions to come closer to each other can also be traced in the <sup>1</sup>H NMR spectrum of triphenyloctaethylporphine **21**: the degree of the distortion of the macrocycle increases with an increase in the number of peripheral substituents.

The results of quantum-chemical calculations and <sup>1</sup>H NMR spectroscopic data suggest that dodecaphenylporphyrine (**7**) is distorted to the greatest extent. The protons of the NH groups in its <sup>1</sup>H NMR spectrum resonate in the lowest field, at  $\delta$  −0.85. The protons in the *meta*- and *para*-positions of the *meso*- and  $\beta$ -phenyl substituents are not resolved and appear as a multiplet at  $\delta$  6.69. The signals for the *ortho*-protons of the phenyl groups in the  $\beta$ -positions are observed at  $\delta$  7.06, while those in the *meso*-positions are observed at  $\delta$  8.02.

Analysis of <sup>1</sup>H NMR spectroscopic data revealed that the introduction of the phenyl substituents in the *meso*-positions of  $\beta$ -octaethylporphine causes distortion of the aromatic tetrapyrrole core which increases in the following order: **2** < **18** < **19** < **20** < **21** < **3** < **7**.

Porphyrins containing from 8 to 12 phenyl substituents have been synthesised and their <sup>1</sup>H NMR spectra have been analysed.<sup>31</sup> The strength of the ring current of the macrocycle decreases with an increase in the number of peripheral substituents (Table 8). One of two decaphenyl porphine derivatives, *viz.*, the non-symmetrical *cis*-isomer, manifests a higher degree of distortion than the 5,15-substituted *trans*-analogue.

**Table 8.** <sup>1</sup>H NMR spectra of phenyl-substituted porphyrins in CDCl<sub>3</sub> (TMS as an internal standard).<sup>31</sup>

| Porphyrin                                   | $\delta$ |                |
|---------------------------------------------|----------|----------------|
|                                             | NH       | <i>meso</i> -H |
| $\beta$ -Octakis(4-isopropylphenyl)porphine | −3.03    | 10.32          |
| <i>trans</i> -Decaphenylporphine            | −2.06    | 10.15          |
| <i>cis</i> -Decaphenylporphine              | −2.0     | 9.92           |
| Undecaphenylporphine                        | −1.10    | 9.63           |
| Dodecaphenylporphine                        | −0.90    | —              |

The dynamics of conformational changes in spatially distorted porphyrins in solution was monitored by following the temperature dependence in the <sup>1</sup>H NMR spectra.<sup>24, 25, 27, 57, 58</sup> At 298 K, dodecaphenylporphine (**7**) gives three low-field signals corresponding to the protons of the phenyl groups (Fig. 17). Splitting of two multiplet signals at  $\delta$  6.5–7 into two triplets is observed at temperatures below 253 K; the doublet at  $\delta$  ~7.6 corresponding to the *ortho*-protons of the *meso*-phenyl rings undergoes splitting at temperatures below 243 K. At 193 K, the <sup>1</sup>H NMR spectrum contains six doublets and nine triplets with the integral intensities of unity each. Similar temperature-dependent changes are observed in the <sup>1</sup>H NMR spectrum of the dication H<sub>4</sub>P (**7**)<sup>2+</sup>. An unusually broad range of chemical shifts of the signals for the *ortho*-protons of the  $\beta$ -phenyl rings of dodecaphenylporphine is observed.

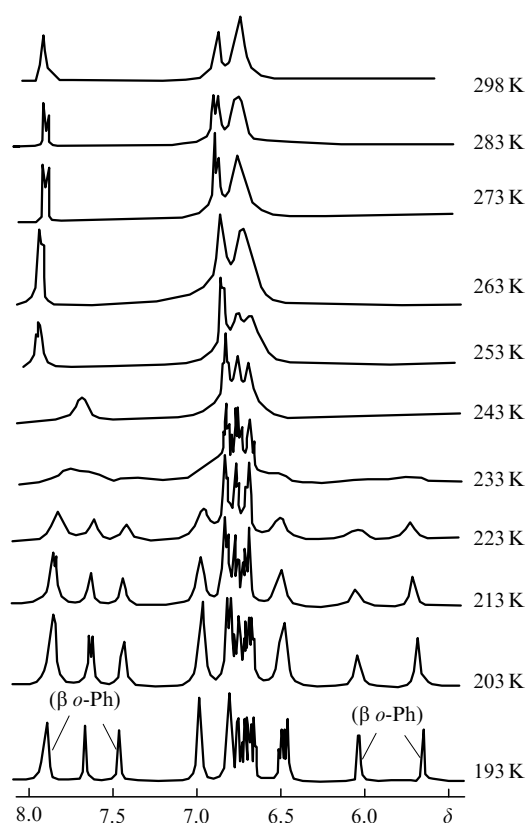


**Figure 17.** Temperature dependence of the  $^1\text{H}$  NMR spectrum of dodecaphenylporphyrine in  $\text{CD}_2\text{Cl}_2$ .<sup>25</sup>

nylporphyrine and its protonated form at low temperatures was attributed<sup>25</sup> to different positions of these protons relative to the macrocyclic core and, correspondingly, to different effects of the ring current on these protons. The *ortho*-protons of the  $\beta$ -phenyl group deviate from the mean plane of the porphyrin skeleton to a larger distance and are shielded to a lesser degree in comparison with aromatic ring protons less deviated from the plane.

Analysis of the temperature dependence of the  $^1\text{H}$  NMR spectrum of the porphyrin **7** revealed that its molecules take part in two dynamic processes. One of them is NH-tautomerism.<sup>58</sup> The value of the Gibbs activation energy,  $\Delta G^\ddagger$ , calculated for this reaction is  $54 \text{ kJ mol}^{-1}$  (see Ref. 25), *i.e.*, is commensurate with the corresponding values for planar tetraarylporphyrins.<sup>49</sup> The second dynamic process, which is more characteristic of distorted porphyrins,<sup>19,29</sup> entails inversion of the macrocycle. The  $\Delta G^\ddagger$  value of this process for the porphyrin **7** is  $\sim 46 \text{ kJ mol}^{-1}$  (see Ref. 25). Only one dynamic process, *viz.*, inversion of the macrocycle ( $\Delta G^\ddagger = 45.5 \text{ kJ mol}^{-1}$ ), is observed for the dication  $\text{H}_4\text{P}(\text{7})^{2+}$ . It is noteworthy, however, that no dynamic processes take place in the case of the nickel dodecaphenylporphyrine complex ( $\Delta G^\ddagger < 30 \text{ kJ mol}^{-1}$ ) despite the same degree of distortion of the molecule. Presumably, the barrier to inversion of the macrocycle

in the complex  $\text{NiP}(\text{7})$  is too low to be recorded. This is consistent with the data for nickel complexes of octamethyl-, octaethyl- and octapropyltetraphenylporphyrines where the barriers to inversion of the macrocycles are much lower than those in the corresponding free bases and their dications.<sup>24</sup>

Distortion of the porphyrin core also manifests itself in the Raman spectra.<sup>59–61</sup> The frequency range ( $1300–1700 \text{ cm}^{-1}$ ) of porphyrin complexes, which comprises a series of structure-sensitive ‘marker’ lines ( $\nu_2–\nu_4$ ) corresponding to the stretching of the  $\text{C}_\alpha–\text{N}$  ( $\nu_2$ ),  $\text{C}_\alpha–\text{C}_{ms}$  ( $\nu_3$ ) and  $\text{C}_\beta–\text{C}_\beta$  ( $\nu_4$ ) bonds, is the most interesting and informative one.<sup>61</sup> Analysis of a series of distorted nickel complexes of octaalkyltetraphenylporphyrines and planar complexes of octaalkylporphyrines has shown<sup>60</sup> that in the former case the ‘marker’ line frequencies in the Raman spectra increase with an increase in the size of the coordination cavity. Contrariwise, in the case of octaalkylporphyrine complexes an increase in the size of the coordination cavity results in a shift of the structure-sensitive lines  $\nu_2$ ,  $\nu_3$  and  $\nu_4$  towards the lower frequencies. Based on the data obtained, the lines  $\nu_2–\nu_4$  were termed as ‘core-size marker lines’. The Raman spectra of a series of distorted porphyrin **3** complexes with Ni, Co, Cu and Zn have been analysed.<sup>16</sup> A correlation between the size of the central cavity and the frequency of the bands  $\nu_2–\nu_4$  was opposite to the dependence established<sup>60</sup> for a series of nickel complexes of  $\beta$ -octaalkyl-*meso*-tetraphenylporphyrines. The size of the coordination cavity is determined by both the deviation of the porphyrin core from planarity as a result of introduction of peripheral substituents and the size of the metal cation; however, the contribution of each of these factors is different.

It was found<sup>16</sup> that the size of the central cavity is not a crucial factor in determining the position of the ‘marker’ lines. The angle  $\text{C}_\alpha–\text{N}–\text{C}_\alpha$  is yet another parameter that influences the frequency of these marker lines. The lines  $\nu_2$ ,  $\nu_3$  and  $\nu_4$  are always shifted towards the lower frequencies with an increase in the angle  $\text{C}_\alpha–\text{N}–\text{C}_\alpha$ . Apparently, the magnitude of this angle is closely related to the vibration frequencies of the bonds contributing to the ‘marker’ lines.

The frequencies of the ‘marker lines’ in solution and in the crystalline states differ insignificantly, which suggests the similarity of the conformations of the macrocycle both in solution and in the crystal (Table 9).

Distortion of the tetrapyrrole core is manifested specifically in the electronic absorption spectra. The electronic absorption spectra of some *meso*-phenyloctamethylporphyrine derivatives in acetic acid are shown in Fig. 18.<sup>55</sup> With an increase in the degree of distortion of the porphyrin macrocycle, all absorption bands manifest bathochromic shifts. These spectral changes are so characteristic that the red shift of all electronic absorption spectra bands can be reliably interpreted as the deformation of the tetrapyrrole macrocycle.<sup>8</sup>

The data from the electronic absorption spectra of octaethylporphyrine, its *meso*-phenyl derivatives and dodecaphenylporphyrine are listed in Table 10. As can be seen, the absorption maxima of the porphyrins are shifted regularly towards the red region with an increase in the degree of extraplanar distortion of the macrocycle irrespective of the solvent used. The reason for these spectral

**Table 9.** ‘Marker’ vibration frequencies of  $\beta$ -octaethyl-*meso*-tetraphenylporphyrine complexes (**3**) in  $\text{CS}_2$  and in the crystalline state.<sup>16</sup>

| Complex                 | $\nu_4/\text{cm}^{-1}$        |             | $\nu_3/\text{cm}^{-1}$        |             | $\nu_2/\text{cm}^{-1}$        |             | $\nu_\phi/\text{cm}^{-1}$     |             |
|-------------------------|-------------------------------|-------------|-------------------------------|-------------|-------------------------------|-------------|-------------------------------|-------------|
|                         | for solution in $\text{CS}_2$ | for crystal | for solution in $\text{CS}_2$ | for crystal | for solution in $\text{CS}_2$ | for crystal | for solution in $\text{CS}_2$ | for crystal |
| NiP ( <b>3</b> )        | 1360                          | 1360        | 1504                          | 1506        | 1563                          | 1565        | 1598                          | 1599        |
| CoP ( <b>3</b> )        | 1354                          | 1356        | 1500                          | 1506        | 1560                          | 1558        | 1597                          | 1599        |
| CuP ( <b>3</b> )        | 1354                          | 1356        | 1503                          | 1503        | 1556                          | 1557        | 1596                          | 1598        |
| ZnP ( <b>3</b> ) · MeOH | 1348                          | —           | 1495                          | —           | 1548                          | —           | 1594                          | —           |

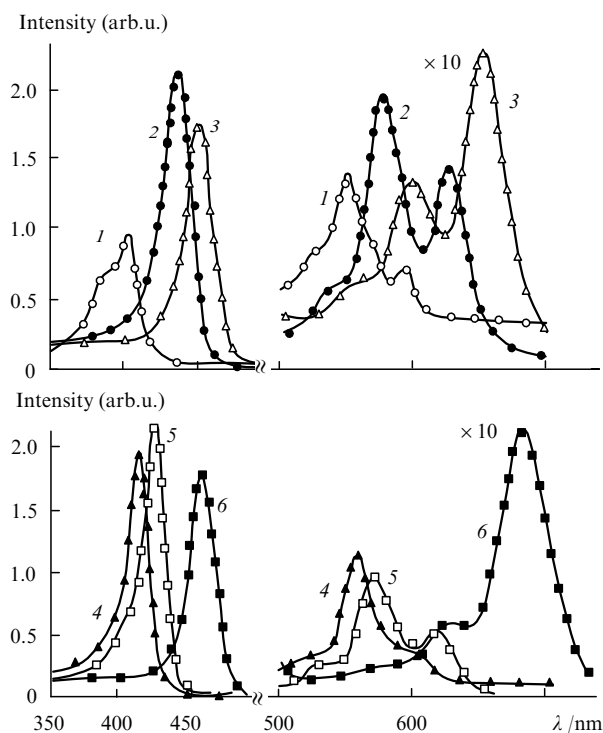


**Figure 18.** Electronic absorption spectra of  $\beta$ -octamethylporphyrine (**1**) and its *meso*-phenyl derivatives: 5,10-diphenyl- (**2**), 5,10,15-triphenyl- (**3**), 5-phenyl- (**4**), 5,15-diphenyl- (**5**) and 5,10,15,20-tetraphenyl-2,3,7,8,12,13,17,18-octamethylporphyrine (**6**) in acetic acid.<sup>55</sup> The intensities of the bands in the visible region of the spectrum are increased 10-fold.

changes is the deformation of the macrocycle, which reduces its aromaticity.

The ruffled and saddle conformations of zinc complexes of unsubstituted porphyrine (**22**) and *meso*-tetrakis(trifluoromethyl)porphyrine (**23**) were optimised using the density functional theory-

based analysis of configuration interaction calculations with single excitations (DFT/SCI).<sup>62,63</sup> An artificial distortion of the macrocycle of the zinc porphyrine complex was performed in order to prove the appearance of a bathochromic shift in the absorption spectra in the absence of electronic effects of substituents. The distorted skeleton of ZnP (**23**) with all the *meso*-CF<sub>3</sub> groups replaced by hydrogen atoms was used to derive a ruffled conformation of ZnP (**22**). A similar approach was used to derive a saddle conformation of ZnP (**22**) based on  $\beta$ -octamethyl-*meso*-tetraphenylporphyrine.

The results of DFT/SCI computations (Tables 11 and 12) provide an adequate description of excited states of different types of porphyrins.<sup>62,64,65</sup> As can be seen from Table 12, the *Q*-bands of the non-planar conformations of ZnP (**23**), *viz.*, the ruffled conformation at 582 nm and the saddle conformation at 576 nm, are shifted bathochromically relative to the *Q*-band of the planar conformation of ZnP (**22**) (by 24 and 18 nm, respectively), which is consistent with the experimental data.<sup>66,67</sup> The calculated data on simulated distortions of the ZnP (**22**) macrocycle also predicted a long-wavelength shift of the bands in the electronic adsorption spectra of the ruffled and saddle conformations (by 17 and 27 nm, respectively). The *B*-bands in all distorted porphyrins are shifted towards the red region, apparently as a result of destabilisation of their upper occupied orbitals.

Semiempirical quantum-chemical calculations of saddle, ruffled and dome-like conformations of a magnesium porphyrine complex<sup>68</sup> gave similar results, *viz.*, with an increase in the degree of distortion of the planar structure of the porphyrin core, all absorption bands manifested a bathochromic shift due to the advanced destabilisation of the HOMO.

The results of spectroelectrochemical<sup>69,70</sup> and electrochemical measurements<sup>70–75</sup> provide additional experimental evidence in favour of stronger destabilisation of the HOMO upon deformation of the macrocycle than the LUMO. The redox potentials of zinc complexes of tetrakis(pentafluorophenyl)porphyrine (**24**) and its octabromo- (**25**), octachloro- (**26**) and octamethyl- (**27**) derivatives are listed in Table 13. As can be seen, the octachloro and octabromo derivatives are reduced more easily (by 0.48 and 0.47 V, respectively) and are oxidised less easily (by 0.26 and 0.20 V, respectively) than the planar complex ZnP (**24**). Hence, the energy gap between the bonding and antibonding orbitals

**Table 10.** Electronic absorption spectra of octaethylporphyrine, its *meso*-phenyl derivatives and dodecaphenylporphyrine.<sup>56</sup>

| Porphyrin | Solvent                                   | Absorption band maxima $\lambda_{\max}$ /nm (log $\epsilon$ ) |            |            |            |            |
|-----------|-------------------------------------------|---------------------------------------------------------------|------------|------------|------------|------------|
|           |                                           | I                                                             | II         | III        | IV         | Soret      |
| <b>2</b>  | CHCl <sub>3</sub>                         | 620 (3.74)                                                    | 568 (3.86) | 535 (4.04) | 499 (4.15) | 400 (5.25) |
|           | pyridine                                  | 620                                                           | 567        | 531        | 497        | 389        |
|           | AcOH                                      | 592                                                           |            | 551        |            | 400        |
| <b>18</b> | CHCl <sub>3</sub>                         | 624 (3.54)                                                    | 573 (3.90) | 538 (3.97) | 505 (4.24) | 405 (5.31) |
|           | pyridine                                  | 626 sh                                                        | 572        | 535        | 502        | 405        |
|           | AcOH                                      |                                                               |            | 560        |            | 413        |
| <b>19</b> | CHCl <sub>3</sub>                         | 627 (3.30)                                                    | 575 (3.87) | 542 (3.76) | 508 (4.25) | 410 (5.35) |
|           | pyridine                                  | 627                                                           | 575        | 538        | 506        | 409        |
|           | AcOH                                      | 621                                                           |            | 574        |            | 430        |
| <b>20</b> | CHCl <sub>3</sub>                         | sh                                                            | 578 (3.89) | sh         | 510 (4.25) | 413 (5.39) |
|           | pyridine                                  | sh                                                            | 593        | sh         | 518        | 420        |
|           | AcOH                                      | 633                                                           |            | 583        |            | 437        |
| <b>21</b> | CHCl <sub>3</sub>                         | 667 (3.79)                                                    | 608 (3.91) | sh         | 534 (4.14) | 438 (5.28) |
|           | pyridine                                  | 679                                                           | 613        | 570        | 533        | 432        |
|           | AcOH                                      | 661                                                           |            | 608        |            | 456        |
| <b>3</b>  | CHCl <sub>3</sub> + 0.5% NEt <sub>3</sub> | 696 (3.75)                                                    | 598 (3.82) | sh         | 551 (4.14) | 452 (5.34) |
|           | pyridine                                  | 698                                                           | 592        | sh         | 548        | 456        |
|           | AcOH                                      | 688                                                           |            | 633        |            | 467        |
| <b>7</b>  | CHCl <sub>3</sub>                         | 717 (4.02)                                                    | —          | 612 (4.13) | 561 (4.17) | 465 (5.34) |
|           | pyridine                                  | 742                                                           | —          | 636        | 569        | 491        |
|           | AcOH                                      | 722                                                           |            | —          |            | 492        |

**Table 11.** Energies of highest occupied and lowest unoccupied molecular orbitals of porphyrin metallocomplexes.<sup>64</sup>

| Complex (symmetry)           | Energy of orbitals /eV |                 |                 |                    |                    |                               |
|------------------------------|------------------------|-----------------|-----------------|--------------------|--------------------|-------------------------------|
|                              | LUMO + 2               | LUMO + 1        | LUMO            | HOMO               | HOMO – 1           | HOMO – 2                      |
| ZnP (22) ( $D_{4h}$ )        | –0.73 ( $a_{1u}$ )     | –2.31 ( $e_g$ ) | –2.31 ( $e_g$ ) | –5.33 ( $a_{2u}$ ) | –5.39 ( $a_{1u}$ ) | –6.59 ( $a_{1g}$ )            |
| ZnP (22) (ruffled $D_{2h}$ ) | –0.81 ( $a_1$ )        | –2.33 ( $e$ )   | –2.33 ( $e$ )   | –5.30 ( $b_2$ )    | –5.34 ( $b_1$ )    | –6.51 ( $nb_1$ ) <sup>a</sup> |
| ZnP (23) (ruffled $D_{2h}$ ) | –1.93 ( $a_1$ )        | –3.45 ( $e$ )   | –3.45 ( $e$ )   | –6.23 ( $b_1$ )    | –6.52 ( $b_2$ )    | –7.47 ( $nb_1$ ) <sup>a</sup> |
| ZnP (22) (saddle $D_{2h}$ )  | –0.85 ( $a_1$ )        | –2.35 ( $e$ )   | –2.35 ( $e$ )   | –5.26 ( $b_2$ )    | –5.34 ( $b_1$ )    | –6.68 ( $nb_2$ ) <sup>a</sup> |
| ZnP (23) (saddle $C_{2v}$ )  | –1.86 ( $a_1$ )        | –3.31 ( $b_2$ ) | –3.43 ( $b_1$ ) | –6.22 ( $a_2$ )    | –6.53 ( $a_1$ )    | –7.48 ( $na_1$ ) <sup>a</sup> |

<sup>a</sup>  $n$  is the second highest occupied molecular orbital of the given symmetry.

**Table 12.** Symmetry ( $S$ ) and energies ( $\Delta E$ ) of transitions and oscillator strengths ( $f$ ) of model metalloporphyrins.<sup>62, 65</sup>

| Complex, conformation | Absorption bands | $S$   | $\Delta E$ /eV<br>( $\lambda$ /nm) | $f$   | Main contributions   |                      |                                 |                                  |
|-----------------------|------------------|-------|------------------------------------|-------|----------------------|----------------------|---------------------------------|----------------------------------|
| ZnP (22)              | $Q$              | $E_u$ | 2.22 (558)                         | 0.002 | 50% ( $a_{2u}-e_g$ ) | 49% ( $a_{1u}-e_g$ ) |                                 |                                  |
|                       | $B$              | $E_u$ | 3.92 (316)                         | 1.729 | 38% ( $a_{2u}-e_g$ ) | 42% ( $a_{1u}-e_g$ ) |                                 |                                  |
| ZnP (22), ruffled     | $Q$              | $E$   | 2.16 (575)                         | 0.003 | 49% ( $b_2-e$ )      | 50% ( $b_1-e$ )      |                                 |                                  |
|                       | $B$              | $E$   | 3.82 (325)                         | 0.821 | 20% ( $b_2-e$ )      | 21% ( $b_1-e$ )      | 51% ( $nb_1-e$ ) <sup>a</sup>   |                                  |
| ZnP (23), ruffled     | $Q$              | $E$   | 2.13 (582)                         | 0.012 | 44% ( $b_2-e$ )      | 54% ( $b_1-e$ )      |                                 |                                  |
|                       | $B$              | $E$   | 3.72 (333)                         | 0.223 | 6% ( $b_2-e$ )       | 5% ( $b_1-e$ )       | 85% ( $nb_1-e$ ) <sup>a</sup>   |                                  |
| ZnP (22), saddle      | $Q$              | $E$   | 2.12 (585)                         | 0.002 | 50% ( $b_1-e$ )      | 49% ( $b_2-e$ )      |                                 |                                  |
|                       | $B$              | $E$   | 3.74 (332)                         | 1.403 | 51% ( $b_1-e$ )      | 48% ( $b_2-e$ )      |                                 |                                  |
| ZnP (23), saddle      | $Q_x$            | $B_2$ | 2.14 (578)                         | 0.013 | 44% ( $a_1-b_2$ )    | 55% ( $a_2-b_1$ )    |                                 |                                  |
|                       | $Q_y$            | $B_1$ | 2.15 (576)                         | 0.012 | 54% ( $a_2-b_2$ )    | 44% ( $a_1-b_1$ )    |                                 |                                  |
|                       | $B_y$            | $B_1$ | 3.78 (328)                         | 1.164 | 27% ( $a_2-b_2$ )    | 29% ( $a_1-b_1$ )    | 16% ( $na_1-b_1$ ) <sup>a</sup> | 14% ( $2na_1-b_1$ ) <sup>a</sup> |
|                       | $B_x$            | $B_2$ | 3.79 (327)                         | 1.370 | 31% ( $a_1-b_2$ )    | 35% ( $a_2-b_1$ )    | 14% ( $na_1-b_2$ ) <sup>a</sup> | 10% ( $2na_1-b_2$ ) <sup>a</sup> |
|                       |                  |       |                                    |       |                      |                      |                                 |                                  |

<sup>a</sup>  $n$  and  $2n$  are the second and third highest occupied molecular orbitals of the given symmetry.

**Table 13.** Redox potentials of zinc complexes of porphyrins (V).<sup>69, 70</sup>

| Complex  | $E_{2+/0}^\circ$ | $E_{2+/1+}^\circ$ | $E_{1+/0}^\circ$ | $E_{0/1-}^\circ$ | $E_{1-/2-}^\circ$ |
|----------|------------------|-------------------|------------------|------------------|-------------------|
| ZnP (1)  | —                | 1.16              | 0.80             | –1.33            | –1.66             |
| ZnP (24) | —                | 1.58              | 1.37             | –0.95            | –1.37             |
| ZnP (25) | 1.55             | 1.53              | 1.57             | –0.48            | –0.76             |
| ZnP (26) | 1.60             | 1.57              | 1.63             | –0.47            | –0.75             |
| ZnP (27) | 0.98             | 0.99              | 0.97             | –1.14            | –1.52             |

**Note.** The potentials were measured using a reference chloride electrode in 1.0 M KCl;  $E_{Fc1+/0} = 0.48$  V; 0.1 M  $[NBu_4]^+ [PF_6]^- / CH_2Cl_2$ .

diminishes upon distortion of the porphyrin macrocycle. When analysing the data presented in Table 13, account must be taken of the fact that, unlike the phenyl groups, pentafluorophenyl substituents and halogen atoms possess electron-withdrawing properties and thus make a greater contribution to the stabilisation of the HOMO and LUMO of ZnP (25) and ZnP (26) complexes in comparison with ZnP (24).

Zinc complexes of 2,3,12,13-tetrasubstituted 5,10,15,20-tetra-phenylporphyrins, which contain trifluoromethyl (28) and methyl (29) substituents and bromine atoms (30), have been synthesised.<sup>75</sup> The structures of the complexes (as crystal solvates) of ZnP (28)·(EtOH)<sub>3</sub>, ZnP (29)·(THF)<sub>1.6</sub>·(CHCl<sub>3</sub>)<sub>0.4</sub> and ZnP (30)·MeOH·DMF have been established. Their macrocycles have a saddle, slightly ruffled conformation; the structure of the porphyrin containing trifluoromethyl groups is deformed to the greatest extent (Fig. 19). Presumably, this deformation is due to the square-pyramidal coordination of the zinc cation rather than to the steric repulsion of the peripheral substituents. These structural data can be correlated to spectral and electrochemical characteristics.

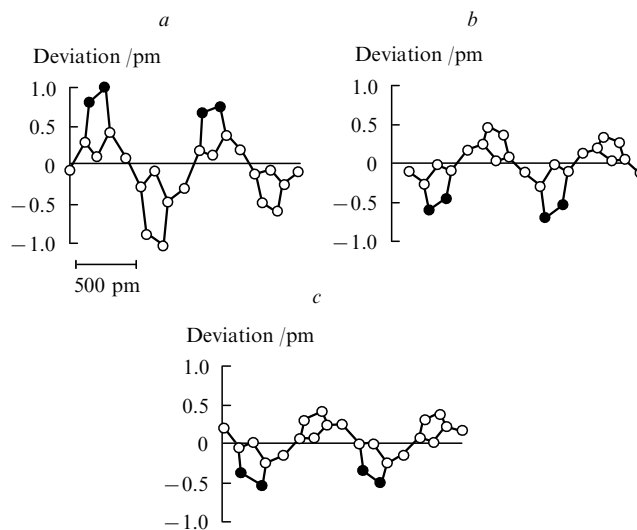


**Figure 19.** Deviations of the atoms in the macrocycles of zinc complexes of porphyrins 28 (a), 29 (b) and 30 (c) from the mean plane passing through four nitrogen atoms.<sup>75</sup> The positions of the substituents are coloured black.

All absorption bands in the electronic spectrum of ZnP (28) are shifted bathochromically in comparison with the electronic spectra of ZnP (29) and ZnP (30) (Fig. 20). Cyclic voltammetric studies of the redox properties of zinc complexes of porphyrins (28–30) revealed that their oxidation and reduction potentials increase with an enhancement of the electron-withdrawing properties of the substituents, these dependences being nearly linear for the oxidation and S-shaped for the reduction (Fig. 21). The

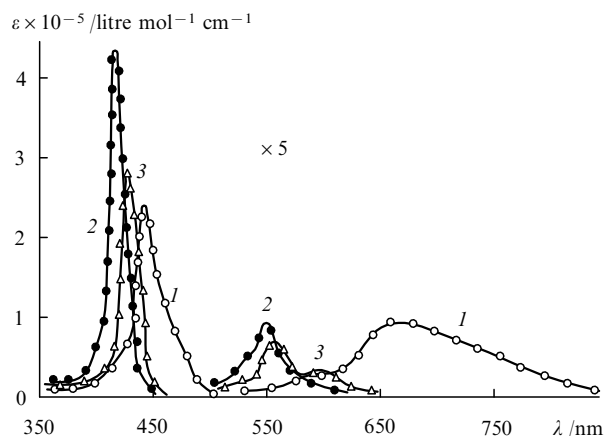


**Figure 20.** Electronic absorption spectra of zinc complexes of 2,3,12,13-tetrasubstituted derivatives of tetraphenylporphine ZnP (**28**) (**1**), ZnP (**29**) (**2**) and ZnP (**30**) (**3**) in  $\text{C}_2\text{H}_4\text{Cl}_2$ . The intensities of the bands in the visible region of the spectrum are increased 5-fold.<sup>75</sup>

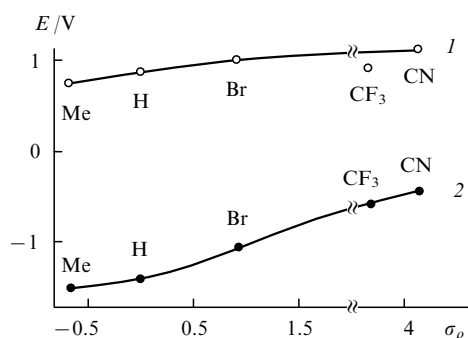


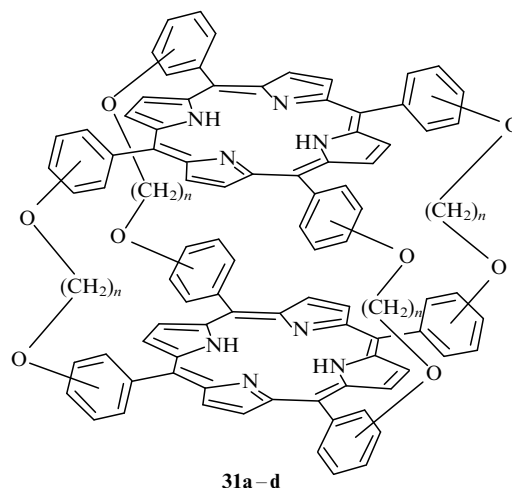
**Figure 21.** Dependences of the first oxidation (**1**) and reduction (**2**) potentials of zinc complexes of tetrasubstituted tetraphenylporphine derivatives measured in  $\text{C}_2\text{H}_4\text{Cl}_2$  vs. a saturated calomel electrode on the values of the Hammett constants  $\sigma_p$  of substituents.<sup>75</sup>

difference between the oxidation and reduction potentials decreases with an enhancement of the electron-withdrawing properties of the substituents, the destabilisation of the HOMO being greater than that of the LUMO. The difference between the orbital energies for ZnP (**1**) is 2.2 V, whereas that for its trifluoromethyl derivative is as small as 1.5 V. Thus, the energies of the MO of porphyrins and their redox characteristics strongly depend on spatial distortion of their central core and the electronic nature of substituents.

#### IV. Coordination properties

The effect of the distortion of the planar structure of a macrocycle on the coordination properties of porphyrins was observed for *N*-substituted derivatives.<sup>76</sup> However, one can hardly distinguish structural changes in the coordination centre of the macrocycle due to substitution from the distortion of the macrocycle itself. The effect of distortion as such on the coordination properties was established in the analysis of the dimeric tetraphenylporphine derivatives **31a–d** where the monomeric fragments are linked through benzene nuclei by four bridges of the type  $\text{O}(\text{CH}_2)_n\text{O}$ ,  $n = 2–4$ .<sup>77–83</sup>

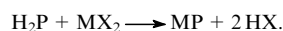
For steric reasons, all C–C bonds of the bridging groups of the cyclophane dimer **31a** cannot adopt *trans*-configurations. The energy required for transition from the transoid configuration of one of these bonds to the gauche configuration is less than 4 kJ mol<sup>−1</sup>. The overall change in the configuration of one bond



*m*-bridge,  $n = 4$  (**a**), *m*-bridge,  $n = 3$  (**b**), *m*-bridge,  $n = 2$  (**c**), *o*-bridge,  $n = 3$  (**d**).

in each of the four bridges suffices for the disturbance of the planar structure of the tetrapyrrole cores in the dimer **31a**.<sup>77</sup> Studies on the kinetics of formation and dissociation of complexes of the dimers **31a–d** containing bridging groups of various lengths have shown<sup>78–83</sup> that the reactivities of these porphyrins increase by a factor of tens of thousands as a result of spatial distortion of their macrocycles. Considering that the acid–base and coordination properties of porphyrins are closely interrelated,<sup>90</sup> it is not surprising that spatially distorted porphyrins significantly exceed their planar counterparts in basicities.<sup>84–89</sup> Stretching and polarisation of the N–H bonds in the transition state of a reacting system ‘a metal solvatocomplex–porphyrin’ make a significant contribution to the energy of complex formation. At the same time, strong interactions of metal cations with tertiary nitrogen atoms of porphyrin occur in the transition state, which decrease both the energy of the transition state and the activation energy of the reaction. Thus, an increase in the electron density on the nitrogen atoms not only provides easier access to them due to the deformation of the macrocycle, but also increases appreciably the rate of formation of metalloporphyrins. This is confirmed by kinetic data on coordination of octamethylporphine, octaethylporphine and their phenyl derivatives by copper and zinc ions in pyridine and DMF (Tables 14 and 15).

The equation of complexation can be presented as follows:



The kinetic order of this reaction with respect to porphyrin for all the porphyrins described in this review is equal to unity. With respect to metal salts, the situation is more complicated, *viz.*, the kinetic order of the reaction depends on the degree of ionisation of the solvatocomplex in solution.<sup>91</sup>

The data presented in Tables 14 and 15 suggest that the complexation rates of phenyl derivatives of octamethyl- and octaethylporphine in pyridine and DMF increase with an increase in the number of peripheral substituents, 5,10-diphenyl derivatives reacting at much faster rates than their 5,15-substituted analogues. The reaction rate increases 3–4 orders of magnitude, while the activation energy decreases 2–2.5-fold on going from planar octaalkylporphines to the most deformed tetraphenyl derivatives. Introduction of eight  $\beta$ -alkyl substituents on going from porphine to etioporphyrin and of four *meso*-phenyl groups on going from porphine to tetraphenylporphine causes only a 7-fold increase in the complexation rate. In other words, the drastic increase in the complexation rates resulting from the introduction of *meso*-aryl substituents into  $\beta$ -octaalkylporphines

**Table 14.** Rate ( $k$ ), energy of activation ( $E$ ) and changes in the entropy of activation ( $\Delta S^\ddagger$ ) of the coordination of octamethylporphine (**13**) and its phenyl derivatives by copper and zinc ions in pyridine.<sup>55</sup>

| Porphyrin | Copper acetate                                                                     |                           |                                                 | Zinc acetate                                                      |                           |                                                 |
|-----------|------------------------------------------------------------------------------------|---------------------------|-------------------------------------------------|-------------------------------------------------------------------|---------------------------|-------------------------------------------------|
|           | $k^{298} \times 10^4$<br>/litre <sup>0.4</sup> mol <sup>-0.4</sup> s <sup>-1</sup> | $E$ /kJ mol <sup>-1</sup> | $\Delta S^\ddagger$<br>/J (mol K) <sup>-1</sup> | $k^{328} \times 10^4$<br>/litre mol <sup>-1</sup> s <sup>-1</sup> | $E$ /kJ mol <sup>-1</sup> | $\Delta S^\ddagger$<br>/J (mol K) <sup>-1</sup> |
| <b>13</b> | 0.01                                                                               | 153.9 ± 0.7               | 148 ± 2                                         | 20.2 ± 0.4                                                        | 102.8 ± 1.0               | 9 ± 3                                           |
| <b>14</b> | 0.31                                                                               | 93.4 ± 0.3                | -25 ± 1                                         | 31.7 ± 0.8                                                        | 70.6 ± 0.7                | -86 ± 2                                         |
| <b>15</b> | 5.46                                                                               | 85.1 ± 0.6                | -30 ± 2                                         | 40.9 ± 0.1                                                        | 64.2 ± 0.5                | -103 ± 2                                        |
| <b>16</b> | 10.1 ± 0.1                                                                         | 85.0 ± 1.1                | -25 ± 4                                         | 754 ± 1.5                                                         | 56.6 ± 1.7                | -101 ± 5                                        |
| <b>17</b> | 105 ± 2                                                                            | 77.3 ± 0.9                | -31 ± 3                                         | 2860 ± 3                                                          | 54.6 ± 0.4                | -97 ± 1                                         |
| <b>4</b>  | 116 ± 1                                                                            | 67.9 ± 1.4                | -70 ± 4                                         | 37310 ± 13                                                        | 47.0 ± 0.9                | -118 ± 3                                        |

**Table 15.** Kinetic parameters of coordination of octaethylporphine (**2**), its phenyl derivatives and dodecaphenylporphine (**7**) by copper ions upon treatment with copper(II) acetate in DMF and pyridine.<sup>56</sup>

| Porphyrin | Pyridine                                                                                 |                           |                                              | DMF                                                                                      |                           |                                                 |
|-----------|------------------------------------------------------------------------------------------|---------------------------|----------------------------------------------|------------------------------------------------------------------------------------------|---------------------------|-------------------------------------------------|
|           | $k_{1.4}^{298} \times 10^4$<br>/litre <sup>0.4</sup> mol <sup>-0.4</sup> s <sup>-1</sup> | $E$ /kJ mol <sup>-1</sup> | $\Delta S^\ddagger$ /J (mol K) <sup>-1</sup> | $k_{n+1}^{328} \times 10^4$<br>/litre <sup>0.5</sup> mol <sup>-0.5</sup> s <sup>-1</sup> | $E$ /kJ mol <sup>-1</sup> | $\Delta S^\ddagger$<br>/J (mol K) <sup>-1</sup> |
| <b>2</b>  | very slow                                                                                |                           |                                              | 34 ± 2                                                                                   | 95 ± 1                    | 19 ± 3                                          |
| <b>18</b> | 0.46 ± 0.02                                                                              | 68 ± 1                    | -108 ± 3                                     | 452 ± 40                                                                                 | 88 ± 1                    | 17 ± 3                                          |
| <b>19</b> | 0.29 ± 0.01                                                                              | 103 ± 2                   | 6 ± 5                                        | 248 ± 10                                                                                 | 57 ± 2                    | -92 ± 5                                         |
| <b>20</b> | 7.14 ± 0.2                                                                               | 94.2 ± 0.2                | 3 ± 5                                        | —                                                                                        | —                         | —                                               |
| <b>21</b> | 38.71 ± 0.6                                                                              | 96 ± 0.8                  | 23.1 ± 4                                     | —                                                                                        | —                         | —                                               |
| <b>3</b>  | 1502 ± 40                                                                                | 61 ± 1                    | -64 ± 3                                      | 5657 ± 200                                                                               | 28 ± 1                    | -164 ± 3                                        |
| <b>7</b>  | 919 ± 20                                                                                 | 21 ± 1                    | -202 ± 3                                     | very fast                                                                                |                           |                                                 |

cannot be due to the electronic effects of the substituents alone and is caused primarily by the changes in the geometry of the porphyrin molecules. Additional evidence in favour of this idea comes from the changes [more than 100 J (mol K)<sup>-1</sup>] in the entropy of activation of the complexation for the porphyrins under study. These structural changes influence indirectly the electronic structure of the macrocycle by decreasing its aromaticity and increasing the electron density on the nitrogen atoms in the coordination centres of porphyrins.

The changes in the reactivities of phenyl-substituted  $\beta$ -octaalkylporphyrins in acetic acid are different in principle (Tables 16 and 17). With an increase in the number of phenyl substituents, the rate of complex formation decreases  $\sim 10^4$ -fold. In acetic acid, no dodecaphenylporphine complexes are formed at all. The activation energy of this reaction increases threefold on going from octaalkylporphyrins to their tetraphenyl derivatives, whereas the changes in the entropy of activation exceed 100 J (mol K)<sup>-1</sup>. This can be attributed to the fact that the basicities of porphyrins increase with the degree of distortion of the tetrapyrrole macrocycles as a result of which tertiary nitrogen atoms acquire an ability to form more stable hydrogen bonds with acetic acid molecules blocking the coordination centre. Thus, the dicationic

form generated by dodecaphenylporphine in acetic acid is inert with respect to coordination by transition metal ions.

The dissociation kinetics of copper(II), cobalt(II) and manganese(III) complexes with spatially distorted porphyrins in mixtures of acetic and trifluoroacetic acids has been studied (Table 18).<sup>56,92,93</sup> The kinetic order of this reaction with respect to metalloporphyrin and trifluoroacetic acid is equal to unity, which suggests a two-step dissociation mechanism<sup>94</sup> according to which the first M–N bond of the metalloporphyrin is cleaved under the action of a strong proton donor, *e.g.*, MeCO<sub>2</sub>H<sub>2</sub><sup>+</sup>, formed upon protonation of the oxygen atom of acetic acid, while the second bond is cleaved by a relatively weak acetic acid present in the system in a large excess. This activation barrier is overcome upon cleavage of the second M–N bond.

As can be seen from Table 18, the dissociation rates of copper and cobalt complexes of porphyrins increase, while the energies of activation decrease with an increase in the degree of distortion of the aromatic tetrapyrrole core. Introduction of the first two *meso*-phenyl substituents affects the kinetic parameters of this reaction to a far lesser degree than the introduction of the next two substituents. Dodecaphenylporphine complexes dissociate upon dissolution in acetic acid in the absence of sulfuric or trifluoro-

**Table 16.** Kinetic parameters of coordination of octamethylporphine and its phenyl derivatives by copper and zinc ions in acetic acid.<sup>55</sup>

| Porphyrin | Copper acetate                                                                     |                           |                                                 | Zinc acetate                                                      |                           |                                                 |
|-----------|------------------------------------------------------------------------------------|---------------------------|-------------------------------------------------|-------------------------------------------------------------------|---------------------------|-------------------------------------------------|
|           | $k^{298} \times 10^4$<br>/litre <sup>0.5</sup> mol <sup>-0.5</sup> s <sup>-1</sup> | $E$ /kJ mol <sup>-1</sup> | $\Delta S^\ddagger$<br>/J (mol K) <sup>-1</sup> | $k^{328} \times 10^4$<br>/litre mol <sup>-1</sup> s <sup>-1</sup> | $E$ /kJ mol <sup>-1</sup> | $\Delta S^\ddagger$<br>/J (mol K) <sup>-1</sup> |
| <b>13</b> | 3676 ± 4                                                                           | 28.3 ± 1.1                | -166 ± 3                                        | 280 ± 1                                                           | 39.2 ± 0.9                | -163 ± 3                                        |
| <b>14</b> | 578 ± 1                                                                            | 55.3 ± 0.8                | -91 ± 3                                         | 102 ± 1                                                           | 45.7 ± 0.6                | -152 ± 2                                        |
| <b>15</b> | 470 ± 1                                                                            | 71.2 ± 1.1                | -39 ± 4                                         | 71.0 ± 0.1                                                        | 70.9 ± 0.1                | -77.8 ± 0.3                                     |
| <b>16</b> | 8 ± 1                                                                              | 72.4 ± 1.6                | -36 ± 5                                         | 60.0 ± 0.1                                                        | 78.8 ± 0.7                | 55 ± 2                                          |
| <b>17</b> | 5.70 ± 0.02                                                                        | 76.8 ± 0.7                | -57 ± 2                                         | very slow                                                         |                           |                                                 |
|           | 0.34 ± 0.01                                                                        | 111.6 ± 0.6               | 36 ± 2                                          | no reaction                                                       |                           |                                                 |

**Table 17.** Kinetic parameters of coordination of  $\beta$ -octaethylporphine, its *meso*-phenyl derivatives and dodecaphenylporphine by copper ions upon treatment with copper(II) acetate in acetic acid.<sup>92</sup>

| Porphyrin | $k_{1.5}^{298}$<br>/litre mol <sup>-1</sup> s <sup>-1</sup> | $E$ /kJ mol <sup>-1</sup> | $\Delta S^\ddagger$<br>/J (mol K) <sup>-1</sup> |
|-----------|-------------------------------------------------------------|---------------------------|-------------------------------------------------|
| <b>2</b>  | 1.66 ± 0.03                                                 | 31.2 ± 0.3                | -144 ± 1                                        |
| <b>18</b> | 0.53 ± 0.01                                                 | 73.0 ± 0.4                | -13.3 ± 1.5                                     |
| <b>19</b> | 0.180 ± 0.005                                               | 65 ± 2                    | -49.1 ± 2                                       |
| <b>3</b>  | 0.00021 ± 0.00001                                           | 44.4 ± 1                  | -174 ± 2                                        |
| <b>7</b>  | complex is not formed                                       |                           |                                                 |

**Table 18.** Kinetic parameters of dissociation of copper, cobalt and manganese complexes of octaethylporphine and its *meso*-phenyl derivatives in acetic acid with 0.069 M CF<sub>3</sub>CO<sub>2</sub>H.<sup>56,93</sup>

| Complex           | $k^{298} \times 10^4$<br>/litre mol <sup>-1</sup> s <sup>-1</sup> | $E$ /kJ mol <sup>-1</sup> | $\Delta S^\ddagger$<br>/J (mol K) <sup>-1</sup> |
|-------------------|-------------------------------------------------------------------|---------------------------|-------------------------------------------------|
| CuP ( <b>2</b> )  | 0.668                                                             | 99.3 ± 0.5                | 0.5 ± 1.5                                       |
| CuP ( <b>18</b> ) | 1.24                                                              | 81.8 ± 0.7                | -53 ± 2                                         |
| CuP ( <b>19</b> ) | 2.27                                                              | 61.3 ± 0.6                | -117 ± 2                                        |
| CuP ( <b>3</b> )  | 1030                                                              | 46.3 ± 1                  | -140 ± 3                                        |
| CoP ( <b>2</b> )  | 0.787                                                             | 69.5 ± 0.7                | -98 ± 2                                         |
| CoP ( <b>18</b> ) | 5.43                                                              | 57.7 ± 1.3                | -122 ± 4                                        |
| CoP ( <b>19</b> ) | 14.5                                                              | 46.6 ± 0.4                | -151 ± 2                                        |
| CoP ( <b>3</b> )  | 954                                                               | 15.7 ± 0.7                | -220 ± 2                                        |
| MnP ( <b>2</b> )  | —                                                                 | —                         | —                                               |
| MnP ( <b>18</b> ) | 0.0249                                                            | 26.9 ± 0.6                | -270 ± 5                                        |
| MnP ( <b>19</b> ) | 0.480                                                             | 27.4 ± 0.3                | -244 ± 6                                        |
| MnP ( <b>3</b> )  | 8.01                                                              | 38.5 ± 0.3                | -183 ± 3                                        |

acetic acid. Apparently, the greater the distortion of the starting porphyrin the stronger are the strains of the coordination bonds M–N and the higher is the effective negative charge on the nitrogen atoms exposed to the electrophilic attack by the solvated proton.

The entropies of activation of the dissociation of copper and cobalt porphyrin complexes decrease regularly with an increase in the number of phenyl substituents, which suggests an increase in the degree of ordering of the ‘metalloporphyrin – solvated proton’ system in the transition state. The energies and entropies of the activation in the dissociation of cobalt complexes are significantly lower in comparison with the copper analogues. This correlates with the properties of Cu(II) and Co(II) cations: the formation of square-planar complexes is more characteristic of the former, whereas the latter largely produce octahedral complexes. Obviously, in the transition state the cobalt cation leaving the coordination centre of the porphyrin is solvated more efficiently than the copper cation.

Porphyrin complexes with Mn(III) are more stable than those with Co(II) and Cu(II) and their dissociation rates are two orders of magnitude lower under comparable conditions (see Table 18). However, the character of changes in the dissociation rates depending on the degree of deformation of the porphyrin ligands is the same: on going from octaethylporphine to the tetraphenyl derivative, the dissociation rate constants of the manganese complex increase by three orders of magnitude in a mixture of acetic and trifluoroacetic acids and 60-fold in a mixture of acetic and sulfuric acids. In these media, the manganese complex of dodecaphenylporphine dissociates at immeasurably fast rates.

Studies of axial coordination of piperidine and 1-methylimidazole by zinc complexes of spatially distorted porphyrins (Table 19) have demonstrated that stabilities of these complexes decrease regularly with an increase in the number of peripheral substituents.<sup>95</sup> This supports again an assumption that the deformation of cores in polysubstituted porphyrins decreases the aromaticity of the macrocycle and increases the negative charge

**Table 19.** Stability constants of axial complexes of zinc porphyrinates with piperidine and 1-methylimidazole in benzene at 298 K.<sup>95</sup>

| Metallo-porphyrin | $K \times 10^{-2}$ /litre mol <sup>-1</sup><br>for the complex<br>with piperidine | for the complex<br>with 1-methylimidazole |
|-------------------|-----------------------------------------------------------------------------------|-------------------------------------------|
| ZnP ( <b>1</b> )  | 198 ± 3                                                                           | 223 ± 5                                   |
| ZnP ( <b>2</b> )  | 125 ± 2                                                                           | 147 ± 6                                   |
| ZnP ( <b>18</b> ) | 81 ± 2                                                                            | 79 ± 1                                    |
| ZnP ( <b>19</b> ) | 47 ± 9                                                                            | 53 ± 2                                    |
| ZnP ( <b>20</b> ) | 48 ± 5                                                                            | 48 ± 7                                    |
| ZnP ( <b>21</b> ) | 37 ± 9                                                                            | 38 ± 9                                    |
| ZnP ( <b>3</b> )  | 24 ± 5                                                                            | 25 ± 2                                    |

on the nitrogen atom which causes a decrease in the effective positive charge on the coordinating metal cation in the metalloporphyrins.

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# The shape memory effect in polymers

V A Beloshenko, V N Varyukhin, Yu V Voznyak

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**Abstract.** The review concerns the state-of-the-art in the field of investigations of the shape memory effect in various polymeric materials, namely, homopolymers, copolymers, polymer blends, filled polymer composites and polymer gels. New theoretical approaches to the description and practical applications of the shape memory effect are discussed. The bibliography includes 205 references.

## I. Introduction

Many polymers are used as structural materials for the production of various items and equipment.<sup>1–3</sup> Such materials must exhibit certain mechanical properties and operating characteristics and their production must be simple and cost-efficient. Another group of materials comprises the so-called functional polymeric materials. The function and field of application of such materials are mainly determined by the specific and sometimes unique properties they possess. Typical representatives of this class of compounds are polymers and polymer composites that possess the ability to recover their shape.

The ‘shape memory effect’ (SME) is characteristic of not only polymers. Initially, the term ‘SME’ was mainly used for metal alloys. In the case of high-molecular-mass compounds, the term ‘thermal shrinkage’ was often used because most studies on the problem were concerned with shape recovery features of stretched samples.

In this review we consider the behaviour of polymers deformed in various manners by applying a tensile, compression or shear deformation; therefore, the use of the term ‘SME’ seems to be appropriate. This effect manifests itself in a complete or partial recovery of the initial size of samples of simple geometrical shape exposed to external action. However, in some cases (if, *e.g.*, the shape variation obeys a ‘rod–helix–rod’ pattern) it is more appropriate to place the emphasis on the shape.

Pioneering communications on the SME in metal alloys and polymers were reported nearly five decades ago. Recently, numerous monographs concerning the SME in metallic materials have been published.<sup>4–10</sup> At the same time there are quite a few monographs or reviews on the shape memory effect in polymers and the results reported are mainly concerned with the behaviour of oriented synthetic fibres.<sup>11–14</sup> A detailed review<sup>15</sup> published in 1992 was also incomprehensive because the authors restricted themselves to coverage of some fundamental problems of thermal shrinkage of oriented homopolymers. That review included no data on more complex polymer systems and contained little information on applied studies and almost no information on investigations carried out by Russian researchers.

Since then there has been a considerable amount of literature on the SME in polymers. The subjects were the development of theoretical concepts of the mechanisms of thermally stimulated strain recovery; new approaches to the description of the deformation and relaxation behaviour of polymers; new information on the shape recovery features of deformed samples; and results of investigations of synthetic polymeric materials possessing unusual properties. Because research in the field covers a wide variety of aspects of the title problem, here we first of all tried to highlight the key recent advances and provide information on modern investigation avenues and practical applications of the SME.

According to Irie,<sup>16</sup> the SME in polymeric materials can be realised in three ways. The first way involves the formation of a shaped sample from melt. If necessary, cross-links can be formed by adding cross-linking agents or by irradiating the sample. Then, the sample is deformed at a temperature similar to the glass transition temperature,  $T_g$ , or the melting point,  $T_m$ , and cooled in order to retain the deformed state. Shape recovery is attained by heating the sample above  $T_g$  or to  $T_m$ . The second way involves a photochemically or electrochemically induced reversible change in the shape of the polymer sample. The third way involves a shape change induced by chemical reactions. In the objects considered in this review the SME occurs following the first way, *i.e.*, on heating. The mechanism and specific features of this kind of SME are to a great extent determined by the nature (structure and morphology) of the polymer.

## II. Glassy polymers

Shape recovery of deformed polymers originates from the system’s ‘quest’ for thermodynamic equilibrium, which is determined by the minimum value of the corresponding thermodynamic potential (*i.e.*, the difference between the internal energy and the

V A Beloshenko, V N Varyukhin, Yu V Voznyak A A Galkin Donetsk Physics and Technology Institute, National Academy of Sciences of Ukraine, ul. R Luxemburg 72, 83114 Donetsk, Ukraine.  
Fax (38-062) 337 90 18, tel. (38-062) 337 93 30,  
e-mail: bel@hpress.dipt.donetsk.ua (V A Beloshenko),  
tel. (38-062) 255 05 18, e-mail: var@hpress.dipt.donetsk.ua  
(V N Varyukhin), tel. (38-062) 334 86 95 (Yu V Voznyak)

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entropy of the components of the macromolecules in the polymer system). Strain-induced orientation of polymer chains causes the entropy of the system to decrease. Therefore, shape stability of a strained polymer would depend on the change in the internal energy. If the internal energy decreases on deformation and compensates the decrease in entropy, a stable structure is formed. This situation can be realised in crystallisable polymers where bonding between polymer chains is strong enough. In glassy polymers, the strain-induced nonequilibrium state is retained only after cooling below  $T_g$ . Because these differences to a great extent determine the laws of manifestation of the SME in the materials mentioned above, they deserve a separate consideration.

Without dwelling on details of macroscopic manifestation of the SME in glassy polymers (most of them have been reviewed<sup>15</sup>), we will point out the most characteristic features. Oriented glassy polymer samples (at least those having a simple shape) completely recover their initial size after heating to the glass transition temperature. The process begins at  $T < T_g$  and its rate and degree of shape recovery increase as the temperature increases.

By fixing the ends of a deformed sample and measuring mechanical stress developed during the constrained recovery it is possible to study the early stages of recovery, characterised by small variation of the size. Typical temperature dependences of shrinkage stress for polycarbonate (PC) oriented by stretching at room temperature with heating at a constant rate are shown in Fig. 1. For an unannealed PC sample, the shrinkage stress  $\sigma_s$  begins to increase at a temperature that is slightly higher than the stretching temperature, reaches a maximum at  $T < T_g$  and decreases down to zero as the temperature approaches  $T_g$ . Heating of an annealed PC sample to a temperature below the annealing temperature causes the shrinkage to virtually disappear. The position of the maximum in the  $\sigma_s(T)$  plot is shifted towards higher temperatures and its height decreases. At the same time the zero  $\sigma_s$  value is achieved under the same conditions as in the case of the unannealed sample, i.e., near  $T_g$ .

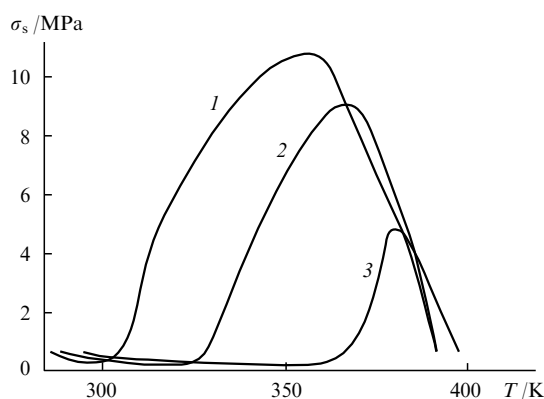


**Figure 1.** Isometric heating curves for PC.<sup>17</sup> Unannealed sample (1) and samples annealed at 348 (2) and 398 K (3).

If a sample with fixed ends is kept at a temperature that is higher than the deformation temperature but much lower than  $T_g$ , an induction period is observed (Fig. 2).<sup>18</sup> Duration of the induction period depends on the test temperature and sample prehistory and can vary by one or even two orders of magnitude. It is believed<sup>18</sup> that the phenomenon can be explained by a high degree of localisation of thermally stimulated molecular shrinkage in certain regions of the amorphous polymer. Activated molecular segments 'try' to shorten the distances between their ends; however, ambient macromolecules preclude shrinkage. Shrinkage forces developed in activated segments are responsible for compression stress in the vicinity of these segments. Therefore, further thermal activation of macromolecules will most probably be followed by shrinkage in the compressed regions. The higher the

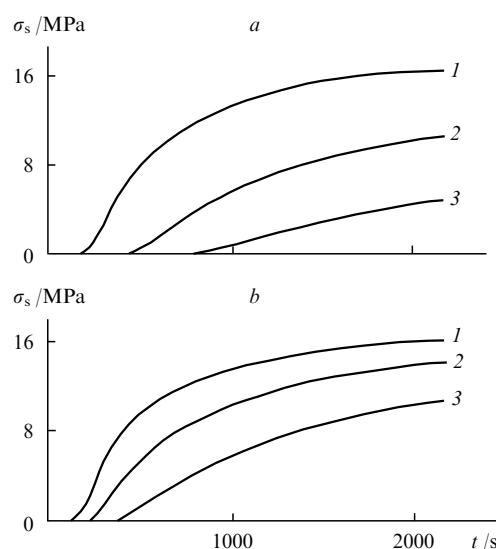


**Figure 2.** Shrinkage stress plotted vs. time for PC.<sup>18</sup> (a) Measured at 323 (1), 328 (2) and 333 K (3) 14 days after deformation; (b) measured at 328 K 2 (1), 5 (2) and 14 days (3) after deformation.

degree of thermal activation, the shorter the induction period. At the same time if the activation energy is insufficiently high, local stress can relax owing to chain slip and thus lead to a decrease in the local orientation without corresponding spatial changes.

Shape recovery of glassy polymers is usually described using simplified phenomenological models. Some of them were considered in detail in a review.<sup>15</sup> Such models are usually based on the concept of one or more energy barriers separating different states of the condensed system. The barriers are treated as hindrances to mobile fragments in the bulk of glassy polymer. In particular, a model involving two energy states of a polymer segment was proposed.<sup>19, 20</sup> It was assumed<sup>19, 20</sup> that any molecular chain in an oriented polymer comprises submolecules that can be in the compressed (a) or stretched (b) states separated by an energy barrier. Assuming a constant number of submolecules in the chain, the relative shrinkage of a model macromolecule induced by temperature variation can be related to the population of states. Transitions between the states are described by the following equation

$$\frac{dn}{dt} = (1 - n_b)k_b - n_b k_a, \quad (1)$$

where  $n_b$  is the population of the state  $b$  and  $k_a$  and  $k_b$  are the rates of transitions to the states  $a$  and  $b$ , respectively,

$$k_a = A \exp\left(-\frac{\Delta E + M}{RT}\right), \quad (2)$$

$$k_b = A \exp\left(-\frac{\Delta E + \varepsilon - M}{RT}\right). \quad (3)$$

Here  $A$  is a constant,  $\Delta E$  is the activation energy for shrinkage,  $M$  is the energy associated with possible application of external stress and  $\varepsilon$  is the energy difference between the states.

Using Eqn (1), it is possible to calculate the temporal or temperature dependences of the populations of states and thus establish the corresponding dependence of thermal shrinkage of the model sample. The results obtained using the two-state model are in qualitative agreement with experimental data.<sup>21</sup> However, the model also has significant drawbacks, e.g., it can not predict the onset of shrinkage forces at the ends of the sample in the isometric heating experiments, because no interaction between submolecules is assumed.

According to Trznadel and Kryszewski,<sup>15</sup> a comprehensive rheological model of thermal shrinkage of oriented glassy polymers must account for:

- the possibility of relaxation of molecular orientation by thermally activated transitions,
- the possibility of propagation of local changes throughout the sample owing to the presence of an elastic physical network and
- the possibility of relaxation of the local stress as a result of intermolecular slip.

The four-state<sup>17,22</sup> and multi-state<sup>23,24</sup> mechanical models are successfully used for calculating the temporal and temperature dependences and for providing an explanation for the appearance of the induction period. The local relaxation can be best predicted at low temperatures, *i.e.*, in the absence of large structural changes. At the same time these models are too simple to describe the shrinkage process over a wide temperature region.

Yang and Sun<sup>25</sup> proposed a model based on the theory of conformational elasticity of molecular chains,<sup>26–29</sup> which allows a chain conformation distribution to be obtained with realistic information on the molecules. The model was used to analyse the experimental results of the SME studies in amorphous poly(ethylene terephthalate) (PETP).<sup>26,27</sup> A relation was established between the local structure of PETP and the structure of the entire system. The ensemble-averaged fraction of a local conformation is given by<sup>25</sup>

$$\langle X_s(r) \rangle = [Z_s(r)]^{-1} \int_r^{R_{\max}} \int_{E_{\min}}^{E_{\max}} P(R, E) X e^{-E/kT} dR dE, \quad (4)$$

where  $X$  is the fraction of the *trans*-conformation of  $\text{OCH}_2-\text{CH}_2\text{O}$  (ethylene glycol residue);  $Z_s(r)$  is the partial distribution function of the system that is locally extended by the distance  $r$ ;  $P(R, E)$  is the chain conformation distribution function and  $R$  and  $E$  are respectively the chain conformation length and energy.

It was established that dependence (4) fits experimental data well. It was shown that the deformation (extension) and shape recovery of cold drawn glassy polymers are different. The extension process involves at least two stages, *viz.*, the yield and molecular coil extension. The third stage, slip, can occur if a certain critical point is reached (in the case under study, at elongations greater than a value of 2.3). The shape recovery process involves a stage characterising the dependence of size on the chain conformation. This fact is explained by differences between the strain and shape recovery rates that are responsible for bringing the molecular chain conformations either closer to or farther apart from the state of thermodynamic equilibrium.

The examples given above show that the thermally stimulated strain recovery mechanism underlying the SME in glassy polymers is rather complicated. It involves the relaxation of the segmental orientation and the molecular chain orientation. These processes were studied<sup>30</sup> in order to establish the differences between the relaxation mechanisms of the local and total molecular orientation taking PC stretched at  $T > T_g$  as an example. The degree of segmental orientation was estimated by IR dichroism using function

$$f = \frac{(R_0 + 2)(R - 1)}{(R_0 - 1)(R + 2)}, \quad (5)$$

where  $R_0$  is the dichroic ratio for the perfectly oriented polymer. The degree of the molecular chain extension was determined as follows

$$\lambda = \frac{L_d}{L_s}, \quad (6)$$

where  $L_d$  is the length of the undeformed sample and  $L_s$  is the length of the shrunken sample.

It should be noted that conditions necessary for attainment of high segmental orientation are in contrast to those which lead to a

high molecular chain extension. In the first case, rapid stretching at temperatures close to the glass transition temperature are needed. In the second case slow stretching and high temperatures are required. With allowance for this, samples deformed at different temperatures and loads were studied.

The relaxation dynamics of segmental orientation and molecular orientation as functions of the deformation temperature  $T_d$  and tensile load  $F$  can be followed using the data shown in Figs 3 and 4. The temperatures of deformation and subsequent heating

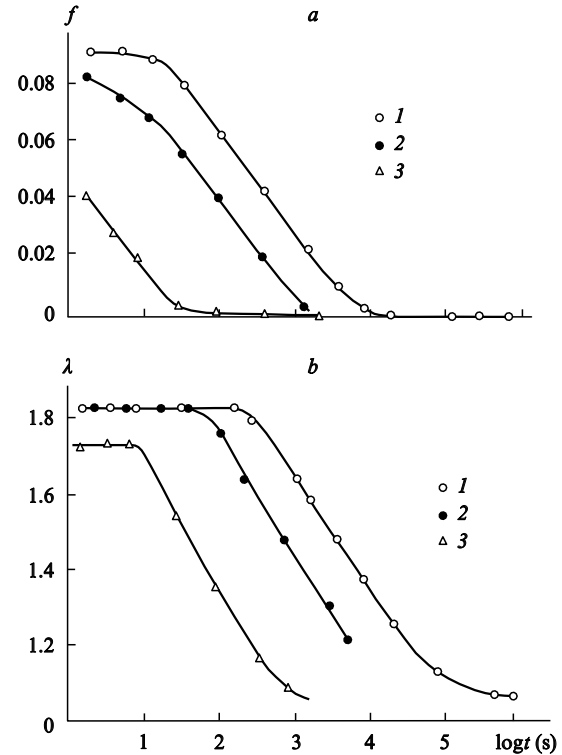


**Figure 3.** Relaxation of segmental orientation (a) and molecular orientation (b) in PC plotted vs. time at different deformation temperatures.<sup>30</sup>  $T_d/\text{K}$ : 426 (1), 433 (2) and 443 (3).

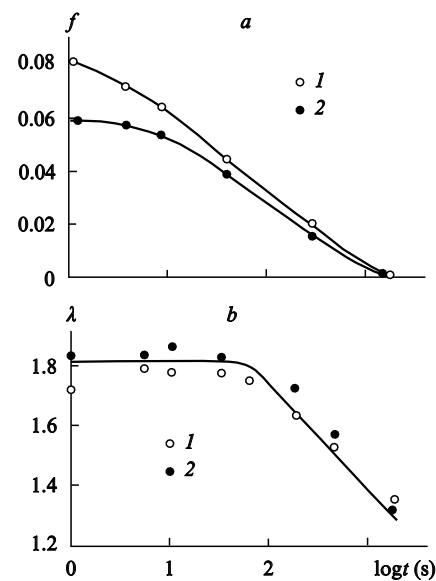


**Figure 4.** Relaxation of segmental orientation (a) and molecular orientation (b) in PC plotted vs. time at different loads.<sup>30</sup>  $F/\text{N}$ : 574 (1) and 846 (2).

were equal. As can be seen, the degree of segmental orientation and the average relaxation time of segmental orientation decrease as the temperature increases (see Fig. 3 *a*). Strain rate (dead load) affects the initial degree of segmental orientation; however, the relaxation time is independent of the strain rate (see Fig. 4 *a*). The character of the relaxation of molecular orientation differs from that described above, namely, an induction period is observed in all  $\lambda(\log t)$  plots obtained under the same pre-stretching conditions at all temperatures (see Fig. 3 *b*). The higher the temperature, the shorter the induction period. No effect of the strain rate was observed for the dead load interval studied in this work (see Fig. 4 *b*).

Comparison of the plots constructed in the coordinates  $f(\lambda)$  allowed the ratio of the contributions of the segmental orientation and molecular orientation at various heating temperatures and loads to be analysed. It was concluded<sup>30</sup> that in a certain temperature interval an almost total relaxation of segmental orientation can occur without any relaxation of molecular orientation. The samples deformed at a higher rate are characterised by a greater loss of segmental orientation during the time before the start of relaxation of molecular orientation.

The character of the relaxation processes investigated was established based on correlations between  $f$  and  $\lambda$ . If the molecular orientation remains unchanged while segmental orientation decreases, the relaxation mechanism is local in character. Its kinetics are independent of the location of the segments along the chain and the process corresponds to a Rouse relaxation between two entanglements.<sup>31</sup> The relaxation of molecular orientation requires large-scale motions which are hindered by surrounding chains. This relaxation corresponds to a contraction inside the tube and to reptation. The results obtained in the study<sup>30</sup> are in good agreement with the assumption<sup>32</sup> that the macromolecule can lose its dichroism owing to local restructuring. They are also consistent with the results obtained by Brown and Windel<sup>33</sup> who found that the molecular orientation is more sensitive to the recovery process than the total deformation.

As a rule, the SME in amorphous polymers occurs without considerable variation of the volume. But if the starting material is characterised by an optimum porosity, shape recovery accompanied by an increase in volume can occur under certain deformation conditions. This is the case in a study<sup>34</sup> where a porous structure was formed in poly(vinyl chloride) (PVC) by dehydrochlorination of PVC powder at 503 K. Compact cylindrical samples of the dehydrochlorinated and cross-linked (in HCl) polymer were then compression deformed in a cylindrical cell of the same diameter. Heating of the samples obtained to  $T \geq T_g$  was accompanied by uniaxial volume recovery due to elongation of the samples. The effect was most pronounced at a degree of dehydrochlorination,  $x$ , of 12.9%.

Structural relaxation was described<sup>34</sup> in the framework of the two-state model. A number of parameters, in particular, the activation energy, population in the equilibrium state and empirical constants, were obtained for various  $x$ . Unfortunately, the authors did not discuss microscopic aspects of the SME in the objects under study. Considerable attention was paid to this subject in studies<sup>35,36</sup> on the mechanism of plastic deformation of glassy polymers. Two stages of shape recovery in polymer glasses were established. These are the low-temperature recovery (LTR) below  $T_g$  and the high-temperature recovery (HTR) at  $T_g$ . The temperature dependences of the residual strain recovery rates  $\dot{\epsilon}_{\text{res}}$  of uniaxially compressed amorphous PETP samples at  $T < T_g$  are shown in Fig. 5. Both stages are clearly seen. Analogous dependences were also established for other amorphous polymers.<sup>37,38</sup> It was shown<sup>35</sup> that the LTR dominates in the early stage of deformation. At high degrees of deformation, the contribution of the HTR to the overall process is much larger than that of the LTR. The contribution of the LTR increases as the deformation temperature decreases; the LTR process always begins near the deformation temperature, whereas the HTR peak lies at  $T_g$ .

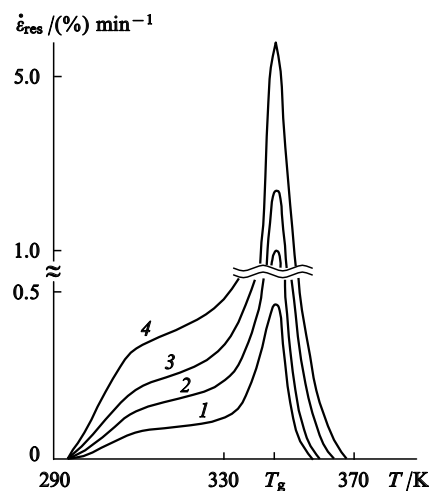


**Figure 5.** Temperature dependences of the residual strain recovery rates for PETP.<sup>35</sup>

$\epsilon_{\text{res}}$  (%): 1.5 (1), 4.5 (2), 7.5 (3) and 14.5 (4).

These and other physical processes accompanying deformation of polymer glasses are explained using the concept of shear defects (SD).<sup>35</sup> Each SD bears a local residual shear strain and corresponding local excess internal energy. Similarly to the total excess internal energy, the total macroscopic residual strain of a sample is the sum of all elementary local energies or strains. An elementary act of a deformation process involves initiation and development of an SD. Heating of a deformed sample to  $T < T_g$  is accompanied by removal of those SD that are associated with the low-temperature stage of recovery and has no effect on the processes responsible for the HTR. Redeformation of the sample causes no increase in the HTR peak until the fraction of the SD-induced deformation reaches again a certain critical value. In other words, the SD can exist in the absence of the processes that initiate the HTR, but not otherwise. The HTR peaks appear during the annealing (at  $T > T_g$ ) of new conformational structures that were formed in the development of SD. These peaks are always preceded by the appearance of the LTR peaks.

Based on the results of studies on the features of the deformation behaviour of glassy polymers, a concept was proposed,<sup>36</sup> according to which the total inelastic deformation and steady-state plastic flow occur in the polymer structure saturated with small-scale plastic shear transformations (PST) rather than the initial polymer structure. In the former case we deal with an excited and therefore metastable structure and corresponding relaxation processes are closely related to the initiation and loss of PST. The appearance of the LTR peak is due to accumulation of PST, which leads to the total residual strain recovery below  $T_g$ . In the plot of the temperature dependence of  $\dot{\epsilon}_{\text{res}}$  the area under the LTR peak is a measure of the concentration of the PST that 'survive' in the unloaded (after deformation) polymer at given  $\epsilon_{\text{res}}$ ,  $T_d$  and ageing time. An increase in  $\epsilon_{\text{res}}$  causes an increase in the area under the LTR peak but is not accompanied by any conformational changes in the macromolecular chains. When the PST concentration reaches a critical value, an HTR peak appears in the recovery curves and increases with an increase in degree of strain. The appearance of the HTR peak indicates conformational transformations within distorted chains. At high strain, the HTR peak dominates while the LTR peak is of low intensity; because of this, no LTR stage was detected in the early studies of the SME in amorphous polymers.

The approach of Perez *et al.*<sup>39–41</sup> to the description of deformation of polymer glasses is analogous to that used in the studies mentioned above.<sup>35,36</sup> According to the model proposed, the main mechanism of deformation in amorphous polymers involves nucleation of localised shear microdomains (SMD) that

carry inelastic strain. The reason for the appearance of plastic deformation is the interaction between two or more SMD, which causes molecular rearrangements and conformational changes in the polymer. Different natures of coupled molecular motions are responsible for different time scales of the recovery of two strain components, namely, inelastic strain and plastic strain (original terms are given) at temperatures  $T < (T_g - 20 \text{ K})$ .<sup>42,43</sup> The former is characterised by fast relaxation while a slow relaxation is a feature of the latter. Inelastic strain can be completely recovered on heating of the material to  $T_g - 20 \text{ K}$ , whereas complete recovery of plastic strain requires heating to at least  $T_g$ .<sup>42-44</sup>

The approach<sup>35,36</sup> treats the LTR as a nonequilibrium polychromatic relaxation. In studies<sup>45-49</sup> the low-temperature component of the relaxation of deformed glassy polymers was associated with conformational changes of macromolecular fragments within local structural regions. Taking poly(methyl methacrylate) (PMMA) as an example,<sup>45</sup> it was shown that the LTR of the samples compressed to different deformation values  $\varepsilon$  at  $T < T_g$  can be described by a generalised curve plotted in the coordinates  $(\varepsilon - \varepsilon_T) - T$  (Fig. 6a), where  $\varepsilon_T$  is the residual strain at a given temperature. Analysis of the plots shown in Fig. 6a showed that the sample contains regions characterised by various packing density and local glass transition temperatures. This confirms structural heterogeneity of organic glasses.<sup>50</sup> Loading of material is accompanied by successive involvement of such structural regions in the deformation process and, therefore, in the recovery process on subsequent thermal activation.

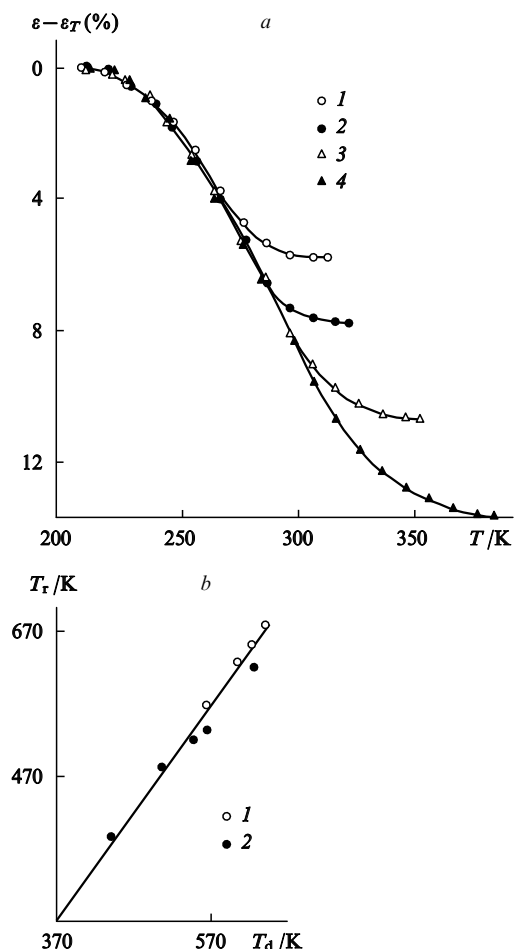


**Figure 6.** Temperature dependences of the differences  $\varepsilon - \varepsilon_T$  (a) and the dependence of the total strain recovery temperature on the deformation temperature (b) for PMMA samples.<sup>45,48</sup>  
(a):  $\varepsilon = 6$  (1), 8 (2), 11 (3), 14% (4); (b): uniaxially compressed (1) and hydrostatically pressed (2) samples.

Treatment of experimental data on thermally stimulated recovery of a large number of deformed polymer glasses allows common features of deformation and recovery of this class of polymers to be established.<sup>46</sup> In particular, the temperature dependences of the residual strain plotted in the coordinates  $(\varepsilon - \varepsilon_T)/\varepsilon_{f,e} - (T - T_g)/(T_g - T_d)$ , where  $\varepsilon_{f,e}$  is the strain corresponding to the forced elasticity limit, fall on the same generalised curve as for glassy polymers. This points to a common deformation and subsequent recovery mechanism of glassy polymers, which is due to similarity in their structural organisation. Recovery of deformed polymers is reduced to successive devitrification of the structural regions with different packing densities and local glass transition temperatures.

Taking into account a quasi-equilibrium character of thermally stimulated recovery of deformed glassy polymers at  $T < T_g$  (see Ref. 45) and the fact that it can be described by a common generalised curve,<sup>46</sup> it is possible to explain the results,<sup>48</sup> namely, an increase in the complete recovery temperature,  $T_r$ , with an increase in the deformation temperature. Indeed, at a specified degree of deformation an increase in  $T_d$  is accompanied by involvement of structural regions with higher packing density (within these regions the recovery occurs at higher temperatures) in the deformation process.

Figure 6b presents the complete recovery temperatures of uniaxially compressed (by 6%) and hydrostatically pressed (0.3 GPa) PMMA samples plotted vs. deformation temperature.<sup>48</sup> They fall on the same straight line whose extrapolation to  $T_r = 0 \text{ K}$  gives a deformation temperature of 100 K. The case  $T_r = 0$  means that a PMMA sample deformed at  $T_d \leq 100 \text{ K}$  undergoes elastic recovery at any temperature, on unloading. With allowance for this fact the temperature found (100 K) can be treated as the transition temperature from ideal elastic deformation to plastic deformation, i.e., the temperature of transition from the brittle failure to the ductile failure mechanism.

Glassy polymers are structurally inhomogeneous. The inhomogeneity size varies from a few to tens of Ångström,<sup>51,52</sup> inhomogeneities have a fluctuative character. This is responsible for severe experimental difficulties in the studies of structural rearrangements, because they can not be visualised by traditional structural methods. Using an original microscopic technique which allows structural rearrangements in deformed amorphous polymers to be visualised, previously unknown features of the LTR were revealed<sup>53,54</sup> and a new mechanism of thermally stimulated recovery of polymer glasses was proposed. The method involves investigation of the structural-mechanical characteristics of deformed polymer films with thin solid coatings.<sup>53-59</sup> A direct microscopic investigation of the structural evolution of the coating during film recovery showed that thermal shrinkage causes the appearance of a regular microrelief on the polymer surface. The character of the microrelief depends only slightly on both the coating material and the substrate material. The relief is characterised by three types of morphological features.<sup>58</sup> The most pronounced is the first type, namely, irregular closed cellular structures formed by rather high buckles of the coating. The second type is represented by specific wavy structures inside the cells with somewhat lower buckles and the third type are rectilinear folds crossing the whole sample. Studies of such a microrelief gave important information on the structural rearrangements accompanying deformation of the polymeric substrate. This information also allows fine details of the LTR to be established.

Characteristic temperature dependences of the size recovery of glassy polymer (PETP) samples deformed below and above  $T_g$  are shown in Fig. 7.<sup>54</sup> Planar orientation of the PETP films was performed according to Refs 53 and 60. As can be seen, the size recovery of a film oriented at 373 K mainly occurs near the glass transition temperature. PETP deformed at room temperature completely recovered its size at temperatures below  $T_g$ . The LTR during annealing of the PC and PMMA samples deformed

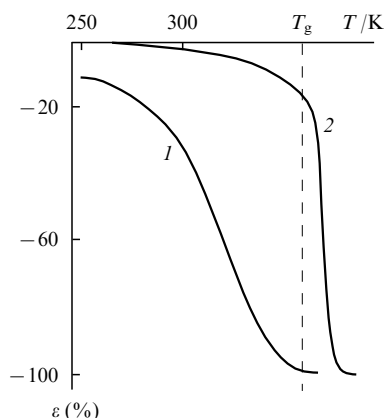


**Figure 7.** Temperature dependences of strain recovery for PETP.<sup>54</sup>  $T_d$ /K: 293 (1) and 373 (2).

by the classical crazing mechanism<sup>61,62</sup> or by stretching in air occurs analogously.

Deformation of a polymer sample below  $T_g$  causes the appearance of specific zones containing oriented polymer and separated by well-defined interfaces.<sup>54,62</sup> In the case of both crazing and the development of shear bands, these zones penetrate throughout the bulk of the polymer and impart to the polymer the properties characteristic of oriented highly disperse material. The key factor responsible for the LTR is a decrease in the glass transition temperature of the surface layers. On progressive devitrification of the oriented material, filling the zones of localised deformation induces the force responsible for the LTR. It should be emphasised that the low-temperature recovery occurs in the shear bands that appear during deformation below and near the yield point and retain their individual features even after transition of the whole polymer to the oriented state. That is why the low-temperature shrinkage begins within these zones. The HTR is associated with the relaxation of molecular orientation in the bulk of the polymer, acquired during deformation after the yield point was achieved.<sup>62</sup>

Compared to the number of studies on the SME in linear amorphous polymers, the number of studies on this effect in polymer networks is much smaller (see, *e.g.*, Refs 63–67). Most experiments were carried out using epoxide polymers (EP) and by and large revealed the same laws. Namely, recovery of the initial sizes of samples on heating in the free state begins below  $T_g$  and completes at  $T \approx T_g$ , long-term ageing at  $T_d$  leads to complete relaxation of  $\varepsilon_{res}$  and the recovery curves of the samples deformed above and below  $T_g$  differ appreciably. The last-mentioned fact indicates a change in the residual strain recovery rate on heating deformed EP (Fig. 8).<sup>36,63</sup> A sample deformed by compression below  $T_g$ , always recovers a part of its residual strain below the glass transition temperature (LTR). The sample deformed above  $T_g$  exhibits no LTR peak.

The temperatures at which the  $\varepsilon_{res}$  recovery begins are related to  $T_d$  only but not to the relaxation transition temperatures in the glass ( $T_\beta$ ,  $T_\gamma$ , *etc.*).<sup>36</sup> At the same time the onset of shape recovery correlates with  $T_g$ .<sup>64,65</sup> An analogous correlation was also established for the maximum stress developed on heating oriented samples with fixed ends.<sup>64,65</sup> Polymer networks (in contrast to linear amorphous polymers) have a narrower temperature interval of shape recovery. The maximum stress developed in this case increases with an increase in the degree of deformation and in the effective node density of the network.<sup>65,67</sup>

Shape-memory glassy polymers have found wide practical applications. For instance, they are used for the production of thermally shrinkable films utilised as packing material, thermally shrinkable insulating sleeves, details and profiles in the compressed state (convenient for transportation), rivets and fittings for all-in-one-type adhesive couplings for pipes.<sup>68–76</sup> In particu-

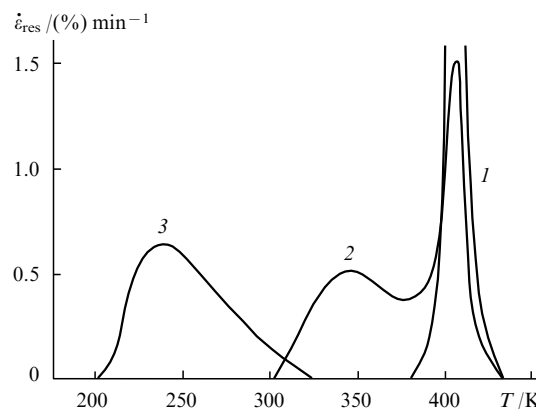


**Figure 8.** Temperature dependences of residual strain recovery rate for EP.<sup>36</sup>

$T_d$ /K: 423 (1), 293 (2) and 173 (3).

lar, such fittings made of EP (first of all couplings) allow fabrication of strong and pressure-tight constructions made of various (including different-type) materials that withstand high internal pressures of gas and liquids.<sup>74,77–80</sup> This is achieved by using a specific epoxy adhesive along with the thermally shrinkable coupling made of a material which possesses a good adhesion towards various substrates. The temperature–time regimes of coupling shrinkage and adhesive hardening are chosen in such a way that shrinkage be followed by hardening; this precludes formation of adhesive-free spots, thus forming a very thin adhesive layer which provides a joint of maximum strength.

Physical ageing processes in polymers are closely related to the SME.<sup>15</sup> The ageing is considerably enhanced with oriented polymers.<sup>81</sup> Therefore, to solve the ageing problem, it is necessary to know specific features of manifestation and the mechanism of the SME in such polymers. Often, solving particular engineering problems requires suppression of the SME.<sup>82,83</sup>

### III. Crystallisable polymers

#### 1. Amorphous-crystalline homopolymers

In contrast to the amorphous polymers mentioned above, the molecular orientations of both phases in amorphous-crystalline homopolymers can be locked at temperatures above the  $T_g$  of the amorphous phase because the stability of the orientation is determined by the network of crystalline domains. These homopolymers exhibit a more complex relation between the degree of molecular orientation and stability of oriented materials. Enhancement of molecular orientation can lead to formation of a structure with a high degree of continuity, which improves the stability in spite of high internal stress.<sup>14</sup> The SME occurring with an increase in temperature is due to (i) structural rearrangement of the amorphous phase with possible crystallisation of this phase; (ii) destruction and recrystallisation of crystallites with imperfect shape, (iii) thickening of crystalline blocks and (iv) melting of the crystalline phase.

The SME mechanisms considered in the study,<sup>15</sup> taking thermal shrinkage as an example, are based on such molecular ordering models as transformation of the paracrystalline phase into the crystalline phase; transformation of crystallites with extended chains into crystallites with packed chains; melting of crystallites; disorientation of amorphous regions followed by crystallisation and some other mechanisms. The authors<sup>15</sup> give no preference to a particular thermal shrinkage mechanism but seem to highlight the mechanisms based on the fibrillar structure models,<sup>84,85</sup> which allow quantitative description of the process.

In spite of the numerous publications concerned with the SME in amorphous-crystalline homopolymers (including recent communications<sup>16,86–101</sup>), investigations of this phenomenon are far

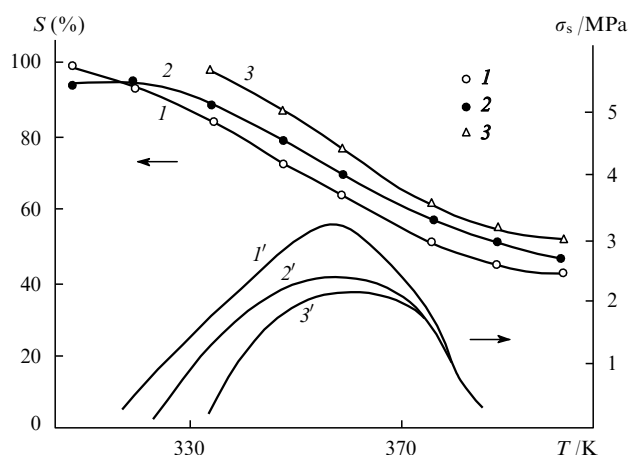


**Figure 9.** Degree of shrinkage ( $I-3$ ) and shrinkage stress ( $I'-3'$ ) of LDPE plotted vs. temperature.<sup>89</sup>  $T_d$ /K: 293 ( $I, I'$ ), 313 ( $2, 2'$ ) and 333 ( $3, 3'$ );  $\lambda = 4$ .

from being completed. At the same time a number of undoubted facts and laws were established, which are common to these materials. As a rule, they concern thermal shrinkage of film or block samples, mainly polyolefins. A typical example is shown in Fig. 9 where the degree of shrinkage,  $S$ , of low density polyethylene (LDPE) samples oriented by hydrostatic extrusion is plotted vs. temperature<sup>89</sup>

$$S = \frac{l_0 - \Delta l}{l_0},$$

where  $l_0$  is the initial length of extrudate and  $\Delta l$  is the shrinkage due to annealing. The shrinkage increases with an increase in the annealing temperature and with a decrease in  $T_d$ . Similar results were obtained for polyethylene and polypropylene (PP) films.<sup>88, 102</sup> As in the case of glassy polymers, the shrinkage onset temperature of oriented crystallisable polymers decreases as the degree of deformation increases.<sup>86, 90-92</sup>

Heating of LDPE samples with fixed ends to 350–355 K is accompanied by an increase in  $\sigma_s$ . Then,  $\sigma_s$  somewhat decreases and dramatically decreases after transition of the material to the molten state (see Fig. 9). The maximum values of shrinkage stress  $\sigma_s^m$  increase with an increase in the degree of extension,  $\lambda$ , and with a decrease in  $T_d$  (Fig. 10). Shrinkage stress disappears if samples are aged at  $T \geq 388$  K, which approximately corresponds to the melting completion temperature of crystallites in oriented LDPE [according to differential scanning calorimetry (DSC) data].

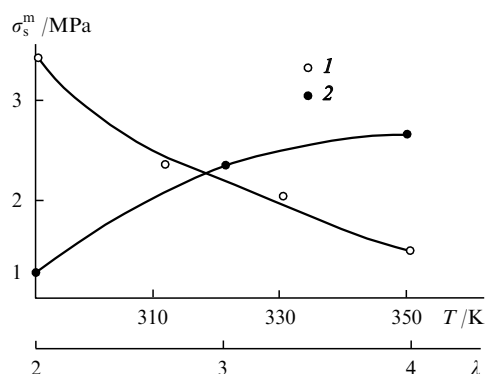


**Figure 10.** Maximum shrinkage stress of LDPE plotted vs. temperature of deformation ( $I$ ) and degree of molecular chain extension ( $2$ ).<sup>89</sup>  $\lambda = 4$  ( $I$ ) and  $T_d = 313$  K ( $2$ ).

A study<sup>89</sup> of LDPE extrudate morphology showed that deformation is accompanied by formation of layered structures (crystalline lamellae arranged normal to the extension direction). As  $T_d$  increases, the lamellae become thicker. Macromolecular fragments in the bulk of the crystallites that form layered structures acquire now a preferred orientation along the deformation direction. Shrinkage forces (entropic in character), which are developed in thus formed strained throughout-going chains or their clusters, are compensated by elastic forces in the layered crystalline cage. Heating of oriented LDPE samples is accompanied by shrinkage of extended macromolecules or their fragments under the action of entropic factors by transformation of the crystalline cage; this is the reason for such a molecular shrinkage.

Maxima of  $\sigma_s$  are observed in the temperature interval 358–363 K (see Fig. 9) corresponding to completion of the  $\alpha$ -transition in LDPE.<sup>103, 104</sup> On further heating the forces that hold the shrinking throughout-going chains within the block become weaker than the forces necessary for block displacement. As a result, chain slip through lamellae begins, resulting in a decrease in  $\sigma_s$ . The higher the temperature, the easier the slip of macromolecular fragments. Therefore, the number of strained throughout-going chains decreases with an increase in  $T_d$ , thus leading to a decrease in both  $\sigma_s$  and the degree of shrinkage. The latter is first of all due to the disappearance of the strained throughout-going chains in defect crystallites whose breakdown requires the lowest activation energy. Owing to the absence of low-temperature relaxators, the beginning of the shrinkage process is shifted towards higher temperatures (see Fig. 9). At the same time DSC data show that the shift of the  $\sigma_s$  maximum towards higher temperatures with an increase in  $T_d$  is due to the formation of the layers comprised of crystallites with increased cross sections (breakdown of these particles requires a higher activation energy).

Yet another factor responsible for structural rearrangement on heating of oriented LDPE samples, is thickening of lamellae during annealing. In this case certain segments can be drawn into the lamellae, thus leading to disordering of crystalline blocks and development of internal stress. This mechanism can also contribute to an increase in  $\sigma_s$  for the samples oriented at low temperatures. Namely, as  $T_d$  increases, partial annealing does occur, as indicated by the thickening of lamellae.<sup>89</sup>

Of particular interest is the investigation of the SME in microporous crystallisable polymers, which are widely used for, e.g., filtration, separation of liquid media, deaeration, etc. Shrinkage of microporous high-density polyethylene (HDPE) films prepared by melt extrusion, subsequent annealing at fixed size, uniaxial extension during pore formation stage and thermal fixation of porous structure was studied.<sup>94, 95</sup> Correlations between the shrinkage and the draw ratio, temperature of thermal fixation and the degree of extension ( $\epsilon$ ) were established.

The dependence of shrinkage on the degree of extension passes through an extremum (maximum) at  $\epsilon = 150\%$  whose position is independent of shrinkage temperature.<sup>94</sup> The results obtained were explained by competition between (i) orientational processes (pulling apart and bending of lamellae) and deformation of chains connecting lamellae and (ii) breakdown of the throughout-going chains. At low degrees of extension, the throughout-going chains are not stretched and lamellae are slightly bent. Temperature variation causes strained lamellae held by the throughout-going chains to return to the initial state; however, lamellae (both weakly strained or non-connected by the throughout-going chains) show low deformability; therefore, a small shrinkage is observed at small  $\epsilon$ . At  $\epsilon \approx 150\%$ , most throughout-going chains appear to be bent and strained, the degree of pulling apart a lamellae becomes high and the connecting chains still withstand the stress. This is the case for maximum shrinkage. At  $\epsilon > 150\%$ , a fraction of the throughout-going chains are broken and do not contribute to subsequent relaxation of the sample on heating.

The shape memory effect in microporous films is used in chemical cells. Such films act as membrane separators that are permeable to electrolyte and separate the anode and cathode



compartments.<sup>94, 95, 105</sup> For instance, to avoid ignition of lithium cells, the power source must be prevented from overheating. This is achieved by shrinkage of the separator, which results in closure of through pores and termination of cell operation.

Formation of a network of chemical cross-link points in crystallisable polymers offers additional possibilities of control of thermal-shrinkage characteristics. Such a network can be formed using radiation-induced, chemical or photochemical cross-linking. A hot-drawn polyethylene film prepared by radiation-induced cross-linking exhibits improved ultimate strength, shrinkage stress and a more stable shrinkage factor as compared to non-irradiated film oriented under the same conditions.<sup>106–108</sup> Similarly to the non-irradiated film, shrinkage increases with both an increase in the degree of deformation and a decrease in  $T_d$ . A distinctive feature of this material is a characteristic dependence of  $\sigma_s$ , which exhibits a plateau near  $T_m$ . For instance, the parameter  $\sigma_s$  of LDPE shows a dramatic increase at  $T = 353–383$  K, a constant value to 413–433 K and subsequent gradual decrease.<sup>108</sup>

Photochemically cross-linked and radiation-modified polyolefin samples exhibit a similar shrinkage behaviour.<sup>88</sup> They mainly differ in absolute values of the effects observed. However, this holds for those polymers that were oriented after cross-linking. The situation changes if orientation precedes cross-linking. Exposure to ionising radiation causes a considerable decrease in  $\sigma_s$ , while photochemical cross-linking has little effect on thermal shrinkage. The results of photochemical cross-linking also depend on the nature of initiators employed.<sup>88</sup>

If an amorphous-crystalline polymer contains a network of chemical cross-link points, orientation leads to an increase in the number of throughout-going chains. This is the reason for improved stress-strain properties<sup>88</sup> and increased  $\sigma_s$ . The shrinkage stress determined by the elastic properties of a uniaxially extended network of chemical cross-link points manifests itself in full measure only at  $T > T_m$ . In the case of radiation-induced cross-linking a large proportion of chemical cross-link points is formed as a result of recombination of radicals that were generated in crystallites and experience a diffusion motion towards relatively ordered transient layers on folded lamellae surfaces.<sup>109, 110</sup> These cross-links can control the degree of 'untwisting' of certain macromolecules and act as additional fixators of crystalline blocks with respect to transfibillar throughout-going chains, thus precluding chain slip at high temperatures.<sup>88</sup> The density of transient layers, in which efficient radiation-induced cross-linking can occur, is close to the density of crystallites;<sup>111</sup> therefore, they are inaccessible to photoinitiator molecules localised only in amorphous inter-lamellae regions.<sup>112</sup> This is the reason for their different influence on the formation of microfibrillar structure during deformation of cross-linked polyethylene (PE).<sup>88</sup> Lower efficiency of fixation of crystalline blocks on the throughout-going chains, due to inaccessibility of lamellae surfaces to cross-linking in the photoinitiated process, is the reason for insignificant differences between the  $\sigma_s$  regions for the samples cross-linked before and after orientation.

Improvement of the stress-strain and thermal-shrinkage characteristics, achieved as a result of cross-linking of polymers, favours a wide use of polymers in the production of thermally shrinkable items for electronics, the aviation industry, spacecraft industry, automotive industry and the shipbuilding industry.<sup>113</sup> Not only one-layer thermally shrinkable insulating sleeves but also two-layer coatings made of polymeric materials with different properties and different functions have come into use.

## 2. Copolymers

The synthesis of copolymers is an efficient method of modification of polymer structures and expansion of their functional possibilities. Among recent publications concerned with the SME in copolymers, we will first of all point out the studies of thermoplastic polyurethanes (PU).<sup>114–136</sup> Increased interest in these materials is due to relatively low cost, good processability, high stability to the surrounding atmosphere, convenient (for practical

applications) shape-memory temperature intervals and the high degree of shape recovery of PU.

Segmented PU having an SME-appropriate structure were first synthesised by researchers at Mitsubishi Heavy Industries (Japan)<sup>115, 116</sup> from 4,4'-diphenylmethane diisocyanate and polyol using 1,4-butanediol as a chain extender. The structures of these materials consist of soft and hard segments (reversible and 'frozen' phase, respectively). The reversible phase has an amorphous structure while the 'frozen', or fixed, phase has a crystalline structure. In the temperature range between the glass transition temperature and the melting temperature of the crystalline phase, the polymers are in the rubbery state. Deformation at  $T_g < T < T_m$  followed by cooling under load to  $T < T_g$  causes fixation of the shape acquired. If the material is then again heated to a temperature in the range  $T_g < T < T_m$ , the initial shape is recovered.

These materials exhibit not only shape memory but also a considerable change in the elastic modulus near the glass transition temperature. This is suggesting of elasticity memory,<sup>116</sup> which is widely used in temperature sensors, drives, low-power engine chokes, *etc.*;<sup>115, 116</sup> therefore, it is of great importance to know the behaviour of such materials in cyclic tests.

Figure 11 presents the residual and recoverable ( $\epsilon_r$ ) strain plotted vs. number of load/unload cycles ( $N$ ). The data were obtained in the extension of oligoester polyol PU samples characterised by a high elastic modulus at elevated temperatures.<sup>115</sup> Each cycle in the experiment included loading at a constant rate until maximum deformation,  $\epsilon_m$ , at 338 K ( $T_g = 318$  K) followed by cooling to 298 K under load and subsequent unloading. Initially, the  $\epsilon_{res}$  and  $\epsilon_r$  values differ appreciably (see Fig.11). As  $N$  increases,  $\epsilon_{res}$  also increases and  $\epsilon_r$  decreases; the greatest changes are observed at  $N < 5$ . At  $N > 20$ , the differences between  $\epsilon_{res}$  and  $\epsilon_r$  become small and the parameters remain practically unchanged on further cycling. Therefore, attainment of constant  $\epsilon_{res}$  and  $\epsilon_r$  values for this material requires cyclic preloading (5–20 cycles).

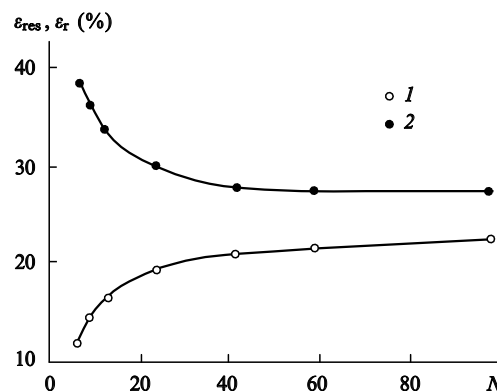


Figure 11. Residual (1) and recoverable (2) strain plotted vs. number of load cycles for PU.<sup>115</sup>

The parameter  $\epsilon_r$  of the PU in question can be as high as hundreds per cent; however, most shape-memory elements operate in the recoverable strain region ( $< 20\%$ ).<sup>116, 129</sup> This is due to the fact that the SME is often imparted by bending deformation. Even at  $\epsilon > 3\%$ , a nonlinear deformation can begin, which must be taken into account in the design of shape-memory elements.<sup>128</sup> A reference thermomechanical model proposed<sup>128</sup> with allowance for this fact includes nonlinear stress terms in the elastic and viscous components of the linear model.<sup>130</sup>

Plastic deformation recovery in the unloaded state is described by the following equations<sup>130</sup>

$$\dot{\epsilon} = \frac{\dot{\sigma}}{E} + \frac{\sigma}{\mu} - \frac{\dot{\epsilon} - \epsilon_{ur}}{\lambda} + \alpha \dot{T}, \quad (7)$$

$$\varepsilon_{ur} = S\varepsilon_{res}, \quad (8)$$

where  $E$ ,  $\mu$ ,  $\lambda$ , and  $\alpha$  are respectively the elastic modulus, viscosity, delay time and thermal expansion factor,  $\varepsilon_{ur}$  is the unrecoverable strain, and  $S$  is the coefficient of proportionality. With inclusion of nonlinear terms one has

$$\dot{\varepsilon} = \frac{\dot{\varepsilon}}{E} + m \left( \frac{\sigma - \sigma_y}{k} \right)^{m-1} \frac{\sigma}{k} + \frac{\sigma}{\mu} + \frac{1}{b} \left( \frac{\sigma}{\sigma_c} - 1 \right)^m - \quad (9)$$

$$- \frac{\varepsilon - \varepsilon_{ur}}{\lambda} + \alpha \dot{T},$$

$$\varepsilon_{ur} = S(\varepsilon_c + \varepsilon_p), \quad (10)$$

where  $\sigma_y$  is the yield stress;  $\sigma_c$  is the stress corresponding to  $\varepsilon_c$ ;  $\varepsilon_c$  is the unloading deformation of the sample; and  $\varepsilon_p$  is the time-independent plastic deformation. The results of calculations<sup>128</sup> show that the model gives a correct description of the  $\sigma$ - $\varepsilon$ ,  $\sigma$ - $T$ ,  $\varepsilon_r$ - $T$  and other dependences.

Figure 12 presents the temperature dependences of  $\varepsilon_r$  calculated for different heating rates of unloaded oriented PU samples.<sup>128</sup> Deformation recovery slows down with an increase in temperature, but the  $\varepsilon_{ur}$  rapidly increases at  $\dot{T} > 0.1 \text{ K s}^{-1}$  (Fig. 13). This feature must be taken into account in the design of bulk shape-memory elements for operation under rapid heating conditions because heating of surfaces to a preset temperature does not ensure the SME in the bulk of the material.

Kim *et al.*<sup>126</sup> reported polyurethanes with crystalline hard segments from the reaction of 4,4'-diphenylmethane diisocyanate

and 1,6-hexanediol and amorphous soft segments from the reaction of hexamethylene diisocyanate and 1,2-butanediol and studied their thermal, stress-strain and physico-mechanical properties and the SME in this type of PU. First, the materials show sharp glass-transition temperatures that could be used as shape-recovery temperatures. Second, as the block lengths decrease, phase mixing increases and hysteresis in the shape-memory behaviour decreases. Third, too low a content of hard segments (shape-'memorising' phase) increases the hysteresis in the shape-memory behaviour.

New information on the behaviour of segmented PU with a reversible amorphous phase was reported by Chun and co-workers.<sup>127</sup> who studied a material with diphenylmethane diisocyanate hard segments and poly(tetramethylene glycol) soft segments. The shape retention of PU samples with 30 mass %, 35 mass %, 40 mass % and 45 mass % of hard segment content was estimated after they were deformed by 50% at  $T = T_g + 20 \text{ K}$ , cooled under load at  $T = T_g - 20 \text{ K}$  and then unloaded. All the tested samples showed more than 90% shape retention. Shape recovery measured after the samples were kept at  $T = T_g + 20 \text{ K}$  with load removed varied from 80% to 95%. However, shape recovery was not observed at 20 mass %, 25 mass % and 50 mass % of hard segment content. This behaviour was associated with the character of intermolecular interactions between PU segments. The high degree of shape recovery at  $T > T_g$  is due to PU stabilisation by dipole-dipole interactions, hydrogen bonds and induction interactions between the hard segments. The PU samples with 20 mass % and 25 mass % of hard segment content cannot have strong intermolecular interactions and physical cross-links due to the low proportion of hard segments, which results in the loss of shape memory effect. At a hard segment content of 50 mass %, intermolecular interactions between them are strong enough to form a rigid structure, which is inappropriate for SME to occur.

Polyurethanes with the glass transition temperature of the soft segments close to room temperature have found wide application. They are characterised by a stepwise change of many parameters near  $T_g$ . The shape-memory function underlies the operation of studs, catheters, fittings, re-writable compact disks, implants for cardiology, *etc.*<sup>136-138</sup>

Crystallisable soft segments can also play the role of the reversible phase in segmented PU. A schematic illustration of the SME in segmented PU with both crystallisable phases and corresponding evolution of the polymer structure is shown in Fig. 14.<sup>117</sup> Crystalline regions formed by hard segments play the role of physical cross-links while soft segments can 'freeze' rubber-like elastic deformation. Initial samples can show microphase separation and both types of segments can crystallise separately with random distribution of crystallites over the sample without any macroscopic anisotropy. In this case at temperatures above the melting temperature,  $T_{ms}$ , of soft-segment crystallites but below the melting temperature,  $T_{mh}$ , of hard-segment crystallites, the sample is in the rubbery state. Samples can recover their initial sizes even at a high degree of extension. However, isometric cooling of extended samples down to low temperatures makes it possible to 'freeze' and retain the rubbery elastic deformation owing to crystallisation of soft segments. Reheating of such samples leads to melting of soft-segment crystallites and the elastic energy stored causes recovery of the initial geometric sizes.

According to the concept of existence of soft-segment and hard-segment crystalline regions, the crystal perfection, crystalline phase morphology and, hence, crystallisation conditions must significantly influence the shape memory of polyurethane samples. For instance, taking PU prepared from 4,4'-diphenylmethane diisocyanate and toluene diisocyanate and containing caprolactone soft fragments as an example, it was established<sup>117</sup> that some weak cross-links in the samples are broken after the first cycle of deformation, which results in the formation of a dynamically perfect elastic network capable of nearly complete shape recovery. Samples with short soft segments and low hard segment content exhibit small recoverable strain. Long soft segments and

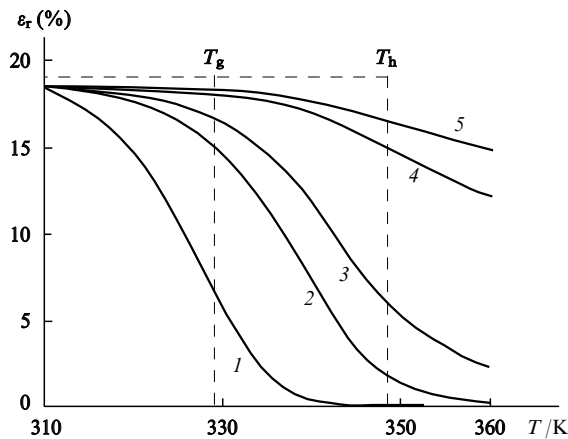


**Figure 12.** Temperature dependences of recoverable strain for PU.<sup>128</sup>  $\dot{T}/\text{K s}^{-1}$ : 0.0167 (1), 0.0833 (2), 0.167 (3), 0.833 (4) and 1.67 (5).

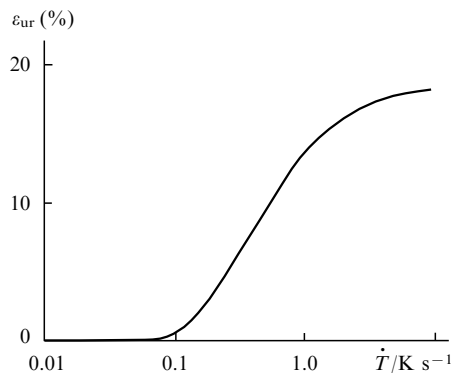


**Figure 13.** Dependence of unrecoverable strain on the heating rate for PU.<sup>128</sup>  $T = T_h$  (see Fig. 12).



Graft copolymers are considered as promising shape-memory materials along with the segmented copolymers. Studies<sup>143</sup> of the PE–nylon-6 system with nylon content of 5 mass %–20 mass % showed that the role of physical cross-links is played by the nylon domains of size at most 0.3  $\mu\text{m}$ , dispersed in the polyethylene matrix. All the samples studied showed good shape recovery (the degree of shape recovery exceeded 95%). The recovery rate was comparable with that of irradiated polyethylene with a high density of chemical cross-links. However, it should be noted that these graft copolymers contain a certain proportion of chemical cross-links because of the use of initiator (dicumyl peroxide) in the course of sample preparation. Since the density of cross-link points is low, it is the nylon domains that are responsible for excellent shape-memory behaviour of the material. The authors proved this statement by the results of their study,<sup>144</sup> according to which, at a low density of chemical cross-links in PE, this component shows no necessary shape-memory characteristics. In particular, the strain mainly remains irreversible.

As in the case of homopolymers, radiation-induced cross-linking improves the properties of shape-memory copolymers. For instance, taking modified PE obtained by copolymerisation of ethylene with octene as an example, it was shown<sup>145</sup> that exposure to  $\gamma$ -radiation (at relatively low absorbed dose) leads to the formation of a material suitable for the production of thermally shrinkable items with a long working life. This material can remain in a stressed state more than 10 years after the origination of shrinkage stresses in it. At the same time the initial shrinkage stress of this radiation-modified copolymer is 1.3 and 1.9 times higher compared to HDPE and LDPE, respectively.

#### IV. Polymer blends and filled polymer composites

Polymer mixing techniques allows a gradual variation of their physico-mechanical properties including the SME parameters (recovery temperature and rate; shape fixity; stress developed during shape recovery, *etc.*).<sup>146</sup> Nevertheless, only a few studies on the SME in polymer blends are available. Among the reports published in the last decade, mention may be made of the studies<sup>147–154</sup> concerned with various methods for preparation of this class of materials with desired characteristics.

The authors of the studies<sup>147, 148</sup> (see <sup>†</sup>) used blends of thermoplastic PU having soft polycaprolactone segments, with PVC and phenoxy resin. It was established<sup>147</sup> that the structure of PU–PVC blends comprises amorphous domains of the mixed PVC–polycaprolactone phase and crystalline domains formed by the hard segments of PU. Partial mixing of the soft and hard segments increases as the polycaprolactone segments are shortened. The glass transition temperature of the mixed phase gradually varies as the blend composition changes. Although these variations are small, the initial shape recovery temperature of this polymer system is lower than that of PVC. Cyclic tensile tests of the PU–PVC samples (2 : 8 molar ratio) showed a smaller hysteresis compared to PVC. At the same time the samples with a 4 : 6 molar ratio of the components exhibited an increase in the residual deformation compared to PVC. This behaviour is associated with a change in the elastic modulus in the glassy and rubbery states caused by the variation of the blend composition.

The glass transition temperature of the system PU–phenoxy resin<sup>148</sup> (here, the amorphous mixed domain is formed by the polycaprolactone segments) also gradually changes depending on the component ratio, similarly to the PU–PVC system. Hysteresis in the shape recovery decreases with an increase in the hard segment content and with shortening of these segments, because a highly dispersed distribution of the hard segments constituting the ‘frozen’ phase favours better ‘memorising’ of the initial shape.

Polymers based on interpenetrating polymer networks (IPN) whose components strongly differ in hardness exhibit a specific deformation and shape recovery (shrinkage) behaviour. The results of studies<sup>64, 65</sup> carried out using a polyurethane–polyesteracrylate (PU–PEA) system suggest that orientational hardening affects mainly the elastic component, PU. Hardening is due to the fact that the hard network (PEA) precludes relaxation of the stressed PU chains by forming macromolecular entanglements each acting as a kind of stopper. At low PEA content, the deformation hardening is insignificant because the density of entanglements is low and the elastic component can relax with ease. As the PEA content increases, the degree of the orientation hardening also increases, but at a PEA content of nearly 30 mass % mechanical degradation processes begin, involving both the elastic and hard chains.

The temperature interval corresponding to the characteristic change in  $\sigma_s$  of the IPN studied (Fig. 15) indicates the dominant role of the elastic component. The decrease in the half-width of the  $\sigma_s(T)$  maximum with an increase in  $\varepsilon$  points to a simultaneously increasing contribution of destructive processes (materials with imperfect structure break down faster in the course of  $\sigma_s$  measurements). As  $\varepsilon$  increases, the height of the  $\sigma_s(T)$  peak varies non-monotonically (not shown in Fig. 15) and passes through a maximum. This behaviour of  $\sigma_s$  is associated to the network loosening and partial stress relaxation in the samples tested and kinks in the right branch of the bell-shaped  $\sigma_s(T)$  curve are related to the contribution of the hard component.

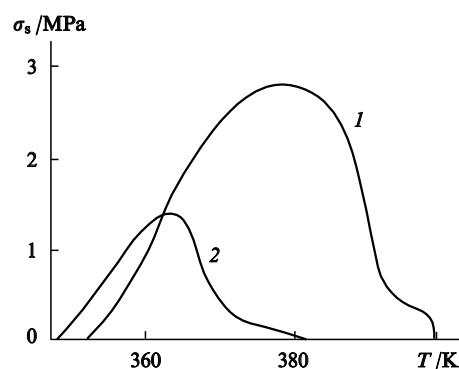


**Figure 15.** Temperature dependences of shrinkage stress for PU–PEA (70 : 30) blend.<sup>65</sup>  
 $\varepsilon$  (%): 25 (1) and 40 (2);  $T_d = 358$  K.

PE–PP blends are the most widely studied polymeric systems. In spite of the thermodynamic incompatibility of these polymers the stress-strain properties of their blends at small deformations (small extension) change in additive fashion depending on the blend composition.<sup>155–157</sup> At large deformations, deviations from the additive behaviour of the parameters are observed (decrease in ductility is particularly pronounced<sup>156</sup>). This is due to a weak interphase interaction between the components.<sup>152, 155</sup> To avoid undesired results, various methods are used, *e.g.*, photochemical cross-linking.<sup>52</sup> Figure 16 presents the temperature dependences of  $\sigma_s$  obtained for photochemically cross-linked LDPE films and for LDPE–PP (50 : 50) blend films deformed at room temperature. To reveal peculiarities of the behaviour of blends with different component ratios the temperatures were specified, corresponding to the onset of shrinkage ( $T_1$ ), maximum shrinkage stress ( $T_2$ ) and kinks associated with the melting temperature ( $T_3$ ). The  $\sigma_s$  peak is observed in the pre-melting region of the polymer blend. The parameter  $\sigma_s$  decreases due to slip of certain stressed chains between crystalline blocks (‘holders’). In contrast to non-cross-linked samples, the cross-linked ones retain a certain level of  $\sigma_s$  at temperatures above  $T_m$  owing to the elastic properties of the network. As the PP content in the blend increases to 50 mass %, the

<sup>†</sup> These studies are in essence a continuation of earlier studies<sup>123–126</sup> on shape memory effect in segmented PU.

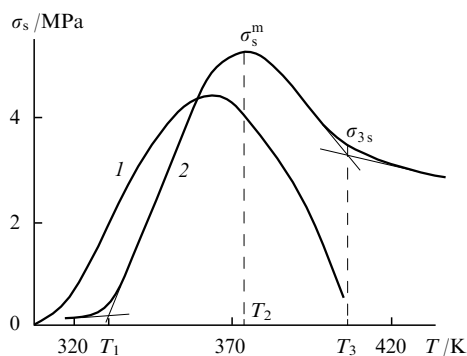


**Figure 16.** Temperature dependences of shrinkage stress for LDPE (1) and LDPE–PP (50 : 50) blend (2).<sup>152</sup>

the  $\sigma_s^m$  and  $\sigma_{3s}$  values and the characteristic temperatures ( $T_1$ ,  $T_2$ ,  $T_3$ ) increase (Table 1) and the samples exhibit shape-memory behaviour at  $T > T_3$  ( $T_3$  much exceeds the melting temperature of LDPE). Thus, introduction of PP into LDPE followed by cross-linking of the blend favours retardation of relaxation processes in the oriented samples.

**Table 1.** Thermal shrinkage characteristics of photochemically cross-linked oriented LDPE–PP blends.

| $\frac{[\text{LDPE}]}{[\text{LDPE}] + [\text{PP}]}$ | $T_1/\text{K}$ | $\sigma_s^{\text{max}}/\text{MPa}$ | $T_2/\text{K}$ | $\sigma_{3s}/\text{MPa}$ | $T_3/\text{K}$ |
|-----------------------------------------------------|----------------|------------------------------------|----------------|--------------------------|----------------|
| 1.0                                                 | 47             | 4.4                                | 86             | 0.97                     | 122            |
| 0.9                                                 | 48             | 4.45                               | 87             | 1.56                     | 124            |
| 0.8                                                 | 48             | 4.52                               | 87             | 2.04                     | 125            |
| 0.7                                                 | 52             | 5.13                               | 91             | 2.89                     | 127            |
| 0.5                                                 | 54             | 5.30                               | 96             | 3.35                     | 129            |

To attain rather high degrees of extension in creating orientation order in LDPE–PP blends, hydrostatic extrusion was employed.<sup>151</sup> The technique permits nondestructive deformation of brittle materials. Similarly to cross-linked film samples,<sup>152</sup> LDPE–PP extrudates lose the shape at higher temperatures compared to LDPE samples (the higher the PP content, the better the shape fixity). The degree of shape recovery was estimated<sup>151</sup> from the change in the extrudate cross sections on heating

$$\Psi = \frac{d_h^2 - d^2}{d_h^2},$$

where  $d$  and  $d_h$  are the extrudate diameter before and after heating. It was established that the dependences of  $\Psi$  on the degree of extension  $\lambda$  in the whole temperature interval studied are non-monotonic and pass through a maximum near  $\lambda = 3-4$ . Both the  $\lambda$  value corresponding to the extremum and the respective  $\Psi$  value decrease as the PP content in the blend increases from 0 mass % to 60 mass %. The residual deformation increases as  $\lambda$  increases. This unusual (at first glance) pattern of the  $\Psi(\lambda)$  dependence is due to simultaneous action of two factors that cause swelling of an extrudate, namely, relaxation of viscoelastic deformations in the extrudate at the die outlet and an increase in the cross section of the extrudate on heating owing to the SME. A decrease in the maximum  $\Psi$  values and their shift towards smaller  $\lambda$  with an increase in the PP content are due to the lower shape recovery ability of the LDPE–PP blends compared to LDPE and to differences between the die swelling and  $\lambda$  for the materials under comparison.

A study<sup>151</sup> of thermal shrinkage characteristics of samples with fixed ends showed that the characteristic temperatures of thermal shrinkage processes (see Fig. 16) depend only slightly on  $\lambda$

and on the PP content and obey laws identical to those established for the film samples oriented by uniaxial stretching (see Table 1). The  $\sigma_s^m$  values increase with an increase in  $\lambda$  and PP content in the blend. Similarly to the case of cross-linked samples,<sup>152</sup> the process of stress relaxation is not completed at the melting temperature of the polyethylene phase; rather, it extends to a wider temperature range. The shrinkage stress corresponding to this temperature interval ( $\sigma_{3s}$ ) increases as  $\lambda$  and PP content increase.

In the preceding paragraph we described the behaviour of monolithic samples of LDPE–PP blends prepared using a Banbury-mill type mixer and orientationally stretched under high hydrostatic pressure. Using the method of plunger extrusion of polymeric powder billet,<sup>158</sup> which combines monolithisation and orientation stretching, the authors<sup>149</sup> prepared and studied samples of PP blends with LDPE and ultra-high-molecular-mass PE (UHMPE) as well as PVC–UHMPE blends. For comparison, the behaviour of UHMPE extrudates prepared by the same technique was studied. It was found that the UHMPE extrudates behave similarly to homopolymers on heating. Namely, the samples studied showed an increase in diameter accompanied by a decrease in length [i.e., the initial shape (dimension) recovery] at temperatures  $T$  such that  $T$  exceeds a value of 373 K, being close to the temperature of UHMPE melting (extrusion) (403 K). The volumes of the extrudates did not change. Relaxation processes in the polymer blends began at lower temperatures compared to the extrusion temperatures of the materials (433 K). For all the systems under study raising the heating temperature was accompanied by monotonic increase in the sample diameters and an unusual change in the degree of shrinkage. An increase in the length of the sample at the beginning was followed by its sharp decrease as a temperature close to the melting temperature of one of the components was achieved. According to calculations, these changes in the size of the sample cause an increase in volume (Fig. 17). The maximum value of the relative change in volume,  $(V - V_h)/V$ , where  $V$  and  $V_h$  are the extrudate volumes in the initial state and after heating to a preset temperature, lies in the concentration range corresponding to equal mass fractions and nearly equal volume fractions of the

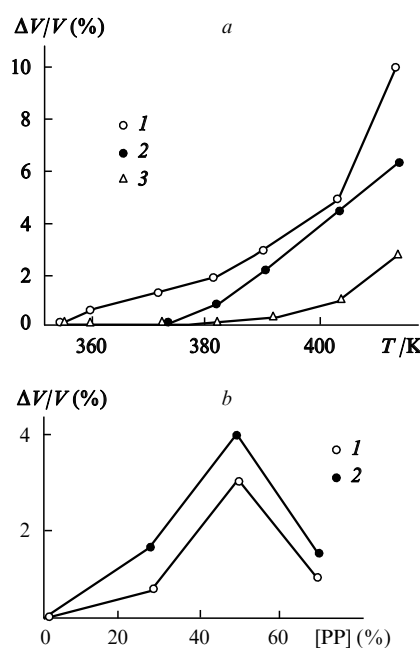


**Figure 17.** Relative change in volume of polymer blends plotted vs. temperature (a) and concentration (b).<sup>149</sup>  
(a): PP–UHMPE (60 : 40) (1), PP–UHMPE (70 : 30) (2) and PP–PVC (40 : 60) (3); (b): PP–UHMPE blend,  $\lambda = 2$ ;  $T_h$ , K: 383 (1) and 393 (2).

components. The maximum increase in volume is attained at  $\lambda = 2$ .

The observed increase in volume is related to stress relaxation during the shape recovery process, accompanied by the appearance of discontinuities at interfaces. The anomalous increase in the extrudate length on heating was explained in terms of a model for extrusion of a two-phase composite, which is based on the self-consistent field approach.<sup>159</sup> The model assumes that the two-phase composite has a matrix–inclusion structure. The total deformation of a composite is given by<sup>149</sup>

$$\varepsilon_1 = \delta(1 - \delta) \left( \varepsilon_1^m - \varepsilon_1^i \right)^2, \quad (11)$$

where  $\delta$  is the relative volume fraction of the inclusions;  $\varepsilon_1^m$ ,  $\varepsilon_1^i$  are respectively the plastic deformation of the matrix and the plastic deformation of the inclusion. From expression (11) it follows that  $\varepsilon_1 > 0$  and the maximum  $\varepsilon_1$  value is attained at  $\delta = 0.5$ , i.e., the maximum stretching must be observed at a volume fraction of inclusions of 50%, which is consistent with experimental data (see Fig. 17).

A DF-10 composite based on polyarylate and copolyethersulfone also exhibits unusual behaviour during the heating of samples prepared by plunger extrusion of polymeric powder billet.<sup>160</sup> The shrinkage,  $S$ , defined as the relative change in the extrudate length after keeping at a preset temperature, decreases with an increase in  $\lambda$  and changes its sign near  $\lambda = 4$ . In other words, the length of the sample increases rather than decreases at a high degree of extension. A scheme illustrating deformation of macromolecular coils in the case of solid-phase extrusion was proposed.<sup>160</sup> According to this scheme, shrinkage is due to return of macromolecular coils to the initial state. The degree of return can be estimated as follows

$$\Psi_m = \frac{C_{\infty}^{\perp} - C_{\infty}^{\parallel}}{C_{\infty}^{\perp}}, \quad (12)$$

where  $C_{\infty}^{\perp}$  and  $C_{\infty}^{\parallel}$  are the characteristic ratios,  $C_{\infty}$ , calculated along the normal and parallel to the extrusion axis, respectively. The parameter  $C_{\infty}$  serves as a measure of the relative flexibility of the macromolecule and of the degree of compactness of the macromolecular coil.<sup>161, 162</sup>

Thermal shrinkage occurs until the macromolecular coil adopts a symmetrical shape, which corresponds to  $C_{\infty}^{\perp} = C_{\infty}^{\parallel}$ . Comparison of the parameters  $S$  and  $\Psi_m$  revealed their similarity in absolute value and an identical type of dependence on  $\lambda$ . Moreover, the  $C_{\infty}^{\perp}$  and  $C_{\infty}^{\parallel}$  values calculated from the equation derived<sup>160</sup> invoking the mechanism of plastic deformation of amorphous polymers (see Ref. 163), show inversion of absolute values at  $\lambda > 4$ .

Recently, considerable attention has been paid to blends of engineering polymers with liquid-crystalline polymers (LCP).<sup>164–169</sup> The addition of LCP improves not only the mechanical properties of thermoplastics but also the corresponding processing conditions. Therefore, interest in these systems in the framework of SME studies is not occasional. Peculiarities of the shape memory behaviour of a HDPE–LCP blend were studied.<sup>153</sup> The LCP was a liquid-crystalline copolyester of 40% PETP with 60% of 4-hydroxybenzoic acid. Stretching of samples was preceded by radiation-induced formation of a network structure in them. The shape memory effect was studied under conditions of isometric heating and cooling; to this end, thermorelaxation stress  $\sigma_{tr}$  (on heating) and thermal shrinkage  $\sigma_s$  (on cooling) were measured.

The samples of HDPE and HDPE–LCP blends containing 5 mass % and 10 mass % of LCP exhibit quite different temperature dependences of  $\sigma_{tr}$  and  $\sigma_s$ . Indeed, HDPE shows a dramatic increase in  $\sigma_{tr}$  in a narrow temperature interval near  $T_m$ , whereas the blends are characterised by a gradual increase in  $\sigma_{tr}$  over a wide temperature range (from 323 to 423 K for the HDPE–LCP blend containing 10 mass % of the LCP). This behaviour is due to the  $\alpha$ -

and  $\alpha'$ -transitions in the PETP phase of the LCP. At temperatures above 423 K, the  $\sigma_{tr}$  value remains virtually unchanged up to 533 K. The  $\sigma_s(T)$  dependence obtained for the blends also differs from the corresponding dependence for HDPE (kinks between 333 and 373 K in the former vs. nonmonotonic change in  $\sigma_s$  in the latter case). It is important that the  $\sigma_s$  value of the HDPE–LCP blend containing 10 mass % of LCP is 1.5 times higher than the  $\sigma_s$  value for pure HDPE. As the absorbed radiation dose increases from 50 to 150 kGy, the  $\sigma_{tr}$  and  $\sigma_s$  values increase but then decrease due to accumulation of radiation-induced defects in the material.

Physical modification of polyolefins by cross-linking them with various elastomers is one of the most efficient methods of preparation of thermosetting plastics possessing the properties of both elastomer and plastic, namely, flexibility, high impact toughness at low temperatures, etc. This modification technique is also of interest for obtaining shape-memory materials exhibiting the properties mentioned above. In particular, the behaviour of LDPE–ethylene/propylene/diene copolymer (EPDC) blends prepared by chemical (series A) and radiation-induced (series B) cross-linking and then orientationally stretched at 403 K and cooled to room temperature under isometric conditions was studied.<sup>170</sup> Series-A samples showed low  $\sigma_{tr}$  and  $\sigma_s$  values, the former increasing with an increase in the content of the cross-linked elastomer. Maxima in the  $\sigma_s$  plot were observed at minimum EPDC content in the blend, because their magnitudes are determined by the crystalline phase of LDPE. Series-B samples also exhibited a similar behaviour of  $\sigma_{tr}$  and  $\sigma_s$ , except for much higher absolute values of  $\sigma_s$  (compared to series-A samples) at the same LDPE/EPDC ratios. This is due to the fact that irradiation of samples causes cross-linking in both phases rather than in one phase. As a result, according to scanning electron microscopy data, fibrillation of the molecular structure occurs.

A study<sup>154</sup> of HDPE–ethylene-propylene rubber terpolymer (SKEPT)–LCP composite was carried out in a continuation of earlier investigations.<sup>153, 170</sup> Here, rubber is mainly introduced in order to improve the elasticity of the material and its adhesive interaction with steel; this is necessary for the improvement of the technical characteristics of the items produced. The effect of SKEPT and LCP on the maximum  $\sigma_{tr}$  and  $\sigma_s$  values can be followed using the plots shown in Fig. 18. With the SKEPT content below 40 mass % the LCP additive allows thermorelaxation and, of particular importance, shrinkage stress to be enhanced.

Long-term serviceability of items made of thermally shrinkable materials depends on the stability of size when stored; being mounted, they must provide sufficient compression stress during their service life. Hence, the reverse deformation effects (in unloaded state) and stress relaxation (when loaded) must be

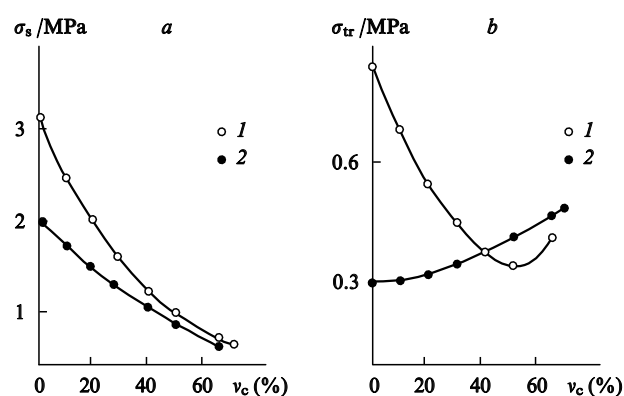


**Figure 18.** Thermal shrinkage at 293 K (a) and thermorelaxation stress at 433 K (b) plotted vs. SKEPT content in HDPE–SKEPT–10 mass % LCP (1) and HDPE–SKEPT (2) blends.<sup>154</sup>

small. In radiation-modified PE, the crystalline phase hampers the return deformation. As to HDPE–SKEPT blends, an increase in the SKEPT content causes the proportion of the crystalline phase of PE to decrease, which can lead to shortening of service life. This assumption was tested<sup>153</sup> by measuring the return deformation (with load removed) of radiation-modified (absorbed dose 150 kGy) HDPE–SKEPT and HDPE–SKEPT–LCP samples heated to 423 K and stretched by 100% during cooling to room temperature in the loaded state (with fixed ends).

As samples are released from the clamps, a conditionally instantaneous shrinkage occurs. Subsequent reverse deformation is damping in character. A decrease in the preset extension depends on the material's composition. In particular, the decrease for the HDPE–SKEPT (20:80) blend was 33% [cf. 8% for the HDPE–SKEPT–LCP (25:65:10) blend] after 1000 h; *i.e.*, the addition of LCP improved the size stability of the oriented articles. Clearly, the reverse deformation is hampered by not only the crystalline phase of HDPE but also the liquid-crystalline polyester, which acts as a reinforcing agent when oriented.

Few studies on the SME in filled polymer composites are available. This may be due to the fact that the addition of fillers usually deteriorates the operating parameters of SME. Publications<sup>90, 92, 93, 171</sup> are concerned with the shape memory behaviour of polymerisation-filled, UHMPE-based composites extruded using a process proposed in Ref. 158. The fillers used were aluminum and bauxite. It was established that composites and UHMPE exhibit qualitatively similar dependences of the degree of shape recovery  $\Psi$ , estimated from the change in the cross section of extrudates, on  $\lambda$ . In both cases a nearly linear increase in  $\Psi$  is observed as  $\lambda$  increases from 1 to 9. However,  $\Psi$  decreases in absolute value in the order UHMPE–UHMPE-bauxite–UHMPE–Al. It was shown that shape recovery is due to rearrangement of the crystalline phase, as indicated by correlations between, *e.g.*,  $\Psi(T)$  and the temperature dependences of the degree of crystallinity and between  $\Psi$  and an increase in the degree of crystallinity due to orientational stretching.

Thermal shrinkage and molecular orientation of polymerisation-filled composites can be correctly described in the framework of the rubbery elasticity theory, namely, by the Mooney–Rivlin phenomenological equation<sup>171</sup>

$$\lambda_c^m = (\lambda^2 - \lambda^{-1}) \left( \frac{2C_1 + 2C_2}{\lambda} \right), \quad (13)$$

where  $\lambda_c^m$  is the degree of molecular orientation corrected for the presence of filler<sup>2</sup> and  $C_1$  and  $C_2$  are constants. In the case of molecular orientation,  $C_2 = 0.615$  for UHMPE–Al (70 mass %) and 0.53 for UHMPE–bauxite (45 mass %), the corresponding values for thermal shrinkage are 0.015 and 0.030; the  $C_1$  constants are zero in both cases.<sup>171</sup> Since the constant  $C_1$  is associated with the entropy contribution, it was concluded that entropy does not contribute to molecular orientation and thermal shrinkage and that the driving force of these processes is rearrangement of the crystalline phase during solid-phase extrusion. Comparison of the  $C_2$  constants for molecular orientation and thermal shrinkage showed that in the former case the proportion of structural regions involved in the rearrangement is much higher. While molecular orientation occurs involving the whole crystalline phase, thermal shrinkage involves only defect crystallites formed in the course of orientation crystallisation. This also follows from the fractal model for shrinkage.<sup>93</sup>

Conventionally, shape memory effect in polymeric materials is not accompanied by considerable changes in volume. However, as mentioned above, if a porous structure was created in the initial homopolymer billet<sup>34</sup> or discontinuities appeared as a result of internal stress relaxation on heating of oriented polymer blend samples,<sup>149</sup> shape memory effect is accompanied by an increase in volume. This effect can also be achieved by introducing a porous filler, in particular, thermoexpanded graphite (TEG) into the polymer matrix.<sup>172–176</sup> TEG has good compactibility, which

allows large deformations to be obtained when fabricating a compact billet. Subsequent heating of the billet will not be accompanied by recovery of the initial dimensions. At the same time, at particular TEG content in the EP–TEG system, it is possible to prepare a composite, which is well-deformable and possesses the ability to complete shape recovery, which occurs on heating to a temperature above the glass transition temperature.

Figure 19 presents the results of a study<sup>175</sup> of cylindrical rods deformed by compression in a mould. Heating of such samples in the unloaded state causes an increase in their length but their diameters remain unchanged. The largest  $\Delta l/l$  or  $\Delta V/V$  values can reach 45% at a TEG content of 6 mass %–8 mass %. As the degree of deformation decreases, this interval extends towards higher TEG content.

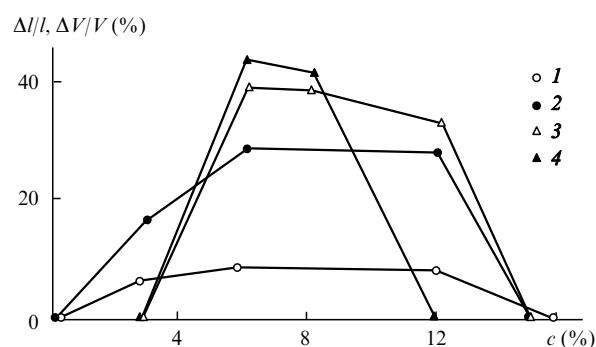


**Figure 19.** Relative change in length (volume) plotted vs. TEG concentration in an EP–TEG system.<sup>175</sup>  
 $\varepsilon$  (%): 10 (1), 30 (2), 40 (3), and 45 (4);  $T_h = 358$  K.

Taking into account the results considered above, thermal shrinkage studies of sleeve-shape samples were carried out. It was found that at a TEG content of 6 mass % in the composite, a piped sample can be deformed by up to 60%. On subsequent heating of the sample in the unloaded state the internal diameter decreases to the initial value while the outer diameter and length remain unchanged.

Rod-like articles capable of increasing their diameter with retention of length on heating were prepared using hydrostatic compression of cylindrical billets with fixed ends at 50–100 MPa. Such rods can be used for fabrication of disks with radial increase in volume.

By and large, TEG-filled composites based on UHMPE and PP behave similarly to EP–TEG composites.<sup>175</sup> At the same time, in contrast to the thermosetting composite, the degree of shape recovery for these materials is less than 100% up to the melting temperature of the crystalline phase of the polymer.

A physical model proposed to describe the kinematics of deformation of the porous composite is available.<sup>173, 175, 176</sup> The model was employed to construct the limiting surface of the material in the strain space. The limiting surface restricts the region where the material deforms without failure and represents the surface of a pyramid (Fig. 20). The basal plane,  $S_0$ , of the pyramid corresponds to the situation where the material deforms with no change in volume; the plane  $S_1$  corresponds to the limiting compaction of the composite; and the  $A$ -point corresponds to failure of the composite under cubic strain only. The compact material can be deformed only within the  $S_0$  triangle, on the boundaries of which the polymer fails. The porous polymer can be deformed within the truncated pyramid with the bases  $S_0$  and  $S_1$ . On the lateral surface of the truncated pyramid, the polymer matrix fails while the upper base corresponds to complete closure of pores.

At a sufficiently high porosity, the  $S_1$  plane will move beyond the  $A$ -point. In this case the reversible strain of the porous composite will be restricted by the pyramid of the limiting surface.

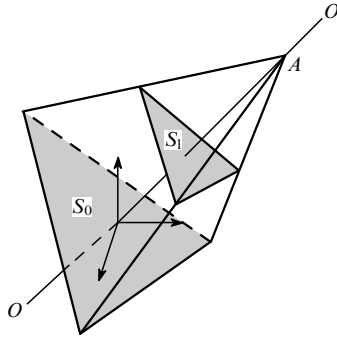


**Figure 20.** Limiting surface of porous composite in the strain space.<sup>175</sup>

Attempts at further compacting of the material in the stage of initial straining will lead to destruction of the polymer matrix and the recovery of the sample on heating will be incomplete.

Theoretical analysis showed that by prestraining the porous polymer or composite it is possible to form structures which, when recovering their shapes, imitate materials with different (including negative) Poisson ratios (coefficients of proportionality between the longitudinal and lateral strain developed during shape recovery of the sample).

The limiting relative change in the volume of the composite is given by<sup>175</sup>

$$\varepsilon_{\text{lim}} = \frac{\delta_V(1 - \theta)}{1 + \delta_V}. \quad (14)$$

Here  $\delta_V$  is the volume fraction of the filler prior to deformation ( $\delta_V = V/V_p$ , where  $V$  and  $V_p$  are the volumes of the porous filler and the polymer matrix, respectively),  $\theta$  is the relative bulk density of the filler in pores of the composite prior to deformation ( $\theta = V_1/V$ , where  $V$  and  $V_1$  are the volumes of the filler prior to and after deformation, respectively). This relationship shows that the lower the bulk density of the filler, the larger the absolute value of  $\varepsilon_{\text{lim}}$  and, therefore, the farther the  $S_1$  plane from the origin. This conclusion is in agreement with experimental results.

From relation (14) it follows that, at a high TEG volume fractions in the composite, the absolute value of  $\varepsilon_{\text{lim}}$  can become so large that the  $S_1$  plane will shift beyond the vertex  $A$  of the limiting surface. This means that there is a maximum permissible concentration of the carbon material in the composite.

Thermally expanded graphite is a conducting filler; therefore, shape-memory studies of the TEG-filled composites are of particular interest because the carbon material affects peculiar features of the shape memory effect<sup>173–177</sup> while the effect in question in turn affects the conductivity of the composites. Particular attention should be paid to the polymer composites with the nearly threshold filler content, at which the insulator–conductor transition occurs.<sup>178, 179</sup> In particular, being heated, these materials exhibit the effect of self-regulation of the heating temperature, which consists in a dramatic increase in the resistance in a certain critical temperature interval and is due to the thermal expansion of the polymer matrix.<sup>178</sup> However, the range of threshold concentrations is characterised by a very large scatter of resistance values owing to nonuniform distribution of the filler particles over the volume of the matrix, which hampers the attainment of the result mentioned above.<sup>180</sup> This problem can be solved by using those materials which recover their shape with simultaneous increase in volume on heating. Shape-memory behaviour is characterised by a much greater increase in the distances between contacting filler particles that are involved in the conduction process compared to thermal expansion of the polymer matrix. From here one has a wider interval of filler concentrations in which the resistance increases jumpwise.

We studied the resistance of the EP–TEG composite based on diglycidyl phthalate and a block oligomer of aliphatic epoxy resin with acid oligoether cured with isomethyltetrahydrophthalic anhydride. It was established that, at the TEG concentration of nearly 6 mass %, heating of the billets deformed by mould compression causes a sharp increase in the resistance near  $T_g$ . The bulk resistivity ratio corresponding to the deformed ( $\rho_d$ ) and recovered ( $\rho_r$ ) states can be as high as three orders of magnitude (Table 2).

**Table 2.** Characteristics of carbon-containing epoxy composites.

| Composite               | $\varepsilon$ (%) | $\rho_d$<br>/ $\Omega$ m | $\rho_r \times 10^{-3}$<br>/ $\Omega$ m | $\rho_r/\rho_d$ |
|-------------------------|-------------------|--------------------------|-----------------------------------------|-----------------|
| EP + 3% TEG             | 20                | 64 000                   | 502                                     | 11              |
| EP + 6% TEG             | 20                | 138                      | 60                                      | 435             |
|                         | 20                | 109                      | 60                                      | 550             |
|                         | 30                | 91                       | 60                                      | 659             |
|                         | 40                | 69                       | 60                                      | 870             |
| EP + 10% TEG            | 25                | 38                       | 10                                      | 263             |
| EP + 6% TEG + 2% kaolin | 25                | 154                      | 11                                      | 71              |
| EP + 6% TEG + 3% kaolin | 25                | 5.6                      | 4                                       | 714             |
| EP + 6% TEG + 4% kaolin | 25                | 90                       | 30                                      | 333             |

Introduction of a binary filler including kaolin powder led to significant changes in the electrical properties of the composite (see Table 2). At the same (with the EP–TEG composite)  $\varepsilon$  values, the absolute values of  $\rho_d$  and  $\rho_r$  decrease in the presence of kaolin. The minimum  $\rho_d$  value and simultaneously maximum  $\rho_r/\rho_d$  ratio were established for the EP–TEG–kaolin (100 : 6 : 3) composite.

Analysis of the strain kinematics and subsequent strain relaxation showed the following. Low bulk density and good compactibility of TEG favour the decrease in the volume of the TEG-filled cavities in the initial cured billet upon deformation due to compression of the filler and filling of the voids thus formed with the polymer. The concentrations of TEG in the composites under study is high enough to ensure the conducting state of the materials, *i.e.*, the presence of a continuous infinite cluster of the filler particles. An increase in the TEG concentration or the degree of deformation of the material causes an increase in the contact area between the TEG particles and thus a decrease in the  $\rho_d$  value (see Table 2). When heated to temperatures close to  $T_g$ , at which the mobility of the chain fragments between cross-link points of the polymer network unfreezes, the deformed samples recover their shape (their volumes increase) through sample elongation. The polymer leaves pores and TEG remains in the compacted state. Breakage of bonds between the particles of the conducting cluster causes a decrease in the contact area and, as a consequence, an increase in resistance. The process goes to completion when the glass transition temperature is achieved and the shape recovery induced change in the length of the sample ceases.

Microstructural studies showed that the TEG distribution over the bulk of the polymer matrix in the presence of kaolin is more uniform, which favours an increase in the conductivity of the system. The results obtained are consistent with the published data (introduction of kaolin into epoxy polymer filled with graphite also led to a decrease in the system's resistivity).<sup>181</sup> This effect can be used in short-circuit thermal protection, namely, current limiters can be made of a shape-memory material.

## V. Polymer gels

Considerable interest<sup>16, 182–196</sup> of researchers in polymer gels as shape-memory materials is due to the fact that their volume can change by three orders of magnitude under the action of external factors (*e.g.*, temperature, solvents, electromagnetic field, *etc.*). Particular attention should be paid to polymer hydrogels in which water molecules fill the intermolecular space of the polymer



network. These materials are soft and ‘wet’, which improves their compatibility with biological tissues.<sup>186, 187</sup> The shape memory effect underlies the design of temperature-sensitive diaphragms, thermally activating clamps, ‘soft’ machines and other medical instruments.<sup>186</sup>

The mechanical properties of many water-swollen gels strongly depend on temperature. For instance, a gel prepared by copolymerisation of acrylic acid with *n*-stearyl acrylate<sup>188</sup> behaves as a hard plastic below 298 K. But at temperatures above 323 K it becomes very soft and can be stretched by 50% relative to its initial length. The elastic moduli of this material decrease by three orders of magnitude on heating, which can be due to reversible order–disorder transition associated with interactions between the alkyl side chains of the stearyl acrylate units. At  $T < 323$  K, long alkyl chains form the crystalline structure which reinforces the material. Above this temperature, the material has an amorphous structure, being soft and flexible. It is believed<sup>186</sup> that this mechanism (formation of crystalline aggregates between the side chains) causes the SME in the material.

The gel ‘remembers’ the shape in which it was initially formed. To show the shape memory, the gel is heated above the transition temperature (323 K), deformed (*e.g.*, stretched or coiled) and then cooled in the deformed state. If the unloaded, deformed gel is again heated, at  $T > 323$  K it recovers its initial shape and size in ten seconds.<sup>186</sup> It should be noted that the shape recovery rate and the degree of swelling can strongly depend on the temperature at which the gel was prepared. For instance, at  $T_p = 293$  K the degree of swelling of *N*-isopropylacrylamide gel is low ( $d/d_0 = 1.2$ , where  $d$  and  $d_0$  are the diameters of the swollen and freshly prepared gel, respectively). However, as  $T_p$  approaches the phase separation temperature (305 K) the  $d/d_0$  ratio considerably increases and then again decreases to 1.46 at  $T_p > 305$  K, which correlates with spatial inhomogeneity in the gel.<sup>197</sup> In turn, the shrinking time decreases from 500 min at  $T_p \leq 293$  K to 2 min at  $T_p \geq 299$  K.

Spatially modulated polymer gels prepared by restricting interpenetration of gel networks are widely used for fabrication of articles for biomedical applications.<sup>185, 195</sup> These are, *e.g.*, a bigel plate, which can bend and eventually form a ring with an increase in temperature or solution concentration; a gel, which changes its shape from a straight line to a pentagon and then to tetragon depending on temperature; a gel ‘hand’ which can clench or unclench various material things on temperature variation. The operation of these ‘devices’ is based on the ability of gels to change their volume depending on the environmental conditions.<sup>198–200</sup> Examples of spatially modulated gels are provided by the systems based on *N*-isopropylacrylamide (IPA) and acrylamide (AAM) gels.<sup>185</sup>

It is known<sup>201</sup> that the volume of ionic IPA gel rapidly decreases at  $T > 310$  K, whereas such is not the case for the AAM gel. In turn, it is the AAM rather than IPA gel that shows a large shrinkage in water-acetone mixtures. At room temperature, a completely swollen bigel plate is bent towards the AAM gel. If  $T > 310$  K, the plate is gradually bent due to shrinkage of the IPA gel and eventually forms a ring. Being immersed in a water-acetone mixture at room temperature, the plate hoops in the opposite direction but the ring can also be formed. Transition from the linear to a bent shape is reversible and the change in the degree of bending depends only slightly on the number of straightening–bending–straightening cycles, being at most 3% after 9 cycles.

Bending deformation can be estimated from the angle  $\theta$  between two tangent lines drawn to the ends of the gel arch,

$$\varepsilon = \frac{\theta d}{L},$$

where  $d$  and  $L$  are the diameter and the length of the gel sample, respectively. The maximum deformation of bigel is 49%.<sup>185</sup> This greatly exceeds the deformation developed in the polyvinyl alcohol–poly(sodium acrylate) system on application of an

electric field ( $\varepsilon = 20\%$ ).<sup>202, 203</sup> The kinetics of the shape memory effect in the bigel plate mentioned above can be followed using the plots shown in Fig. 21. Deformation of gel immersed in a high-temperature bath (311 K) increases with time; on cooling to 295 K the bigel gradually recovers its initial shape and size.

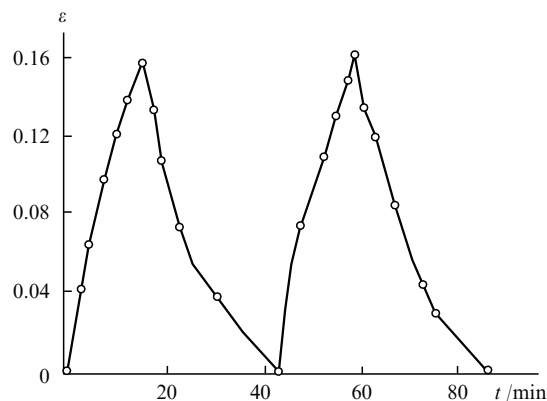


Figure 21. Bending deformation cycles plotted vs. time for bigel.<sup>185</sup>

The bigel bending mechanism<sup>185</sup> differs from the mechanisms of shape memory effects induced by electric field<sup>187, 192, 202, 203</sup> or by heating with an IR laser.<sup>184</sup> In the last two cases trigger-type bending of macroscopically homogeneous gels requires the presence of an electric or temperature field gradient. Clearly, these methods are inappropriate to achieve a high degree of deformation ( $\theta > 180^\circ$ ) owing to difficulties in the creation of high field gradients. The thermal expansion coefficients of two gels can differ much more than the corresponding parameters of two metals (*cf.* more than 0.5 per degree for the IPA–AAM bigel vs.  $\sim 7 \times 10^{-6}$  per degree for a typical brass–steel bimetallic plate; the difference is nearly five orders of magnitude). Therefore, bigels are much more sensitive to temperature changes in the environment compared to bimetals.

Compared to the bigels considered above, gels with a more complex modulated structure allow a variety of reversible transitions to occur. In addition to the ‘straight line–pentagon–tetragon’ transition (see above), they also include transitions to a sinusoid and helix, a transition from a planar sheet to a tube, *etc.* Such a diversity of transitions at different temperatures is achieved by appropriate modulation of particular regions of the polymeric systems. In this Section we restricted ourselves to illustration of those possibilities of polymer gels that are related to the thermally induced SME. A great body of information on the subject, including modern practical applications and promising projects, was summarised and analysed in a review.<sup>191</sup>

## VI. Conclusion

In the last decade, the shape memory effect in polymers has been the subject of intensive research. This provides diverse information on the structure of oriented polymers and mechanisms of their deformation and favours better understanding of the kinetic laws of thermally stimulated relaxation. New studies begin, aimed at the design of polymeric materials offering new possibilities for the shape memory effect to occur; this is important for the extension of the spectrum of practical applications of these materials. Interest in the SME studies is in line with rapid development of research on the so-called ‘smart’ or ‘intellectual’ materials including shape-memory polymers. Compared to shape-memory metal alloys, shape-memory polymers offer a number of advantages (low density, high strain-recovery ability, ready processability and dyeability and relatively low cost). It is also important that the SME in polymeric materials occurs at temperatures close to room temperature and in some cases these

materials can be controlled with ease by varying the chemical composition of the polymers.

Among recent achievements, there are considerable advances in studies of the properties (in particular, the LTR mechanism) of glassy polymers;<sup>46–48, 62</sup> preparation of unusual shape-memory polymeric materials (polymer composites with compactible filler,<sup>173, 175</sup> spatially modulated polymer gels<sup>185, 195</sup>); and fabrication of various articles for technological and biomedical applications from shape-memory functional materials.<sup>94, 95, 116, 127, 142</sup> There are also a number of problems that are still to be solved and require further investigations. In particular, the mechanism of SME in amorphous-crystalline polymers is still to be clarified and the mechanism of shape recovery and its relation to the state of the structure of such promising materials as oriented biodegradable polymers<sup>204, 205</sup> and the polymer blends and composites modified by various additives remain poorly studied. Search for new fields of application of shape-memory polymeric materials also remains an important investigation avenue.

Solving problems mentioned above requires further investigations of various aspects of SME in polymeric materials, aimed at gaining a deeper insight into the mechanisms of the shape memory effect, generalisation of experimental data and formulation of practical recommendations for potential users.

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# Directed evolution as an approach to the design of efficient biocatalysts

S N Zagrebelny

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**Abstract.** Methodical approaches to the modification of the catalytic properties of enzymes by various means of directed evolution are summarised. A number of particular examples of the design of enzymes with new and enhanced properties, including higher thermal stability, solubility, substrate specificity, stereoselectivity, *etc.*, are considered. The prospects for further development of the directed evolution strategy for enzymes and proteins with other functions are discussed. The bibliography includes 67 references.

## I. Introduction

Enzymes are used more and more often in industrial engineering processes. The well-known advantages of enzymes over conventional catalysts include reduced energy consumption due to much higher efficiency, lower material consumption due to high specificity, simpler process design due to a smaller number of product isolation and purification stages, and so on. However, in some cases, these advantages turn into drawbacks. Enzymes, like other proteins, are subject to irreversible denaturation with temperature rise, treatment of organic solvents, or at higher or lower pH values. The too high specificity often does not allow the use of enzymes for reactions of the same type with a broad range of substrates belonging to the same class of compounds but having somewhat different structures. This brings about the task of modifying the properties of enzymes in order to extend the scope of their applicability.

The state-of-the-art knowledge of the principles of organisation of protein molecules does not allow one to predict what properties would arise upon targeted replacement of particular amino acid residues, although methods for such replacement have been developed rather thoroughly at the level of modifications of the corresponding genes. In recent years, methods for enzyme

modification by introducing random changes into the structure of the protein macromolecule have been proposed. This gives rise to a broad range of structures which may include the optimal ones for the solution of the particular problem. Then molecules with preferred properties are selected. These manipulations are repeated in several consecutive stages to finally obtain a variant that complies with the task. This approach is called 'directed evolution.' This review presents consideration of various types of this method and evaluation of the results, relying on the data published in 1993–2003.

## II. Key ways of directed evolution of enzymes

The modification of enzymes has been known for long time. Over several decades, this has been done mainly using specific chemical methods and has aimed at elucidating the role of particular amino acid residues in the mechanism of the catalytic action of enzymes.

The accumulation of data on the structures of enzyme-encoding genes and the development of the experimental procedures for work with genetic material provided the possibility of modifying the enzyme molecules by directed mutagenesis. This allowed more detailed investigation of the structure-functional organisation of enzymes. Simultaneously, attempts to modify enzymes in order to improve their operation properties for use in industry have been undertaken. This gave rise to a new line of research in molecular biology, 'protein engineering.'

However, currently it is impossible to predict the influence of one or other amino acid replacement on protein function. This is despite the numerous data on the 3D structures of enzymes obtained by X-ray diffraction and development of computer modelling (for example, molecular dynamics calculations). This is why methods of modification of enzyme properties along a specified direction based on the introduction of random replacements at the gene level followed by selection of the mutant variants according to a specified criterion have experienced vigorous development. In the numerous publications in this direction, one can distinguish several major approaches.

### 1. Incremental truncation for the creation of hybrid enzymes

Benkovic and co-workers<sup>1</sup> proposed a combinatorial approach in genetic engineering called incremental truncation. For this purpose, the gene encoding this enzyme is split into unequal parts in

S N Zagrebelny Novosibirsk State University, ul. Pirogova 2, 630090 Novosibirsk, Russian Federation. Fax (7-3832) 39 71 01, tel. (7-3832) 30 06 56, e-mail: snz@post.nsu.ru

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two different ways using different restriction endonucleases so that in one fragment pair, the fragment encoding the N-terminal part of the protein is longer, while in the other pair, the longer fragment is that encoding the C-terminal part. The longer fragments are cloned in different plasmids. This gives the overlapping fragments of a gene, which can be modified independently. Then each fragment is truncated 'from the inside' by treatment with exonuclease. This results in generation of variants with deletions in the gene fragments that encode the N- and C-parts of the protein. The plasmids thus obtained are introduced simultaneously into the same cells devoid of the enzyme under study. The combined expression of gene fragments restores the ability of cells to grow on a minimum medium until the catalytic site of the enzyme is damaged due to shortening of the gene fragments. Using this method, the points at which some of the inner sections of the polypeptide chain can be removed without substantial damage of the catalytic properties of the enzyme were identified, and the monomeric enzyme (glycinamide ribonucleotide formyltransferase from *E. coli*, PurN) was converted into its functional heterodimer.

It is evident that the proposed method allows one to study the structure-functional organisation of the enzyme. Subsequently, chimeric enzymes were produced, irrespective of the degree of DNA homology, using the Incremental Truncation for Creation of Hybrid Enzymes (ITCHY) technique. Figure 1 shows a diagram showing the use of this method to create libraries of modified genes.

The possibility of this non-homologous recombination giving rise to interspecies functional hybrids was demonstrated<sup>2</sup> in relation to PurN and its analogues, the human GART enzyme (hGART), which have only a 50% homology at the DNA. ITCHY libraries between the amino end of PurN and the carboxy end of GART were obtained by successive truncation of the encoding sequences with exonuclease III and ligation of products. The most active PurN-GART hybrid was about 500 times less active than the wild-type PurN.

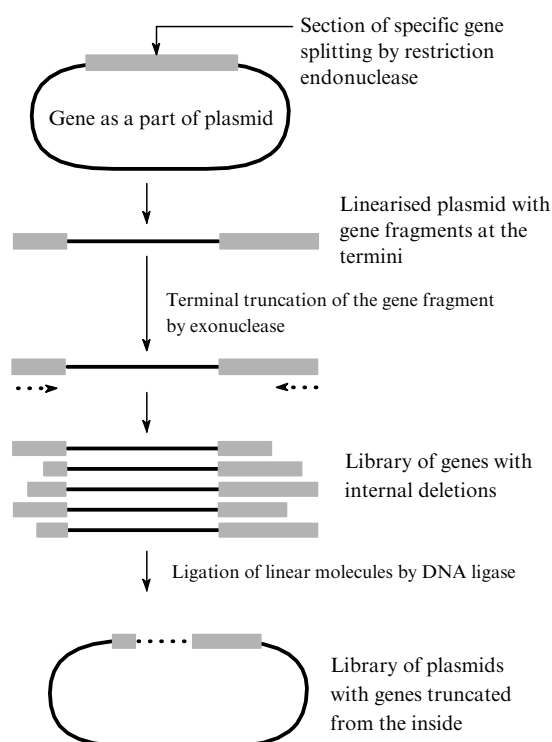


**Figure 1.** Block diagram for the creation of the library of modified genes by stepwise truncation of enzyme genes with non-homologous recombination.

Subsequently,<sup>3</sup> more general approaches to the compilation of libraries of shortened gene fragments have been proposed based on the possibility of assembling enzyme molecules from large numbers of molecular building units. To this end, when conducting the polymerase chain reaction (PCR),  $\alpha$ -thionucleoside triphosphates are added to the reaction mixture in order to insert  $\alpha$ -thiophosphate units into the chain being formed. During the subsequent cutting of gene fragments, exonuclease 'stops' at these units. The positions in which the thiophosphate residues occur are generated randomly, thus giving a set of fragments that compose the library. Its components can further undergo recombination *in vitro* in any combinations. Using *E. coli* PurN and its analogue, hGART, functional hybrids with recombination points in the regions with minimum homology were obtained.

The advantages of molecular evolution with non-homologous recombination *in vitro* require further investigation.

## 2. Evolution of enzymes by DNA family shuffling

The term 'DNA shuffling' has been proposed by Stemmer.<sup>4,5</sup> Figure 2 shows the pattern of creation of gene libraries by this method. The key idea of the approach is to generate short fragments of the nucleotide sequence of the gene, to multiply fragments using error-prone PCR (as a method for introducing random mutations), to assemble full-size gene sequences by means of PCR and finally to select the variants that meet the conditions imposed by the task set. The fragmentation is accomplished by hydrolysis of a large gene (the researcher cited used a ~1 kb long gene) with DNase I up to a pool of random fragments with a size of 10–50 bp. These fragments can further be assembled into a full-size gene by repeated hybridisation cycles in the presence of a DNA polymerase. The fragments themselves serve as primers due to the presence of homology, recombination taking place when

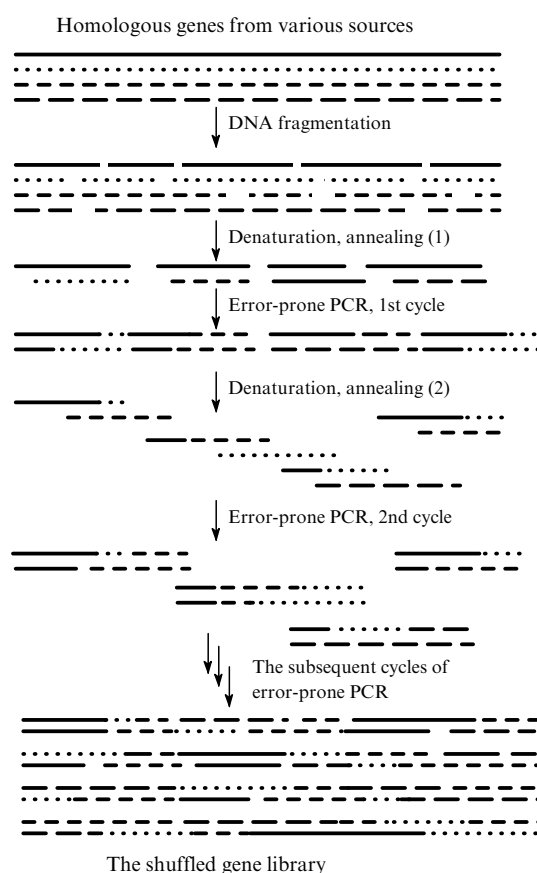


**Figure 2.** Block diagram for the creation of the library of modified genes by DNA family shuffling.

fragments from one copy of the gene initiate the synthesis on the other copy (which results in template switching). At the end of this round of procedures, selection is performed the pattern of which is chosen in conformity with the project goal. The selected best variant (or several promising variants) is subjected to one more set of the same procedures with the subsequent selection. Several DNA shuffling and selection cycles result in a satisfactory variant, which is subsequently cloned in vectors ensuring a high expression level. Stemmer demonstrated the potential of this approach in relation to *E. coli*  $\beta$ -lactamase and  $\beta$ -galactosidase and to interleukin 1. Shuffling can be performed for one gene to obtain its multiple variants or for families of homologous genes from different sources including those encoding enzymes that catalyse transformations of substrates with related structures. In the latter case, the probability of obtaining improved variants is higher; however, if the number of variants is too great, the selection process would be hampered.

It should be noted that each DNA shuffling gives rise to point mutations. This is undesirable when working with large genes, because the number of variants, among which selection is to be performed substantially increases. A new DNA shuffling protocol increases the accuracy of the procedure at the stages of fragmentation of the modified gene by DNase I, PCR and the assembly of the full-size gene.<sup>6</sup> This protocol includes, in particular, the replacement of  $Mg^{2+}$  ions by  $Mn^{2+}$  ions, the limited use of PCR (whenever possible) and the application of more accurate DNA polymerases. The frequency of mutations also decreases when a mixture of *Taq* and *Pfu* (or *Pwo*) in a 1 : 1 ratio is used. Finally, the mutation frequency was decreased to 0.05% and even below; in the case of large genes, this provides the possibility of obtaining a sufficient number of active variants. Further improvement of the protocol can be directed at decreasing the number of PCR cycles and using only *Pfu* polymerase, characterised by higher accuracy than *Taq* polymerase, in the last cycle.

The DNA family shuffling or evolution by recombination *in vitro* of natural homologous genes has been used to improve some properties of enzymes. The thymidine kinase of the herpes simplex virus (HSV TK) is used to obtain thymidine analogues suitable as antiviral agents. The homologous human enzyme has a high specificity towards thymidine, and its use for the synthesis of virus replication inhibitors is of low utility. In a study,<sup>7</sup> shuffling was performed for the two most closely related thymidine kinase genes from different strains of this virus (78% of DNA homology) in order to select chimeras with an enhanced ability to phosphorylate zidovudine (3'-azidothymidine, AzT). Four shuffling cycles resulted in two clones, which increased the sensitivity of the *E. coli* TK to AzT by a factor of 500 relative to the more active HSV-1 enzyme and by a factor of 4000 relative to HSV-2. The shuffling involving HSV-2 increased the yield of sensitive clones, although this enzyme is more stable with respect to AzT.

Under real conditions, an improvement of combinations of enzyme properties is as important as the enhancement of particular features. The shuffling of 26 subtilisin genes from various sources (56%–99% of DNA identity) has been reported.<sup>8</sup> Subtilisins are proteinases of the bacterial origin, which are used in food industry (to upgrade tough meat), in leather industry (to remove hair from the skin of animals), in medical industry (to prepare protein hydrolysates for parenteral feeding), *etc.*, are of substantial practical interest. Genes from various bacteria were used to generate chimeric libraries, which were evaluated using four parameters: activity at 23 °C, thermal stability, resistance against organic solvents and the pH dependence of the activity. Chimeras possessing all combinations of properties of the individual parent enzymes were identified, and structures with markedly improved particular properties have been found.

Controlled evolution methods have been used<sup>9</sup> to study the relationships between the stability and the activity of the mesophilic esterase. Previous studies of these properties in homologous enzymes have shown that the rise of the inactivation temperature under thermal treatment is incompatible with retention of a high

catalytic activity at low temperatures. One reason is the different conformation states (in particular, flexibility) responsible for stability and activity. Six generations of statistical mutagenesis, recombination and selection have substantially stabilised the *Bacillus subtilis* *p*-nitrobenzyl esterase (the inactivation temperature increased by more than 14 °C) without deterioration of the catalytic activity at lower temperatures. Analysis of the stability and the activity for a large number of random mutants has shown that these properties are not inversely correlated; nevertheless, mutations that increase the thermal stability while maintaining the low-temperature activity are very rare. Thus, evolution of one feature through accumulation of single amino acid replacements usually takes place at the expense of another feature, irrespective of whether these features obey an inverse correlation or do not correlate at all.

Directed evolution<sup>10</sup> has been proposed for modification of properties of diversified enzymes. This enables fast optimisation of enzymes as regards one or several properties even when data on the structure or the mechanism of action are missing. Directed evolution experiments make use of a simple Darwinian optimisation algorithm with successive approximations. The molecular diversity is brought about by random mutagenesis and/or recombination of the target gene or a family of connected genes. The modified variants are identified by selection, which allows one to choose the required variants. The genes encoding these improved enzymes are used as the initial ones for the subsequent evolution round.

During shuffling of DNA families, the DNA fragmentation by means of restriction endonucleases (instead of DNase I) increases the yield of recombinants<sup>11</sup> due to an increase in the chimerisation frequency. For example, an increase in the chimerisation frequency from 1% to 100% has been observed between two catechol-2,3-dioxygenase genes (*xylE* and *nahH*) from different sources having a 84% identity in the DNA sequence. Hydrolysis of each of the parent genes by several sets of restriction endonucleases resulted in the formation of more diverse chimeric structures, and the hybrid variants thus obtained were 8–13 times more stable at 50 °C than the parent enzymes.

A DNA shuffling protocol called degenerate oligonucleotide gene shuffling (DOGS) with an enhanced yield of target products in the molecular evolution of the gene has been described.<sup>12</sup> The advent of this new procedure was due to the fact that the proportion of parent (unshuffled) gene variants in the case of DNA fragmentation by DNase I was too high. This stipulated the necessity of labour-consuming screening for the selection of the chimeric genes, especially in the case of shuffling of loosely related DNA sequences. The new approach was tested using a family of xylanase genes from various sources. These enzymes are of interest as regards the development of advanced processes for the treatment of wastes from the wood processing industry: for destroying hemicelluloses and subsequent use of the hydrolysis products (*e.g.*, in the industrial production of ethanol). On the basis of homology of amino acid sequences, fragments were identified in the gene structures and degenerate primers used subsequently for amplification of these gene fragments were constructed. The amplification products were mixed and subjected to joint amplification to obtain full sequences of these genes. This gave a library of chimeric variants. The degree of mosaicism could be varied by specifying the ratio of the initial amplified fragments. The extensive library thus obtained contained variants that differed appreciably in the optimal temperature. Analysis of the nucleotide sequences of these variants identified the origin of the fragments contributing to new properties of enzymes. However, no variants with a changed optimal pH were encountered in this case. This was attributed to the fact that the enzyme active site incorporates two glutamic acid residues, which act as a nucleophile and an acid catalyst, respectively. The replacement of any of them results in the loss of a catalytic activity. This situation is apparently insurmountable in enzyme modification by this method.

A convenient supplement to DNA shuffling is heteroduplex recombination.<sup>13</sup> This method allows one to create libraries of chimeric DNA sequences derived from two homologous parent sequences. First, heteroduplexes are obtained *in vitro* from the parent sequences and then they are used to transform cells of an appropriate host. During the intracellular reparation, chimeric gene libraries are formed. No physical exchange by fragments of the parent genes takes place. The heteroduplex recombination generates numerous chiasmata and can be especially useful for recombination of large genes or whole operons. The method, however, has limitations: the more remote the mutation sites from each other, the higher the recombination frequency. The minimum distance between the mutated units that still allows recombination is 24 bp.

### 3. Staggered extension process (StEP)

The StEP procedure has been proposed by Zhao *et al.*<sup>14</sup> (Fig. 3). A polymerase chain reaction on a target enzyme gene is initiated by one pair of primers with a short-term stage of chain growth. The PCR products are then subjected to denaturation followed by annealing (heat-induced denaturation–renaturation) during which the synthesised fragments are switched to other chains of the template as all fragments possess a sufficient degree of homology. The process continues until a full-size gene is formed. Owing to switching of the growing chains from one template to the

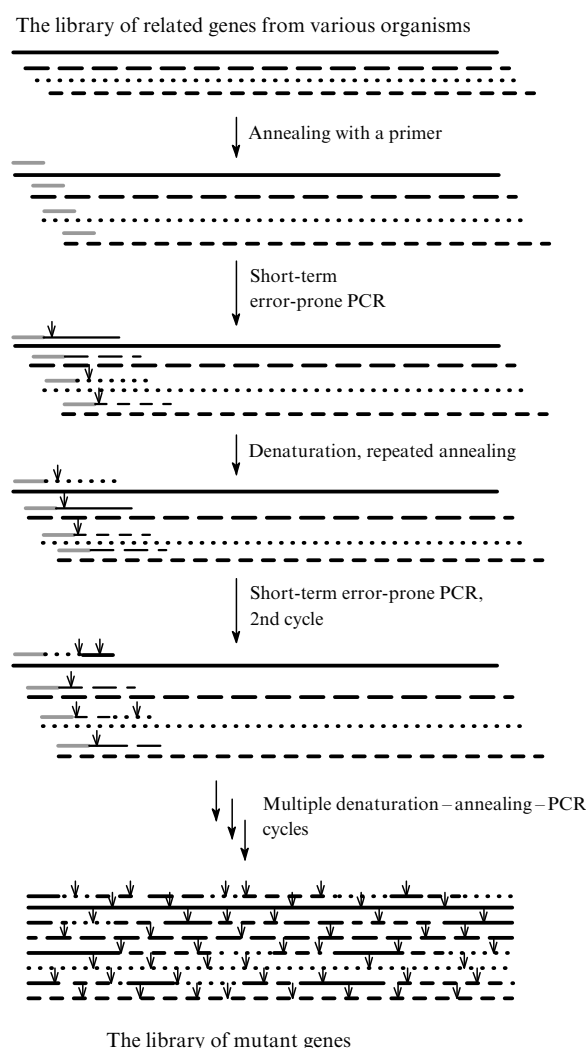


**Figure 3.** Block diagram for the creation of a library of modified genes by the staggered extension technique; v are the positions of random mutations.

other, gene libraries for recombination containing information from different parent genes are formed. This approach has been used to obtain a thermally hyperstable variant of subtilisin E. The wild-type enzyme from the mesophilic strain *B. subtilis* has a half-inactivation time of ~5 min at 65 °C. The mutagenesis using the error-prone PCR and the subsequent selection gave rise to five variants with a 3–8-fold increase in the half-inactivation time. Equal amounts of genes of these five variants were subjected to StEP recombination. About 8000 clones expressing the resulting variants were tested for stability at 75 °C and three variants with half-inactivation times (at 65 °C) 25–50 times longer than those of the wild type were selected.

The efficiency of StEP recombination is close to that of other *in vitro* recombination methods; however, StEP can be used in one pot, as it does not require separation of the parent sequences and recombination products.

### 4. Random priming recombination (RPR)

An even simpler method for the compilation of mutant gene libraries has been proposed<sup>15</sup> (Fig. 4). For this purpose, a copy of the gene subject to modification (obtained by PCR amplification) is used as a template in the PCR, while a random set of oligonucleotides containing six nucleotide residues (dpN<sub>6</sub>) serve as primers. This PCR using an error-prone DNA polymerase generates a large number of short DNA fragments, which prove to be complementary to different sections of the matrix sequence. These fragments contain point mutations due to both the erroneous incorporations of nucleotides by the polymerase and imperfect hybridisation of primers with the template chain. In these complexes, short DNA fragments can act as primers for one another and are assembled into the full sequence by multiple repetition of these rounds with subsequent screening and selection. This method has a number of advantages compared to the DNA shuffling.

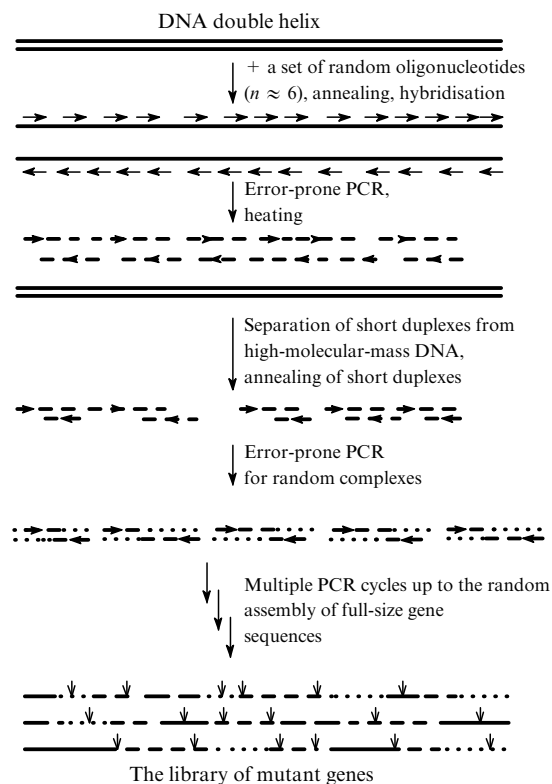


**Figure 4.** Block diagram for the creation of a library of modified genes by random priming recombination; v are the mutation points induced by the error-prone polymerase reaction.



1. For RPR recombination, both single- and double-stranded DNA can be used as the template without intermediate synthesis of the full-size second strand; potential mutations arise both at the level of single-stranded DNA using error-prone DNA polymerases and at the RNA level using RNA-dependent DNA polymerases.

2. DNA shuffling requires DNA fragmentation with the DNase I, which must be thoroughly removed prior to the assembly of a full-size mutant gene variant.

3. The random synthetic primers have equal lengths and do not induce predominant synthesis of any gene fragments. The heterogeneity of the sequence of primers allows them to form hybrids with template chains in many positions, so that each nucleotide of the template can be either copied or mutated, with the same frequency, during the chain growth. The random distributions of short fragments of the growing DNA chain along the template (or templates) and point mutations in the DNA fragment ensure the random character of distribution of the chiasmata and mutations in the progeny full-size genes.

4. The synthesis of DNA with random primers does not depend on the template length. Even on short DNA fragments (200 nucleotides long), the synthesis can be initiated equally efficiently as on large molecules (for example, on the linearised DNA of the  $\lambda$  phage). This provides unique opportunities for the engineering of short peptides.

5. Since the parent DNA chain is used only as the template for the synthesis of growing single strands, the whole cycle requires a 10–20 times smaller amount of the initial DNA than the DNA shuffling technique.

### III. Evolution of thermal stability

The enhancement of thermal stability is the widely used approach in the modification of enzyme properties. The modern concepts in changing thermal stability are discussed in reviews,<sup>16,17</sup> which report the structural features of thermally stable enzymes providing grounds for the development of rational approaches to their design and application in industry. Note the high level of similarity of primary structures of thermophilic<sup>†</sup> and mesophilic enzymes, which demonstrates once again imperfection in the state-of-the-art views on structural organisation of protein molecules and the limited nature of the prognostic conclusions.

The modification of a psychrophilic protease, subtilisin S41, has been reported.<sup>18</sup> Previously, this enzyme was subjected to three rounds of mutagenesis/recombination followed by screening. This gave a product with a half-inactivation time (60 °C) 500 times as great as that of the wild-type enzyme. Five more rounds of laboratory evolution gave a product 1200 times as stable as the wild-type enzyme and 20 times as stable as the homologous mesophilic subtilisins SSII and BPNP. About a half of 13 amino acid replacements in the resulting enzyme variants are mutations at serine residues, which occur in thermophilic enzymes less frequently than in mesophilic ones. The variant obtained after the eighth (the last) round of directed evolution contained the Asp216Glu replacement, which is not encountered in either mesophilic or thermophilic enzymes. A nearly neutral replacement resulted, nevertheless, in one more twofold increase in the subtilisin thermal stability with respect to the preceding variant.

Enzymes of thermophilic organisms are often not active enough at low temperatures. An attempt has been made<sup>19</sup> to increase the catalytic activity of the hyperthermophilic indole glycerophosphate synthetase, an enzyme involved in tryptophan biosynthesis, from *Sulfolobus solfataricus*, at moderate temperatures. Using DNA shuffling, *Sulfolobus solfataricus* mutated gene

variants able to restore the growth of the *E. coli* culture deficient in the proper enzyme were obtained. It was found that the low activity of the thermophilic enzyme at low temperatures was due to the slow dissociation of the reaction product. In modified enzyme variants, this stage is substantially accelerated, which results in a higher catalytic activity with only a minor decrease in the thermal stability. Thus, in some cases, molecular evolution methods also allow one to elucidate the structural factors responsible for the modified properties of enzymes.

The thermophilic xylose isomerase enzyme from *Thermus thermophilus* has been adapted to normal temperatures in a similar way.<sup>20</sup>

The molecular evolution of the fructosylamino acid oxidase from *Corynebacterium* sp. (strain 2-4-1) has been studied.<sup>21</sup> This enzyme is considered as a potential analytical reagent for determination of non-enzymic 'glycation' of proteins in clinical biochemical analysis.<sup>‡</sup> The researchers used mutagenesis *in vivo* by transforming the *E. coli* XL1-Red strain with the plasmid containing the fructosylamino acid oxidase gene.<sup>§</sup>

After selection of the clones with the modified enzyme, four rounds of mutagenesis and selection were carried out; finally, this gave an enzyme-expressing clone, which retained 94% activity at 47 °C (incubation for 10 min) against 1% for the wild-type enzyme. The mutagenesis *in vivo* used has a number of advantages over the error-prone PCR; however, this approach does not cover all the possibilities provided by the creation and use of mutant gene libraries.

An increase in thermal stability with the simultaneous increase in catalytic activity has been described<sup>22</sup> for the D-amino acid amidase from the soil bacterium *Ochrobactrum anthropi* SV3, which facilitates the preparation of optically pure amino acids during the synthesis of pharmaceuticals, agrochemicals and food additives. Unlike the analogues from other sources, this enzyme catalyses the transformations of a broad range of substrates (amides of amino acids), including those with a bulky side chain. The enzyme gene was subjected to molecular evolution, two rounds of PCR mutagenesis and selection gave a variant with a 5 °C higher denaturation temperature and with a higher catalytic efficiency.

### IV. Evolution of protein solubility and expression

The use of enzymes in organic synthesis brings about the problem related to their denaturation in organic solvents. Similar difficulties are faced by the development of cleansing agents that contain proteases and lipases susceptible to denaturation in the presence of detergents. Therefore, attempts have been made to develop enzymes stable against organic solvents. In particular, subtilisin has been modified by molecular evolution methods.<sup>23</sup> This was done using random mutagenesis with a polymerase chain reaction used as the generator of mutations. The selected variant of the PC3 enzyme was 130 times more active than the wild-type enzyme (subtilisin E) in a medium containing 40% DMF. The activity was also retained in a medium with 85% DMF. A study of the primary structure of the selected variant has shown that all 10 amino acid replacements were located near the active and substrate-binding sites of the enzyme. Seven of these can be found in other variants of subtilisin from different strains of the producer. Subsequently, researchers were able to enhance the subtilisin resistance against the organic environment and the thermal stability to an even greater extent.<sup>24,25</sup> Strains producing enzymes with the optimal

<sup>†</sup> The terms 'thermophilic,' 'mesophilic,' and 'psychrophilic' mean that higher, normal and lower temperatures, respectively, are preferred for enzyme functions; the normal temperature is about 37 °C.

<sup>‡</sup> The term 'glycation' is introduced to mean the non-enzymic modification of proteins (unlike glycosylation). This phenomenon takes place in the case of diabetic processes in the body and has a great diagnostic value for evaluation of the patient's condition during the therapy.

<sup>§</sup> *E. coli* XL1-Red is a mutant strain devoid of *mutS*, *mutD* and *mutT* genes, which participate in the DNA repair. The rate of mutations in this strain is 5000 times as high as that of the wild-type strain (see the STRATAGENE catalogue).

pH more convenient for technological purposes and simultaneously with a high stability in the presence of solvents (DMF) have been found<sup>8</sup> in the same library of subtilisin clones.

Attempt have been made<sup>26</sup> to improve the performance properties of the *Bacillus licheniformis* glucose dehydrogenase, which serves as an alternative reagent for glucose determination and ensures regeneration of the cofactor (NAD<sup>+</sup>) in the systems of enzymic synthesis using NAD<sup>+</sup>-dependent dehydrogenases. Using DNA family shuffling, a glucose dehydrogenase variant free from the proneness to dissociation at high pH values has been obtained. Study of the primary structure of the variant showed that it contained only one amino acid replacement with respect to that prepared previously, which, in turn, also differed from the wild-type enzyme by a single replacement. The thermal stability of the enzyme has also markedly increased.

The creation of superproducers of protein products is faced with problems related to the formation of insoluble grains of these proteins inside the producer cells, so-called 'inclusion bodies'. Their formation is usually due to an improper spatial folding of the protein molecules when present in the cell at high concentration. This results in procedural difficulties in the isolation of the target products and in the subsequent 're-folding' to give the native or a functionally active structure.

The molecular evolution technique can be used to solve this problem. When selecting protein variants able to be folded 'properly', the selection procedure is the most complicated. Two promising approaches to the selection according to solubility and protein expression have been developed. In one of these, the target protein is expressed as a recombinant product with the full sequence of chloramphenicol acetyltransferase (CAT) at the N-end.<sup>27</sup> It was shown that the addition of CAT to insoluble proteins induces a much more pronounced decrease in the stability against chloramphenicol than in the case of addition to soluble proteins. This feature provides the possibility to pick the variants with higher solubility. The soluble HIV integrase mutant was selected in this way from the pool of insoluble wild-type constructs.

Yet another method involves the addition of the target protein to the N-end of the GFP protein<sup>¶</sup> (see Ref. 28). The fluorescence of GFP as a part of these recombinants is related to the proper folding of the attached protein. The utility of GFP as a reporter protein has been confirmed by directed evolution of the folding and demonstrated using different examples. After several rounds of shuffling of DNA with a wild-type sequence, readily soluble proteins were selected [H-subunit of the bullfrog ferritin and the mutant form (Cys33Thr) of V protein of F1 bacteriophage], which usually aggregate during expression in *E. coli* due to improper folding. An important advantage of these approaches over mutagenesis with screening of functional activity is elimination of the necessity of the labour-consuming screening. However, testing of the variants selected in this way for functional activity is still necessary, because the solubility of chimeric protein or a proper folding of the reporter protein does not ensure the retention of activity in the target protein.

The molecular evolution with screening based on GFP has been used<sup>29</sup> for expression of the *Mycobacterium tuberculosis* Rv2002 antigen in the soluble form (usually, this protein is expressed in *E. coli* as 'inclusion bodies'). It was possible to obtain the soluble material in amounts required for detailed structural studies.

The same approach has been used<sup>30</sup> to develop a high-performance producer of gene fragments of HIV1 shell protein. The N-terminal recombinants of a fragment of the gp120 protein of HIV1 containing important immunodominant determinants of the virus with GFP were constructed and subjected to DNA shuffling in combination with PCR. Out of the 300 000 cell colonies, those with continuous fluorescence were selected. Only

one such colony was found (the fluorescence protein was distributed over the whole cell volume). The subsequent analysis has shown that under these conditions, the level of synthesis of the target product amounts to ~15% of the total cell protein. This approach led to the desired outcome, despite the lack of a functional test for the target product.

The scope of problems that can be solved by methods of the molecular evolution of enzymes is rather diversified. A study<sup>31</sup> reports an attempt to increase the stability of wild-type  $\beta$ -glucuronidase (GUS) to glutaraldehyde for its use as a reporter in a study of gene expression in the cells of transgene plants. The  $\beta$ -galactosidase system used most often for these purposes is inapplicable, as these cells synthesise their own enzyme. The *E. coli*  $\beta$ -glucuronidase is also not very convenient due to the sensitivity to glutaraldehyde and formaldehyde used to retain the tissue to be studied in order to preserve its structure. These and some other restrictions hampered the use of  $\beta$ -glucuronidase in eukaryotic systems as the reporter enzyme. Using molecular evolution of the enzyme, the sensitivity of  $\beta$ -glucuronidase to aldehydes was reduced. As soon as after one error-prone PCR round and two rounds of DNA shuffling, a mutant variant of GUS stable to higher (~80 times) concentrations of glutaraldehyde was isolated. Although glutaraldehyde is known to modify proteins through the formation of lateral cross-links at lysine residues; only one of the eight replacements involves this amino acid, while the other seven replacements are mapped on the protein surface near the lysine residue. Apparently, the surface amino acid residues affect appreciably the possibility of modification with glutaraldehyde.

An increase in the expression level of the *Myceliophthora thermophila* laccase in the *Saccharomyces cerevisiae* yeast has been attained by the same method.<sup>32</sup> Laccases present substantial commercial interest as ligninolytic enzymes used to degrade aromatic compounds. This problem often arises in developing industrial processes for bioremediation of areas contaminated by petroleum products. The attempts at elaboration of strains convenient for the industrial cultivation with a high level of laccase production does not always result in the desired outcome. However, using directed evolution, it was possible to increase the activity level of the enzyme in yeast 170-fold (due to increase in the enzyme production and taking into account the 8-fold increase in its catalytic activity). The formation of a site recognised by the Kex2 protease in the C-terminal section of the protein processing was found to be the most efficient (resulting in a 10-fold increase in the overall activity). This is the way the expressed protein accommodates itself to processing in the heterologous host.

## V. Modification of substrate specificity

During the design of biocatalysts for industrial use, the problem of adjustment of enzymes to substrates which they do not encounter in nature arises more and more often.

The efficiency of molecular evolution methods in modification of substrate specificity has been convincingly demonstrated<sup>33</sup> using the enhancement of the fucosidase activity of  $\beta$ -galactosidase as an example. The fucose (6-deoxygalactose) glycosides are weakly split by  $\beta$ -galactosidase. The  $\beta$ -galactosidase to  $\beta$ -fucosidase activity ratio of the enzyme attained over eight rounds of DNA shuffling was 1000.

In order to improve the operation characteristics, modification has been performed for xylose isomerase from the thermophilic bacterium *Thermotoga neapolitana*,<sup>34</sup> which also exhibits glucose isomerase activity and, therefore, it is used in the production of glucose-fructose syrups, which is among the largest-scale processes of industrial biotechnology. This enzyme catalyses the glucose to fructose isomerisation much less efficiently than the xylose to xylulose isomerisation. For this reason, attempts at modifying the enzyme for increasing its catalytic activity towards glucose have been undertaken. An increase in the activity of the thermophilic variants of the enzyme at moderate temperatures

¶ GFP — Green Fluorescent Protein — is widely used as a reporter protein in the design of recombinant microbe strains.

and displacement of the optimal pH towards lower values are also improvements of the operating properties of the enzymes. The latter is needed to simplify the process, because the preceding stage, starch conversion, is carried out using glucoamylase operating in a weakly acidic medium. The variant prepared previously was subjected to directed evolution; two rounds of PCR mutagenesis and activity selection (at moderate temperatures and required pH values) gave two new variants, which were much more active at any temperature and pH, the optimal pH being shifted by 0.5 units in the desired direction.

Studies on modification of the substrate specificity of aspartate aminotransferase have been carried out.<sup>35</sup> A combination of DNA shuffling and selection in an auxotrophic *E. coli* strain was used;<sup>†</sup> this markedly increased the enzyme specificity towards amino and keto acids with chain branching in the  $\beta$ -position. After five rounds of selection, one mutant had a  $k_{\text{cat}}/K_M$  ratio for unnatural substrates  $10^5$  times as high as the wild-type enzyme, the catalytic efficiency towards the main substrate being decreased 30-fold. This mutant variant contained 13 replacements of amino acid residues, six of these being responsible for 80%–90% of the effect. Five of these six replacements were stable, being retained in five mutants that exhibited the highest efficiency with respect to  $\beta$ -branched substrates; one of the six residues was located at a distance from the direct contact with the substrate. Thus, long-range interactions in the protein molecule can contribute significantly to functional properties, which hampers the use of a rational approach to the targeted modification of enzymes.

The mutant variants of cephalosporin acylase obtained from the glutaryl acylase *Pseudomonas* SY-77<sup>36,37</sup> make it possible to obtain, in one enzymatic stage, 7-aminocephalosporanic (7-ACA) or 7-aminodeacetoxycephalosporanic (7-ADCA) acids used to modify cephalosporin antibiotics. The solution of this problem markedly improves the economy and environmental characteristics of the industrial production of cephalosporins. These acids are prepared by deacylation of cephalosporin C and adipinyl-7-ADCA, respectively (Fig. 5). The removal of the side-chain acyl residue in the antibiotic is catalysed by glutaryl acylase, which, however, exhibits a low activity with respect to adipinic acid residues. A mutant variant of the enzyme with 10-fold increased activity ratio towards the adipinic-to-glutaric acid residues has been obtained; this markedly extends the scope of enzyme application in the modification of penicillin and cephalosporin antibiotics.

The modification of the specificity of the *Rhodobacter sphaeroides* phytoene desaturase has been described.<sup>38</sup> This enzyme catalyses the successive dehydrogenisation of phytoene in the biochemical pathway to isoprenoids, as shown in Fig. 6. In many bacteria, the process stops after the formation of neurosporene; this is also true for *Rhodobacter sphaeroides*. The product of the next dehydrogenisation stage, lycopene, is more valuable, as it has more pronounced antioxidant properties and, hence, it is used as a component of food additives. By using directed evolution technique, the researchers prepared a variant of the *Rhodobacter sphaeroides* enzyme able to synthesise lycopene.

This task was accomplished by two rounds of random mutagenesis with subsequent selection; modification was carried out for an enzyme belonging to the family of neurosporene producers, whereas most of phytoene desaturases (90% of the known enzymes) belong to another family of proteins. The homology in the primary structure between these two families is relatively low (less than 60%). Nevertheless, specificity modification is attained relatively easily: even a single replacement gave a variant with 39% production of lycopene. The final variant (after two more rounds) produced 90% of lycopene. Enzyme variants able to

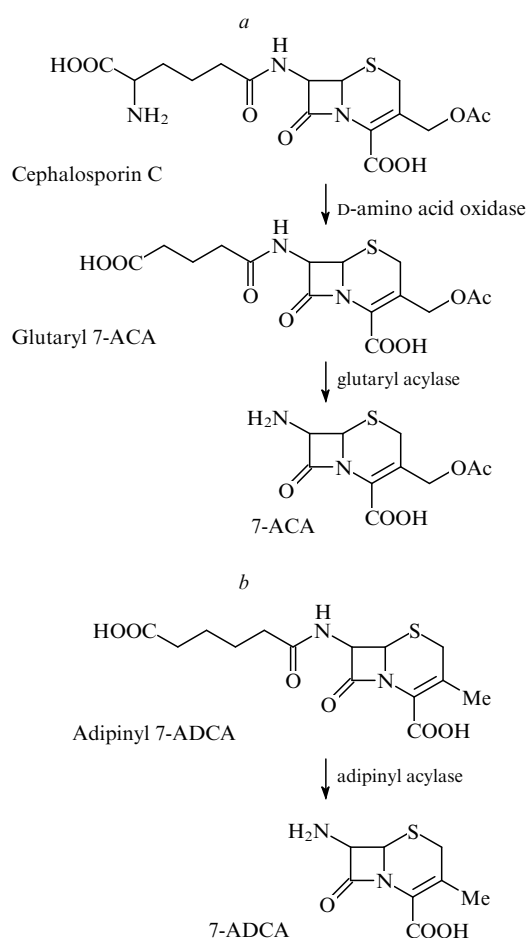


**Figure 5.** Preparation of deacylated cephalosporins by means of glutaryl acylase (a) and adipinyl acylase (b).

catalyse the synthesis of  $C_{35}$  and  $C_{40}$  isoprenoids have also been obtained;<sup>39,40</sup> This opens up the way to the synthesis of new analogues of natural carotene derivatives.<sup>39,40</sup>

In recent years, substantial progress has been attained in the decoding of biochemical routes of microbial degradation of

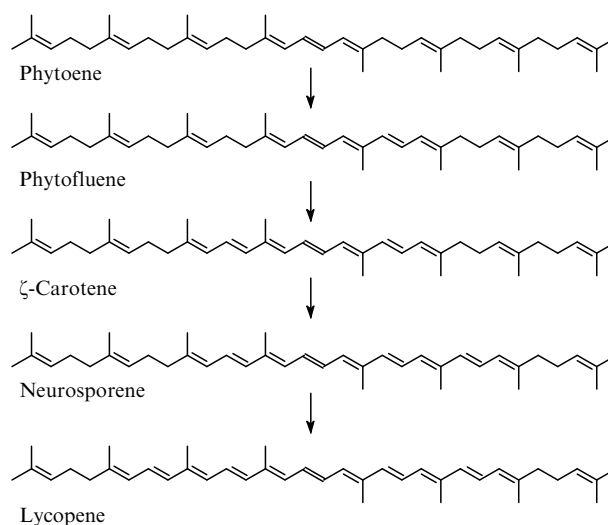


**Figure 6.** Successive stages of phytoene dehydrogenisation during the formation of lycopene induced by phytoene desaturase.

<sup>†</sup> In this case, a strain with a damaged operon of isoleucine biosynthesis was specially designed. This damage could be counterbalanced by providing aspartate aminotransferase with the ability to catalyse transamination of amino acids with a branched side chain.

various aromatic compounds that are frequently encountered pollutants. The attention is focused on the creation of microbe strains able to degrade efficiently these compounds under natural conditions, which can be used for bioremediation of contaminated areas. To this end, attempts have been made<sup>41</sup> to extend the range of substrates for biphenyl dioxygenase by random priming recombination. Two rounds of manipulations with the *bphA1* *Pseudomonas pseudoalcaligenes* KF707 gene gave enzyme variants with new properties, in particular, those able to oxidise not only polychlorobiphenyls but also dibenzofuran, dibenzo-*p*-dioxin, dibenzothiophene, fluorene, *i.e.*, compounds hardly utilised by the initial strain.

The obtained<sup>42</sup> 2-hydroxybiphenyl monooxygenase variant from *Pseudomonas azelaica* HBPI catalyses hydroxylation of indole and its hydroxy and bromo derivatives (wild-type enzymes do not catalyse this reaction). The new variant of the enzyme was found to contain two amino acid replacements separated from each other by 146 residues. The enzymes that oxidise indole and its derivatives can also be used in biotechnological processes to produce indigoid dyes and other products of organic synthesis.

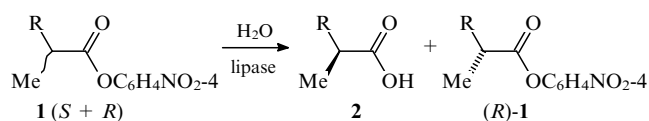
Studies into the development of microorganisms able to biodegrade halogenated organic compounds formed as wastes in the chemical industry or contained in many pesticides, which are degraded with difficulty by the natural populations of microbes in soil and water, are in progress. The activity of the key enzyme for 1,2,3-trichloropropane degradation, haloalkane dehalogenase from *Rhodococcus sp.* (m15-3), has been markedly increased by DNA shuffling.<sup>43</sup> 1,2,3-Trichloropropane is highly toxic and does not occur in nature, but is encountered as a man-made pollutant. The modified gene was introduced into bacteria (*Agrobacterium radiobacter* AD1) that utilise the product made by this enzyme, namely, 2,3-dichloropropan-1-ol. The resulting strain proved to grow on trichloropropane as the only carbon and energy source; thus, it can be used as a bioremediation agent.

## VI. Stereoselectivity and enantioselectivity

The production of enantiopure compounds becomes more and more important for chemical and pharmaceutical industries. In 2000, the world sales volume of optically active drugs was above \$100 billion. The demand in these products is due to the fact that the molecules of efficient drugs should comply with the asymmetry of the receptors. For example, the US Food and Drug Agency demands strict determination of whether it is possible to produce a drug as an optically pure isomer.

One way to solve this problem is to use enzymes in stereospecific reactions. However, the enantioselectivity of enzymes is often too low, but it can be increased using molecular evolution techniques. The results of such studies have been analysed in detail in a review.<sup>44</sup>

An approach to the development of enantioselective catalysts based on directed evolution *in vitro* has been proposed.<sup>45</sup> Hydrolysis of racemic *p*-nitrophenyl 2-methyldecanoate (**1**) was chosen as the test reaction. Free *S*-acid **2** [the product of hydrolysis of *S*-enantiomer of ester **1**] belongs to a class of compounds in which one finds pharmaceuticals, plant protection compounds and intermediates of organic synthesis. The *Pseudomonas aeruginosa* PAO1 lipase composed of 285 amino acids was used as the catalyst.



The wild-type enzyme exhibits only a 2% enantioselectivity in favour of the *S*-configuration. Using the error-prone PCR, the lipase gene comprising 933 bp was subjected to statistical mutagenesis. The frequency of mutations was varied in such a way as to introduce an average of one or two replacements into each copy of the lipase gene. This was attained by appropriate selection of the

PCR conditions (for example, by the change in the concentration of  $\text{Mg}^{2+}$  ions). The mutated genes were inserted into the expression vector, amplified in *E. coli* and introduced in *P. aeruginosa*. After four selection rounds, the enantioselectivity increased from 2% to 81%.

By inverting the enantioselectivity of D-hydantoinase, which is the key enzyme of the multienzyme route for methionine synthesis, the production of L-methionine in *E. coli* was improved.<sup>46</sup> The production of L-amino acids by means of hydantoinases (Fig. 7) is widely used in industry. For methionine, this reaction proceeds preferentially with the D-isomer of hydantoin, resulting in extremely slow transformation of D-*N*-carbamoylmethionine into the target product (D-selective hydantoinase induces accumulation of D-*N*-carbamoylamino acid, which is converted very slowly into the desired amino acid).

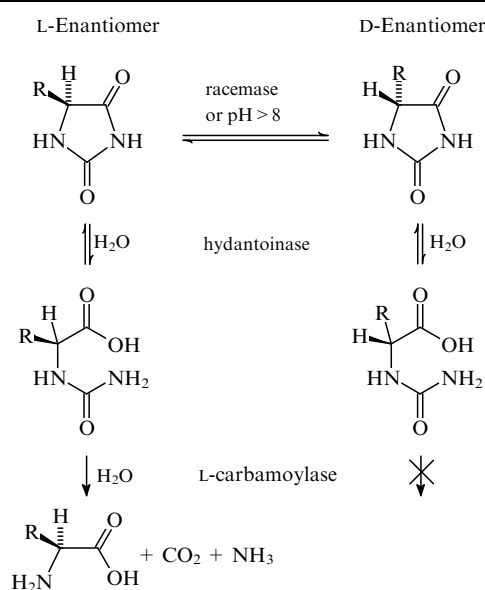


**Figure 7.** Enzymic synthesis of amino acids from racemic 5-substituted hydantoin.

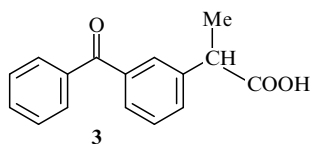
Using successive PCR mutagenesis and screening procedures, the enantioselectivity of D-hydantoinase was inverted [from *ee*(D) 40% to *ee*(L) 20%], the overall activity being increased fivefold. The introduction of the modified L-hydantoinase gene into the recombinant bacterial strain with intact cells as the catalyst increased the productivity with respect to L-Met and decreased the accumulation of undesirable intermediates as compared with wild-type cells. This effect was attained by replacement of only one amino acid. Variants with high D-selectivity [*ee*(D) 90%], which also had a single amino acid replacement, were found. However, due to the lack of efficient screening methods, studies dealing with directed evolution of enantioselective catalysts are few in number.

In recent years, considerable progress has been achieved in the understanding of the role of carbohydrate components in glycosylated proteins; this enhanced the interest in the synthesis of glycoside derivatives of proteins. The chemical synthetic methods in the carbohydrate series are fairly complicated; therefore, enzymic methods become more and more attractive. Commercially justified glycosidases, which exhibit not only hydrolase but also glycosyl transferase activity, are the enzymes of choice. However, the regioselectivity of these enzymes is often inadequate. An attempt to modify the regioselectivity of the *B. stearothermophilus*  $\alpha$ -galactosidase has been undertaken.<sup>47</sup> The wild-type enzyme is specific towards 1,6-glycosidic bonds and, to a lesser extent, to 1,3-bonds. Using statistical mutagenesis and the StEP technique for the molecular evolution, enzyme variants that mainly cleaved the 1,3-glycosidic bonds were

obtained. For the majority of enzyme variants obtained, the activity towards 1,6-bonds decreased appreciably as regards both hydrolysis and transglycosylation. Enzyme variants with an (1,3):(1,6) regiospecificity ratio of 6.9 against 0.3 for the wild-type enzyme have been obtained. However, the transglycosylase activity was markedly lower compared to that of the wild-type enzyme. The researchers believe that they have demonstrated the feasibility of solving this problem; however, further studies are required.

An important application of the stereoselectivity of enzymes is separation of sterically hindered alcohols.<sup>48</sup> Enzymes have already been used for analogous purposes; however, in the case of sterically hindered alcohols, the attempts have often failed. The use of the *Pseudomonas fluorescens* lipase and molecular evolution using the *E. coli* XL1-Red strain with a high frequency of spontaneous mutations resulted in an enzyme variant with an enhanced stereoselectivity towards sterically hindered esters. However, the desired result has not been exactly attained, because mutations are introduced in one variant of the gene. A greater diversity of mutants can be obtained using DNA shuffling.

The esterase from *Pseudomonas fluorescens* KCTC 1767 is used for the preparation of optically pure ketoprofen (**3**) from a racemic mixture of ethyl esters.



The modification of the working properties of the enzyme in order to increase the thermal stability, shift the pH optimum towards higher pH and increase the stability against the action of some organic solvents, non-ionic detergents or high substrate concentrations has been carried out<sup>49</sup> with three cycles of molecular evolution. This example illustrates the possibility of simultaneous 'improvement' of several parameters using molecular evolution.

The modification of enzyme stereospecificity is related most often to changing their substrate specificity with respect to a particular enantiomer. Using a tagatose-1,6-diphosphate aldolase-catalysed reaction as an example, a new, in principle, approach has been proposed.<sup>50</sup> The approach implies the change in the reaction stereochemistry in such a way that the enzyme would catalyse the formation of a different product from the same substrates. After six DNA shuffling rounds, the aldolase subjected to the evolution has demonstrated a 80-fold increase in the  $k_{cat}/K_M$  ratio in the reaction with an unnatural substrate, fructose 1,6-diphosphate, because the enzyme has switched to the preferred (75%) formation of fructose diphosphate from glyceraldehyde 3-phosphate and dioxyacetone phosphate instead of the predominant (99%) formation of tagatose diphosphate. It is noteworthy that the direct reaction catalysed by this enzyme is cleavage of hexose diphosphates to triose phosphate; therefore, the results obtained could be attributed to the usual modification of the substrate specificity. Nevertheless, the use of this enzyme in the synthesis is of obvious interest.

## VII. Selection of the modified gene variants

It has already been noted that the selection procedure is a key stage in directed evolution, which is specific for each particular case. There exist, however, some common techniques that could underlie a selection strategy.

One method is the use of a phage display. This approach implies expression of the target protein as a recombinant with a bacteriophage surface protein, which is exposed on a phage particle and presents the target protein on the surface. The protein is thus brought in contact with the solution and can exhibit the enzymatic activity or present the antigenic determinants of the target protein to antibodies.

An example of using this approach is an attempt to transform the DNA polymerase (the Stoffel fragment of the *Thermus aquaticus* DNA polymerase I) into an RNA polymerase.<sup>51</sup> This was done by mutagenesis of the functional fragments (binding sites of metal ions, polynucleotide duplex, the substrate, and interaction with the matrix) performed separately, which was followed by the assembly of a full-size gene by means of polymerase (two PCR rounds) and by selection using the phage display method. This gave an effective RNA polymerase, which retained the DNA polymerase activity and had a sufficient processivity.

## VIII. Other methods of DNA recombination

The methods of directed molecular evolution of enzymes developed during the last decades has proved to be fairly efficient. Meanwhile, accumulation of the data on structural organisation of enzyme molecules is in progress; this allows also the use of rational approaches to modification of the protein structure in the design and perfection of biocatalysts. In some cases, it is useful to combine both approaches.

The possibility of increasing the thermal stability of glow-worm luciferase has been demonstrated.<sup>52</sup> The enzyme is used as an analytical reagent in medicine and in the quality control of foodstuffs (in particular, to detect some microorganisms). It can be conjugated to antibodies (specific to particular antigens), and the resulting fluorescence induction or suppression is used to judge the presence or absence of a structure containing this antigen. The insufficient thermal stability of the wild-type enzyme restricts its use; that is why attempts have been made to increase the thermal stability.

Molecular evolution has been used<sup>53</sup> to enhance the thermal stability of phytase, the enzyme that splits phytic acid (inositol hexaphosphate), which is the main form of phosphorus storage in plants. This enzyme, common in microorganisms and in herbivorous animal stock, is missing from the gastrointestinal tract of pigs and birds. The addition of inorganic phosphate to the fodder is uneconomic. To enhance the uptake of the green fodder, phytase tablets are added to the fodder, which requires increasing the natural thermal stability of phytase. The enzyme gene was subjected to site-directed and cassette mutagenesis in order to replace the  $\alpha$ -helical fragment of the enzyme from *Aspergillus terreus* by a similar fragment of the *Aspergillus niger* enzyme,<sup>53</sup> which ensured a higher thermal stability of the hybrid.

## IX. Rational approaches to enzyme modification

Rational approaches to increasing the thermal stability of enzymes involve either comparison of the amino acid sequences of the target protein and a thermally more stable related protein or detailed analysis of the 3D structure of the target protein in order to predict promising replacements of amino acid residues on the basis of both structural data and the accepted concepts of thermal stability design; the predictions are to be verified by introducing single mutations in the wild-type protein sequence.

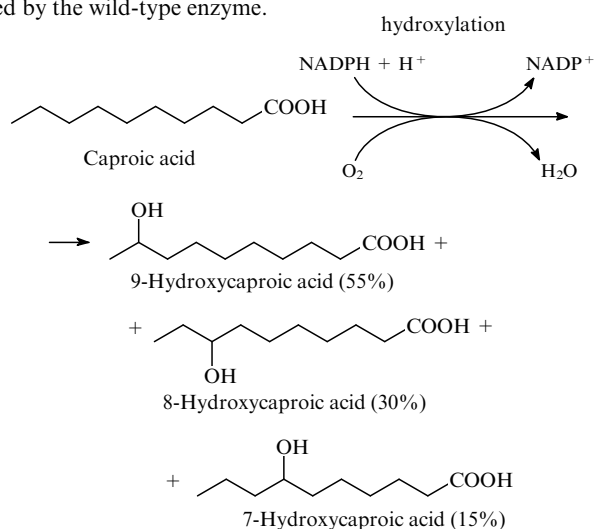
The modern thermostabilisation concepts include, among other issues, the introduction of additional disulfide bridges, improvement of the packing of the hydrophobic core, creation of a network of surface salt bridges or dipole interactions in the  $\alpha$ -helix, change in the proneness to form the  $\alpha$ -helix and entropy changes (e.g., the X  $\rightarrow$  Pro or Gly  $\rightarrow$  Ala replacements). All rational approaches of this type have been used previously; however, the predictions are not always successful. The reason is that the replacement of the amino acid residue cannot only entail a local effect, but also induces unexpected conformational changes in various (including remote) parts of the molecule. Nevertheless, there are examples where rational methods led to the desired outcome. Thus using site-directed mutagenesis, the contributions of all 17 amino acid residues that were different for barnase and binase (bacterial nucleases with a 85% amino acid homology) to the protein thermal stability have been studied.<sup>54</sup> The effect of one

amino acid replacement on the activation energy of denaturation varied from +1.1 to  $-1.1 \text{ kcal mol}^{-1}$ . The multiple mutant that included six amino acid domains demonstrated an increase in the stability by  $3.3 \text{ kcal mol}^{-1}$  compared to the wild type. Thus, comparison of related proteins provides useful information regarding the increase in their thermal stability.

The data obtained by various researchers on the molecular evolution of proteases have been described systematically in a review.<sup>55</sup> The site-directed mutagenesis has been used to construct variants of subtilisin with enhanced storage stability and resistance against oxidation. The replacement of Met222 susceptible to oxidation with oxidation-resistant alanine, serine or glutamine residues in *B. amyloliquefaciens* BPN2 subtilisin resulted in prevention of enzyme inactivation by oxygen. Six individual replacements of amino acids (Asn218Ser, Gly169Ala, Tyr217Lys, Met50Phe, Gln206Cys and Asn76Asp) in different positions of the tertiary structure of subtilisin resulted in an increase in the enzyme stability at elevated temperature ( $65^\circ\text{C}$ ) and in alkaline media (pH 12). Under these denaturing conditions, the inactivation rate of this variant was 300 times lower than that for the wild-type enzyme. Other replacements of amino acids, resulting in a higher enzyme stability, have also been reported.

The rational approach in enzyme reconstruction has been applied<sup>56</sup> to D-amino acid oxidase from the *Rhodotorula gracilis* yeast, which is used to remove the side chain of cephalosporin in the synthesis of antibiotics of this series. Using X-ray diffraction data for the crystalline enzyme, a mutant variant of Met213Arg, capable of catalysing the oxidative deamination of aspartic acid has been obtained (the wild-type enzyme does not use the aspartic or glutamic acids as substrates). This results in a lower activity with respect to alanine; however, the substrate specificity is extended). It is worth noting that D-amino acid oxidase from *Rhodotorula gracilis* is the most promising enzyme for industrial use owing to the high catalytic activity and strong binding of the cofactor (FAD).

The specificity of *Bacillus megaterium* cytochrome P450 BM-3 has been modified<sup>57</sup> in order to make it catalyse hydroxylation of the hydrocarbon radical of short-chain (less than  $\text{C}_{12}$ ) fatty acids at the pre-terminal units. The rational approach was based on X-ray data for the enzyme. However, the choice of the replacement was determined by inclusion into the sequence of PCR primers of triplets of a random sequence into positions planned for the replacement. Finally, the resulting variants catalysed the oxidation of caproic acid, which cannot be hydroxylated by the wild-type enzyme.



Subsequently, modification of cytochrome has been carried out.<sup>58</sup> Thus it became capable of oxidising polycyclic aromatic hydrocarbons (naphthalene, fluorene, acenaphthene and other). To impart these properties to the enzyme, it was sufficient to modify the same amino acid residues as in the case of oxidation of

aliphatic fatty acids, although the replacements were different. The goal was attained in a triple mutant in which the Leu188Gln replacement proved to be the optimal, instead of Leu188Lys.

A concept of increasing the thermal stability of enzymes has been proposed;<sup>16</sup> the concept is based on not only a comparison of amino acid sequences of homologous enzymes from various sources but also on the construction of a consensus sequence from the amino acids found most often. This amino acid sequence is transposed into a nucleotide sequence with allowance for the frequency of codon use (using the library of the amino acid sequences of phytases as an example). Then the gene corresponding to the consensus sequence is synthesised by polymerase assembling, cloned and expressed. The very first variant was much more stable than any of the parent proteins. Several rounds with inclusion of additional genes from new sources into the comparison of sequences have resulted in an enzyme variant with a denaturation temperature of  $88.5^\circ\text{C}$ , which is higher by  $8^\circ\text{C}$  than that for the initial *Aspergillus fumigatus* enzyme. The activity of the consensus enzyme was higher than that of the parent enzymes over the whole pH range. The contribution of each amino acid replacement was evaluated. Later, the denaturation temperature of the consensus phytase was raised additionally by  $2^\circ\text{C}$ .

Most bacterial phytases have the pH optimum in the neutral region, whereas the medium in the gastrointestinal tract of animals is weakly acidic. Therefore, enzyme variants with the pH optimum shifted toward lower pH have been obtained<sup>59,60</sup> by site-directed mutagenesis based on the consensus phytase with replacement of amino acid residues affecting the pH optimum of the enzyme.

Modification of formate dehydrogenases by point replacements of amino acid residues has been reported.<sup>61,62</sup> Formate dehydrogenase is an effective component of systems for regeneration of the  $\text{NAD}^+$  cofactor; it is used in the enzymic synthesis of many pharmaceuticals. An increase in the thermal stability of the enzyme due to enhancement of the hydrophobic character of  $\alpha$ -helical fragments was induced by the replacement of serine residues in positions 131, 160, 184 and 228 by alanine residues by means of site-directed mutagenesis.<sup>61</sup> Interestingly, the effect of multiple replacements is additive, although these residues are rather remote in the protein chain. An enzyme variant capable of regenerating  $\text{NADP}^+$  has been prepared<sup>62</sup> on the basis of computer analysis of the structure by replacement of two neighbouring amino acid residues in formate dehydrogenase from bakers' yeast: Asp196Ala and Tyr197Arg. The ratio of the catalytic efficiencies ( $k_{\text{cat}}/K_M$ ) for NADP and NAD has increased by almost 10 orders of magnitude. This replacement of the cofactor increases the commercial value of the enzyme, because NADP serves as the cofactor for many dehydrogenases used in the synthesis and biotransformations of valuable chiral biologically active compounds. This result should be regarded as significant, despite the fact that the replacement has led to a substantial increase in  $K_M$  of the enzyme with respect to formate compared with the initial enzyme. This fact confirms once again the inadequacy of X-ray diffraction data on the structure of an enzyme globule for an exact prediction of the role of amino acid residues in its functions.

## X. Conclusion

In recent years, the directed evolution of enzymes has become the key technique for the creation of enzymes with new improved properties which are especially important for industrial use. This approach has provided the procedural basis for the design of enzymes with new properties without exact knowledge of the structure and the mechanism of catalytic action.

When choosing the way of solving a particular task, it should be borne in mind, however, that, as versatile as they are, different methods of directed evolution differ in results. In particular, the technique of stepwise truncation of enzyme genes with non-homologous recombination allows the modification of inner

areas of the enzyme, whereas the staggered extension technique results in the formation of hybrids with more homologies in the N-terminal fragment of the gene. The random priming recombination yields an almost uniform distribution of random replacements over the whole enzyme molecule.

The number of variants for the selection of enzymes with 'improved' properties is great with any methods of molecular evolution. Therefore, different ways for optimisation of compilation of gene libraries including computer methods are proposed. Recently, an approach of this type based on accounting of the thermodynamic and kinetic parameters of the DNA shuffling have been proposed and the predictions have been compared with the results.<sup>63</sup>

In some cases, it is necessary to protect an amino acid critical for the protein functions from participation in the mutation events. For this purpose, a procedure has been reported<sup>64</sup> based on introduction into the codon of this amino acid of an oligonucleotide fragment containing the splitting site of some restriction endonuclease. After DNA shuffling, this oligonucleotide is restricted by the restriction endonuclease and ligation is carried out. If mutation events have taken place in the codon, the complementarity of the extending ends of the restriction site is violated, no ligation occurs and these clones are excluded from the subsequent selection.

The molecular evolution techniques can be used not only to 'improve' the properties of particular enzymes but also to solve larger-scale problems, for example, to construct genetic regulatory systems.<sup>65,66</sup> This permits fine tuning of the biochemical parameters of a metabolic circuit done experimentally *in vivo*. By applying the directed evolution to genes that constitute the simple genetic circuit, researchers have demonstrated that a circuit that does not function due to an improper selection of components is rapidly evolved into a functional circuit. A library of genetic tools with different behaviours suitable for the construction of more complicated circuits has been composed.

The methods of directed molecular evolution can also be used successfully in the design of 'nucleozymes,' *i.e.*, catalytically active nucleic acids. A self-phosphorylated DNA has been designed and isolated from a pool of random mutant DNA sequences as a variant able to phosphorylate its own 5'-end.<sup>67</sup> Six selection rounds gave a nucleozyme, which efficiently phosphorylated both RNA and DNA.

The major difficulties faced by directed evolution are related to the development of an efficient strategy for the selection of variants that have enhanced properties compared with the initial material. The solution of this problem mainly rests on researcher's skill. Nevertheless, the information presented in the review demonstrates the exceptionally high potential of molecular evolution in the design of biocatalysts.

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# Theoretical conformational analysis of organophosphorus compounds<sup>†</sup>

Ya A Vereshchagina, E A Ishmaeva, V V Zverev

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**Abstract.** Published data on the theoretical conformational analysis of acyclic tri- and tetracoordinate phosphorus compounds by quantum-chemical methods are generalised and systematised. Theoretical results are compared with experimental data for a wide range of such compounds. The main characteristics and fine conformational details of their structures are considered. The bibliography includes 221 references.

## I. Introduction

The development of conformational analysis is associated primarily with the need to explain and predict the reactivity of molecules from their three-dimensional structures. Pioneering studies by Barton, published in 1950, marked the beginning of extensive progress in this field, which now covers virtually all areas of organic chemistry. Barton is the person to whom Eliel, Allinger, Angyal and Morrison dedicated their monograph 'Conformational Analysis',<sup>1</sup> and it remains a 'textbook' for researchers dealing with molecular structures. The well-known phrase of these authors states that a chemist who does not understand conformational analysis, does not understand organic chemistry.<sup>1</sup> Physical methods of investigating molecular structures and quantum-chemical calculations play an important role in this field of science.

However, theoretical conformational analysis of organoelement compounds remains poorly developed in spite of advances in quantum chemistry. In the cited monograph of Eliel *et al.*, the conformations of organoelement compounds were not even mentioned. For organophosphorus compounds (OPCs) in which the phosphorus atom has a coordination number of 3 or 4, the main geometric parameters of such molecules (bond angles, bond lengths, *etc.*) and the most important fundamental characteristics of their bonds with phosphorus (for example, polarity and polarisability) have not been determined at that time. This hinders the

use of conventional methods of organic chemistry in studies of OPC structures in solution.

Pure conformational control of a particular reaction is rare. For organoelement, in particular, organophosphorus, compounds, such examples are especially lacking. The reactivities of geometric isomers which model a particular conformational situation have received much more attention. This is associated primarily with the synthesis of compounds in which an anchor group (often the *tert*-butyl group or a heterocyclic substituent) stabilises only one conformer. Most of these studies have been carried out on substituted cyclohexanes and their heteroanalogues. For organophosphorus compounds, with rare exceptions, theoretical investigations of the fine details of their three-dimensional and electronic structures were not carried out until the 1980s.

The conformational analysis of organophosphorus compounds has attracted attention because they are widely used and, as a consequence, there is a need to synthesise compounds possessing desired properties. A knowledge of the structures and fine conformational features of these compounds is also of importance in studies of their reaction mechanisms and the reactivities. In the 1970s and 1980s, theoretical analysis of the general and specific features of the OPCs' spatial and electronic structures and comparisons of the results with the general concepts of organic chemistry became of importance.

The development of a methodology for the conformational analysis of complex organic and organoelement compounds, including OPCs, was a considerable step forward. This methodology was described in a review by Vereshchagin and Vulsfon<sup>2</sup> and proved to be very efficient in studies of the structures of a wide range of various compounds in solution, where most chemical reactions occur.

Numerous studies on the experimental conformational analysis of OPCs were performed in Kazan by researchers belonging to the schools founded by Academician B A Arbuzov and the Corresponding Member of the Russian Academy of Sciences A N Pudovik. These studies were carried out using various complementary physical methods (vibrational and photoelectron spectroscopy, NMR spectroscopy, X-ray diffraction analysis, the dipole moment method, Kerr effect measurements, Rayleigh scattering). The results of these studies were covered in several reviews.<sup>3–8</sup>

Attempts to provide a theoretical support for the abundant available experimental data on the conformations of organophosphorus compounds are scarce, although this problem has

**Ya A Vereshchagina** Kazan State Technological University, ul. K Marksa 68, 420015 Kazan, Russian Federation. Fax (7-8432) 38 26 37, tel. (7-8432) 31 54 16, e-mail: yavereshchagina@yahoo.com

**E A Ishmaeva** Kazan State University, ul. Kremlevskaya 18, 420008 Kazan, Russian Federation. Fax (7-8432) 38 70 63, tel. (7-8432) 31 54 16, e-mail: Eleonora.Ishmaeva@ksu.ru

**V V Zverev** A E Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Centre of the Russian Academy of Sciences, ul. Akad. Arbuzova 8, 420088 Kazan, Russian Federation. Fax (7-8432) 75 22 53, tel. (7-8432) 93 21 56, e-mail: zverev@iopc.knc.ru

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<sup>†</sup> Dedicated to Academician Vladimir Minkin on the occasion of his 70th birthday.

**Table 1.** The total energy ( $E$ ) of the *cis* conformer of  $\text{H}_2\text{POH}$  and the energy difference between the conformers  $\Delta E = E(\text{trans}) - E(\text{cis})$  calculated by quantum-chemical methods at different levels of theory.<sup>a</sup>

| Method       | Basis set          | $E$ (a.u.)  | $\Delta E$ /<br>kcal mol <sup>-1</sup> |
|--------------|--------------------|-------------|----------------------------------------|
| Hartree–Fock | 3-21G(d)           | –415.27576  | –0.80                                  |
|              | 6-31G              | –417.22858  | 1.76                                   |
|              | 6-31G(d)           | –417.31424  | 0.11                                   |
|              | 6-31 + G(d)        | –417.319909 | 0.28                                   |
|              | 6-31G(d,p)         | –417.32531  | 0.12                                   |
|              | 6-31 + G(d,p)      | –417.331052 | 0.26                                   |
|              | 6-311G(d,p)        | –417.36867  | –0.62                                  |
|              | 6-311 + G(d,p)     | –417.37360  | 0.09                                   |
|              | 6-311G(2d,2p)      | –417.380881 | –0.56                                  |
|              | 6-311 + + G(2d,p)  | –417.383562 | –0.05                                  |
|              | 6-311 + G(2d,2p)   | –417.384770 | 0.08                                   |
|              | 6-311 + + G(2d,2p) | –417.384820 | 0.08                                   |
|              | 6-311 + + G(3d,2p) | –417.389418 | 0.00                                   |
|              | 6-311 + + G(3d,3p) | –417.389620 | 0.01                                   |
|              | 6-31G(d)           | –417.596726 | 0.69                                   |
|              | 6-31G(d)           | –417.613711 | 0.53                                   |
| MP2          | 6-31G(d)           | –417.618745 | 0.54                                   |
| MP3          | 6-31G(d)           | –417.750979 | 0.22                                   |
| MP4          | 6-31G(d)           | –418.362668 | 0.72                                   |
| B3LYP        | 6-31G(d)           | –418.371584 | 0.72                                   |
| B3LYP        | 6-31G(dp)          | –418.371584 | 0.72                                   |
| DFT/PBE      | TZ2P               | –418.184044 | 0.23                                   |

<sup>a</sup> V V Zverev, unpublished data.

attracted increased attention in recent years. It should be emphasised that we are referring to high-level *ab initio* calculations here, because semiempirical quantum-chemical methods have been used for several decades. In spite of the fact that each method is of limited application and should be used with caution,<sup>9</sup> in some cases the implementation of these methods is justified.<sup>‡</sup> This is demonstrated with particular examples below.

It has been mentioned many times that *ab initio* calculations using the economical 3-21G\* basis set are sufficient for theoretical studies of the various properties of organophosphorus compounds. However, the calculated energies of the *cis*, *trans* and *gauche* conformers of the  $\text{H}_2\text{P}–\text{OH}$  and  $\text{H}_2\text{P}(\text{O})\text{OH}$  molecules (Tables 1 and 2) show that this model is of limited application. In the case of a small energy difference between the conformers, successive extension of the basis set up to 6-311 + + G(2d,2p) is not accompanied by a monotonic change in the calculated properties (analogously to that observed for the total energy), and the inclusion of electron correlation data results in a substantial change in the relative stability of the conformers. Apparently, it follows that the conformational energies of OPCs, estimated by quantum-chemical calculations without analysis of the role of correlation effects, can differ substantially from experimental data. In our opinion, with their large number of approximations used to analyse intramolecular interactions, simplified orbital models deserve attention. In some cases, these models, derived by factorisation of the electron shells, were confirmed by photoelectron spectroscopy.<sup>11–13</sup>

The present review is the first to summarise data on the internal rotation about single bonds of phosphorus obtained by calculation, and these data are compared with experimental results. The review covers organophosphorus compounds con-

<sup>‡</sup> In particular, the results of conformational analysis of a wide range of cyclic systems by *ab initio* (HF/3-21G) and semiempirical (AM1) quantum-chemical calculations and the molecular mechanics method (MM2) were compared in the study,<sup>10</sup> and it was concluded that calculations by different methods gave similar results. However, calculations by the AM1 method, though adequately predicting the molecular conformation, gave erroneous estimates of the relative stabilities of the conformers.

**Table 2.** The total energy ( $E_{\text{min}}$ ) of the *gauche* conformer of  $\text{H}_2\text{P}(\text{X})\text{OH}$  ( $\text{X} = \text{O}, \text{S}$ ), the XPOH torsion angle ( $\varphi_{\text{min}}$ ) and the rotation barrier  $\Delta E = E(\text{cis}) - E_{\text{min}}$ .<sup>a</sup>

| Method                                                    | Basis set          | $E_{\text{min}}$ (a.u.) | $\varphi_{\text{min}}$ /<br>deg | $\Delta E$<br>(see <sup>b</sup> ) |
|-----------------------------------------------------------|--------------------|-------------------------|---------------------------------|-----------------------------------|
| <b><math>\text{H}_2\text{P}(\text{O})\text{OH}</math></b> |                    |                         |                                 |                                   |
| Hartree–Fock                                              | 3-21G(d)           | –489.771315             | 0                               | 0.000                             |
|                                                           | 6-31G(d,p)         | –492.226614             | 0                               | 0.000                             |
|                                                           | 6-31 + G(d,p)      | –492.229600             | 10                              | 0.002                             |
|                                                           | 6-311G(d,p)        | –492.284637             | 20                              | 0.019                             |
|                                                           | 6-311 + + G(d,p)   | –492.326792             | 25                              | 0.061                             |
|                                                           | 6-311 + + G(2d,2p) | –492.290078             | 0                               | 0.000                             |
| MP2                                                       | 6-311 + + G(3d,3p) | –492.317056             | 0                               | 0.000                             |
|                                                           | 6-31G(d)           | –492.678535             | 39                              | 0.297                             |
|                                                           | 6-31G(d)           | –492.683435             | 32                              | 0.120                             |
|                                                           | 6-31G(d)           | –492.694606             | 34                              | 0.163                             |
|                                                           | B3LYP              | –493.615503             | 40                              | 0.334                             |
|                                                           | B3LYP              | –493.624409             | 42                              | 0.323                             |
| DFT/PBE                                                   | TZ2P               | –493.403126             | 40                              | 0.282                             |
| <b><math>\text{H}_2\text{P}(\text{S})\text{OH}</math></b> |                    |                         |                                 |                                   |
| Hartree–Fock                                              | 3-31G(d)           | –810.771315             | 0                               | 0.000                             |
|                                                           | 6-31G(d,p)         | –814.867500             | 0                               | 0.000                             |
| MP2                                                       | 6-31G(d)           | –815.259610             | 22                              | 0.048                             |
| B3LYP                                                     | 6-31G(d)           | –816.581483             | 26                              | 0.059                             |
| DFT/PBE                                                   | TZ2P               | –816.262590             | 21                              | 0.050                             |

<sup>a</sup> V V Zverev, unpublished data. <sup>b</sup> In kcal mol<sup>-1</sup>.

taining at least one P–C or P–XR bond ( $\text{X} = \text{O}, \text{S}, \text{N}$ ; R is a hydrocarbon substituent), in which phosphorus has a coordination number of 3 ( $\text{P}^{\text{III}}$ ) or 4 ( $\text{P}^{\text{IV}}$ ). The structures of low-coordinate phosphorus compounds (see Refs 14–25) and phosphorus-containing heterocycles<sup>26–31</sup> are beyond the scope of this review. Metal complexes containing OPCs are also not included in the review, because this large and specific area of organophosphorus chemistry deserves a separate analysis.

The review summarises the results of theoretical conformational analyses of OPCs performed primarily in the last 10–15 years and covers inclusively data published up to mid-2003. In addition, the most important and high-priority studies and reviews in the field of experimental and theoretical conformational analysis of organophosphorus compounds published earlier are considered.

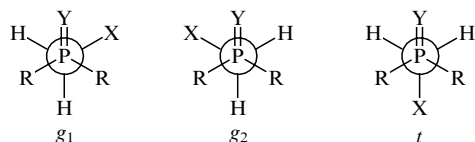
## II. Conformational analysis of tri- and tetracoordinate phosphorus compounds

### 1. Internal rotation about P–C(sp<sup>3</sup>) bonds

The first reviews<sup>5,8</sup> on the conformations of acyclic organophosphorus compounds, in which the  $\text{P}^{\text{III}}$  and  $\text{P}^{\text{IV}}$  atoms are bound to various organogen atoms, were published 20 years ago. The results analysed in these reviews were obtained primarily by experimental methods and semiempirical quantum-chemical calculations (in rare cases, by *ab initio* calculations for a few simple molecules). Conformational studies in this field were accompanied by generalisation and critical analysis of the considerable amount of experimental data obtained by gas electron diffraction, X-ray diffraction analysis, IR, UV, Raman and NMR spectroscopy and quantum-chemical calculations. Along with these general physical methods, a comparison and analysis of experimental dipole moments, the dipole moments calculated according to the vector-additive scheme (hereafter, the dipole moment method) and data on electric-field-induced birefringence (hereafter, the Kerr effect method) play an important role in conformational studies. Photoelectron spectroscopy also makes a great contribution to investigations of conformational equilibria.

The main characteristic features of internal rotation about P—C(sp<sup>3</sup>) bonds in OPCs were revealed. The internal rotation about the P—C(sp<sup>3</sup>) bond has a threefold barrier due to the tetrahedral environment of the carbon atom involved in this bond. From the very beginning, conformational analysis of OPCs assumed that the staggered *gauche* or *trans* conformations with respect to the P—C(sp<sup>3</sup>) bond were the most stable,<sup>5</sup> by analogy with the C(sp<sup>3</sup>)—C(sp<sup>3</sup>) bond (although the eclipsed *cis* conformation was initially also considered because of a lack of data). The Newman projections of the stable conformations of OPCs are shown below.<sup>5</sup>

According to current opinion, staggered *gauche* (synclinal) or *trans* (antiperiplanar) conformations with respect to the P—C(sp<sup>3</sup>) bond are favourable for most OPCs.



This situation occurs regardless of the coordination state of the phosphorus atom (P<sup>III</sup> or P<sup>IV</sup>) and the presence of one, two or three such bonds in OPC molecules. At the same time, specific interactions (for example, intramolecular hydrogen bonding) and conjugation effects (for example, in the O=P—O—Si bond system) can stabilise the eclipsed *cis* (synperiplanar) conformation.

The ratio of the various rotamers and the factors responsible for their stabilisation are determined by the balance between intramolecular repulsive and attractive forces, *i.e.*, from the sum of Coulombic interactions between the dipoles, steric and orientation interactions, intramolecular electronic effects, *etc.* It should be noted that the general and relative stabilities of favourable conformers are, with rare exception, independent of the aggregation state of the compounds under study (crystals, liquids or solutions). The conformations observed in crystals are almost always retained in liquid and solution states, although several staggered rotamers often co-exist in the liquid phase, and the conformational pattern becomes more diverse.

In the last 15 years, the relative stabilities of the conformations of organophosphorus molecules which differ in angle of rotation about the P—C(sp<sup>3</sup>) bond, have been extensively studied by semiempirical and *ab initio* quantum-chemical methods.<sup>32–44</sup> In some studies,<sup>34–36</sup> the spectroscopic and structural data for phosphine oxides and phosphine sulfides were analysed using the semiempirical MNDO/H method, and the conclusion was drawn that this method provides a satisfactory general description of the geometry and various physicochemical characteristics of OPCs. The results of experimental conformational analysis (the temperature dependence of the conformational stability estimated by IR spectroscopy) agree closely with the results of theoretical conformational analysis (*ab initio* calculations) of the ethyldifluorophosphine obtained by Durig *et al.*<sup>38,39</sup> The staggered *gauche* and *trans* conformations are favourable for this compound, the energy difference being small (0.23 ± 0.02 kcal mol<sup>–1</sup>).

Earlier experimental (IR and Raman spectra) conformational analysis and semiempirical calculations, carried out by this research group for the ClCH<sub>2</sub>PF<sub>2</sub>,<sup>43</sup> EtP(S)Cl<sub>2</sub> and CD<sub>3</sub>CH<sub>2</sub>P(S)Cl<sub>2</sub> molecules,<sup>32</sup> led to the same principal results. All these compounds are characterised by the staggered *gauche* (C<sub>1</sub> symmetry) and *trans* (C<sub>s</sub> symmetry) conformations the *gauche* conformer being more stable. In the solid state, the latter conformer is the major one, whereas the *gauche* ⇌ *trans* conformational equilibrium occurs in the liquid state; however, the *gauche* conformation is more stable (the energy difference is 0.60 kcal mol<sup>–1</sup>).<sup>32</sup> The heights of the barriers to rotation about the P—C(sp<sup>3</sup>) bond in EtP(S)Cl<sub>2</sub> (2.22 kcal mol<sup>–1</sup>) and CD<sub>3</sub>CH<sub>2</sub>P(S)Cl<sub>2</sub> (2.71 kcal mol<sup>–1</sup>) estimated in the cited study are consistent with the earlier data.

*Ab initio* calculations of the rotation about the P—C(sp<sup>3</sup>) bond in carbanions stabilised by pentavalent phosphorus<sup>37</sup> demonstrated that in the presence of electronegative substituents, the rotation barriers are higher in compounds containing P=S groups, whereas in the presence of electropositive substituents, the rotation barriers are higher in compounds containing P=O groups. The results of X-ray diffraction studies and theoretical conformational analysis (*ab initio* and semiempirical calculations) of 1-alkoxyethyldiphenylphosphine oxide<sup>33</sup> are also in good agreement with each other.

A recent study of the EtPH<sub>2</sub> molecule<sup>40</sup> by *ab initio* methods using the HF, MP2, BLYP and B3LYP basis sets showed that internal rotation about the P—C(sp<sup>3</sup>) bond gives rise to the two most stable conformers when the methyl group is in *trans* and *gauche* orientations relative to the lone electron pair of the P<sup>III</sup> atom. The optimised structural parameters agree well with the data obtained by microwave spectroscopy. The results of gas electron diffraction and various *ab initio* calculations for bis(trichlorosilyl)-*tert*-butylphosphine are also in satisfactory agreement with each other,<sup>42</sup> although the structure is distorted and the environment of the silicon and carbon atoms deviates from the ideal tetrahedral coordination. The vibrational frequencies of methylphosphine CH<sub>3</sub>PH<sub>2</sub> and its deuterated derivatives were calculated using the Gaussian 98 program (HF, MP2 and DFT/B3LYP/6-311G\*\*), and the results compared with IR spectroscopic data.<sup>44</sup>

Theoretical conformational analysis of a wide range of typical (from the point of view of competition between Coulombic and steric interactions) substituted phosphine oxides R<sup>1</sup>R<sup>2</sup>P(O)CH<sub>2</sub>X (R<sup>1</sup> = R<sup>2</sup> = Me, Et, Pr<sup>i</sup>, Bu<sup>t</sup>, Ph; X = Me, CN, Ph, Cl) was carried out by the semiempirical PM3 method.<sup>45,46</sup> This method adequately reproduced the structural characteristics determined by gas electron diffraction and X-ray diffraction analysis for trialkylphosphine oxides. The corresponding sulfides, selenides and tellurides<sup>47</sup> also demonstrated satisfactory agreement with spectroscopic data. For the phosphine oxides under consideration, calculations adequately interpreted the abundant experimental data (dipole moments, Kerr constants, vibrational spectra of compounds in different aggregation states and solvents at different temperatures) and predicted a noncontradictory set of stable conformations. In particular, the population of the conformation with P=O and C—X bonds in a *trans* orientation was found to decrease as the volumes of the substituents at the phosphorus atom and the methylene group increased.

Data on dialkyl and alkylaryl derivatives R<sup>1</sup>R<sup>2</sup>P(O)CH<sub>2</sub>X containing the above-mentioned substituents retrieved from the Cambridge Structural Database are scarce. Nevertheless, it was noted<sup>45,46</sup> that the conformations of P<sup>IV</sup>—C(sp<sup>3</sup>) with the C—X bond in the *gauche* orientation with respect to the phosphoryl P=O group and the X—C—P—O angles varying from 30° to 60° are statistically most probable taking into account the known crystal structures. The histograms of the torsion angles in phosphine oxides containing the CP(Ph)(O)CH<sub>2</sub>X fragment (Fig. 1) show that, in the crystalline compounds, the orientation of the plane of the arene ring relative to the P=O bond (characterised by the τ<sub>2</sub> angle) is close to an eclipsed conformation. According to the results of gas electron diffraction, an analogous situation is observed for mono- and diaryl-substituted phosphine oxides in the gas phase.<sup>48</sup>

Experimental (X-ray diffraction study, IR spectroscopy, dipole moments) and theoretical (PM3) conformational analysis of the bis(methoxycarbonylmethyl)phenylphosphine oxide molecule PhP(O)(CH<sub>2</sub>CO<sub>2</sub>Me)<sub>2</sub> demonstrated that the synclinal (*gauche*) orientation of the substituents relative to the P—C(sp<sup>3</sup>) and C(sp<sup>3</sup>)—C(sp<sup>2</sup>) bonds prevails in both the crystal and solution states.<sup>49</sup> *Ab initio* calculations (HF, DFT, MP2) of the molecular geometry of related phosphonates (RO)<sub>2</sub>P(O)CH<sub>2</sub>C(O)X, where X = Me, EtS, Ph or Et<sub>2</sub>N, also predicted the staggered *gauche* orientation of the CH<sub>2</sub>—P bond relative to the carbonyl group.<sup>50</sup>

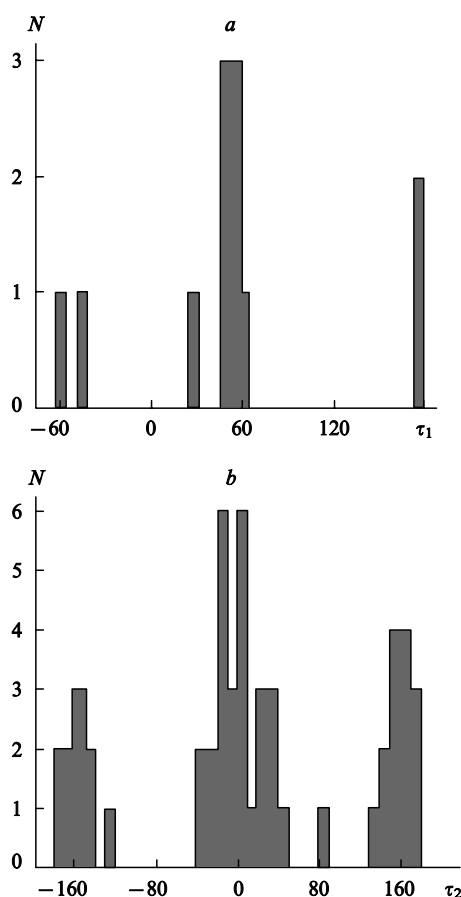


**Figure 1.** Histograms of the torsion angles in phosphine oxide molecules containing the CP(Ar)(O)CH<sub>2</sub>X fragment; the data were retrieved from the Cambridge Structural Database; (a) is the OPCX angle ( $\tau_1$ ), (b) is the ArPO ( $\tau_2$ ) angle (see the text).

As mentioned above, a comparison of the calculated data with the experimental results (IR, microwave and Raman spectroscopy, gas electron diffraction, X-ray diffraction analysis, dipole moments) of conformational analysis for a wide range of OPCs containing one P<sup>III</sup>–C bond,<sup>51–59</sup> one P<sup>IV</sup>–C bond,<sup>60–68</sup> two P<sup>IV</sup>–C bonds<sup>69</sup> or three P<sup>IV</sup>–C bonds<sup>70,71</sup> led to the conclusion that these compounds adopt staggered *gauche* and *trans* conformations regardless of the valence state of the phosphorus atom, the number of internal rotation axes and the aggregation state. For example, *ab initio* calculations for the EtPCl<sub>2</sub> molecule (HF/6-31G\*\*) predicted the classical *gauche* conformation with a torsion angle  $\varphi = 60^\circ$ ; the *trans* conformation being 2.09 kcal mol<sup>-1</sup> less stable. In molecules of other compounds, the *gauche* or *trans* conformation can be stabilised in accordance with the steric and electronic effects of their substituents.

In recent years, interesting conformational analysis results were obtained for OPCs containing the bulky fullerene substituent.<sup>72–77</sup> In the study,<sup>77</sup> the electronic and spatial structure of a new fullerene derivative, phosphorylated methanofullerene C<sub>60</sub>C(CO<sub>2</sub>Me)[P(O)(OMe)<sub>2</sub>], was calculated by density functional theory (DFT/PBE/TZ2P) using the exchange-correlation Perdew–Burke–Ernzerhof (PBE) functional<sup>78</sup> and the three-exponent basis set including two polarisation functions (TZ2P) implemented in the PRIRODA program.<sup>79</sup> The calculations demonstrated that the most stable conformations of phosphorylated methanofullerene are characterised by the Coulombic interaction between the phosphoryl oxygen atom and one carbon atom of fullerene and by polarisation of this fragment, resulting in asymmetry of the bond lengths and atomic charges in the C<sub>60</sub> cluster. The C–C bond lengths in the cisoid polyene fragments

**Table 3.** Total energies [ $E$  (a.u.)], enthalpies of formation ( $\Delta H$  / kcal mol<sup>-1</sup>), relative energies ( $\Delta E$  / kcal mol<sup>-1</sup>) and torsion angles of selected stable conformations of methanofullerene C<sub>60</sub>C(CO<sub>2</sub>Me). [P(O)(OMe)<sub>2</sub>].<sup>77</sup>

| Conformation <sup>a</sup> | <i>E</i> or $\Delta H$<br>(see <sup>b</sup> ) | $\Delta E$ | Torsion angles /deg |        |        |        |
|---------------------------|-----------------------------------------------|------------|---------------------|--------|--------|--------|
|                           |                                               |            | OCCP                | CCP(O) | (O)POC | (O)POC |
| DFT/PBE/TZ2P method       |                                               |            |                     |        |        |        |
| – <i>ac</i>               | –3197.217965                                  | 0.00       | 93                  | –144   | 35     | 50     |
| <i>ac</i>                 | –3197.216779                                  | 0.74       | 91                  | 148    | –55    | –29    |
| <i>sp</i>                 | –3197.214680                                  | 2.06       | 88                  | 23     | 26     | 47     |
| PM3 method                |                                               |            |                     |        |        |        |
| – <i>ac</i>               | 582.20                                        | 0.00       | 91                  | –131   | –42    | 48     |
| <i>ac</i>                 | 582.19                                        | 0.00       | 88                  | 141    | –47    | 45     |
| <i>sp</i>                 | 582.30                                        | 0.10       | 87                  | 20     | –47    | 42     |

<sup>a</sup> –*ac* is (–)-antichiral, *ac* is (+)-antichiral, *sp* is synperiplanar. <sup>b</sup>  $E$  in the DFT/PBE/TZ2P method,  $\Delta H$  in the PM3 method.

adjacent to the *exo*-coordinated C–C bond of the fullerene cage were found to alternate and the differences in the bond lengths decreased with increasing distance from the *exo*-coordinated carbon atoms. The internal rotation of the P(O)(OMe)<sub>2</sub> group about the C<sub>60</sub>C–P bond leads to the three most stable conformations (Table 3), two of which are antichiral (–*ac* and *ac*) with C–C–P = O torsion angles of  $-144^\circ$  and  $148^\circ$ , respectively. These conformations are more stable ( $\Delta E = 0$  and 0.74 kcal mol<sup>-1</sup>).<sup>8</sup> In the third, less stable, synperiplanar (*sp*) conformation ( $\Delta E = 2.06$  kcal mol<sup>-1</sup>), the orientation of the C–C and P–O bonds corresponds to a distorted (toward the *cis* orientation) *gauche* conformation (the C–C–P = O torsion angle is  $23^\circ$ ).

The theoretical study<sup>75</sup> of internal rotation about the P–C bonds in C<sub>60</sub>C[P(O)(OMe)<sub>2</sub>]<sub>2</sub> virtually reproduced the situation observed in the previous study<sup>77</sup> for phosphorus-containing fullerene C<sub>60</sub>C(CO<sub>2</sub>Me)[P(O)(OMe)<sub>2</sub>]. In this case, two antichiral conformations were also found to be most stable, whereas the third most stable conformation was the *gauche* form distorted toward the *cis* orientation (the C–C–P = O torsion angle is  $23^\circ$ ) (Fig. 2). The difference in the results<sup>75</sup> obtained by the DFT/PBE/TZ2P and PM3 methods is attributable to the fact that the stabilising through-space interaction between the phosphoryl group and the C<sub>60</sub> cage, which is reproduced at the DFT/PBE/TZ2P level of theory, is weakly pronounced in calculations by the semiempirical PM3 method. For the MeP(O)(OMe)<sub>2</sub> compound, the *gg* and –*g*–*g* conformers are equivalent, whereas the *ac* and –*ac* (*gg* and –*g*–*g*) conformers of the C<sub>60</sub>C(CO<sub>2</sub>Me). [P(O)(OMe)<sub>2</sub>] molecule differ substantially in energy due to the asymmetrically oriented CO<sub>2</sub>Me group. In the stable conformations of the C<sub>60</sub>CPhY<sup>76</sup> and C<sub>60</sub>CY<sub>2</sub> compounds<sup>75</sup> and the C<sub>60</sub>(CY)<sub>2</sub> bis-adducts,<sup>74</sup> where Y = P(O)(OR)<sub>2</sub>, an additional

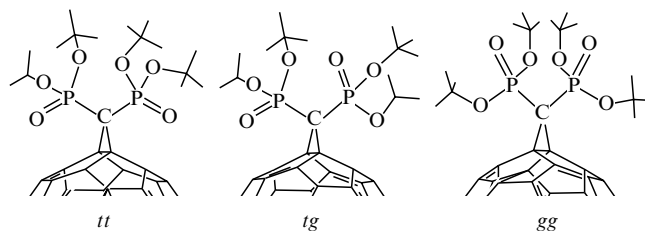


**Figure 2.** Stable conformations of phosphorylated methanofullerene C<sub>60</sub>C[P(O)(OMe)<sub>2</sub>]<sub>2</sub> calculated by the DFT/PBE/TZ2P method.<sup>75</sup>

§ Hereafter,  $\Delta E$  is the energy difference between the molecular conformation under consideration and the most stable conformer.

intramolecular coordination of the phosphoryl group to the fullerene cage is observed.

As mentioned above, analogous favourable conformations are also typical of other OPCs. Therefore, the addition of even such a bulky substituent as the fullerene fragment to the phosphorus atom has only a slight effect on the relative stabilities of different conformations of these compounds. For rotation about the P–C(sp<sup>3</sup>) bonds, staggered (or slightly distorted) conformations remain energetically most favourable for a wide range of compounds.

## 2. Internal rotation about the P–C(sp<sup>2</sup>)(alkene) bond

Most organophosphorus compounds containing a bond between the P atom and alkene fragments are liquids with high boiling points. Hence, methods providing information on their molecular structures in solution are of particular importance. Experimental conformational analysis of OPCs with the P–C(sp<sup>2</sup>)(alkene) bond has been carried out by gas electron diffraction, the Kerr effect method, the dipole moment method, vibrational spectroscopy and NMR spectroscopy. In solutions and in the gas phase, favourable conformations of vinylphosphonic acid dichloride CH<sub>2</sub>=CH–P(O)Cl<sub>2</sub>, divinylphosphinic acid dichloride (CH<sub>2</sub>=CH)<sub>2</sub>–P(O)Cl and vinylphosphonic acid difluoride CH<sub>2</sub>=CH–P(O)F<sub>2</sub> are those which contain C=C and P=O bonds in the *s-cis* orientation or similar conformations, in which these bonds are virtually coplanar.<sup>5</sup> The cisoid structure of the CH<sub>2</sub>=CH–P(O)XY fragment is attributable to steric repulsions between the substituents at the P<sup>IV</sup> atom and the methylene group, not involving electron conjugation. In contrast, the *s-trans* conformation is observed in styrenephosphonic acid difluoride PhCH<sub>2</sub>=CH–P(O)F<sub>2</sub>. Apparently, there is conjugation in this compound due to which the *trans* conformation becomes the most favourable.<sup>5</sup>

In more recent experimental studies,<sup>80–87</sup> the energetically favourable conformations of P<sup>III</sup> derivatives were found to contain the alkene fragments in the *cis* orientation with respect to the lone electron pair of the phosphorus atom. In these systems, the *trans* conformation can be present as the minor component. In  $\alpha$ -cyanostyrenephosphonates,  $\alpha$ - and  $\beta$ -substituted vinylphosphonates and other derivatives of alkenylphosphonic acids (results obtained by the dipole moment method, IR and NMR spectroscopy using lanthanide-shift reagents), the favourability of either *s-cis* or *s-trans* conformations is controlled by electrostatic factors. In all cases, structures with interacting dipoles in an antiparallel orientation are more stable.<sup>5</sup>

Semiempirical calculations (CNDO/2) for the CH<sub>2</sub>=CH–P(O)Cl<sub>2</sub> molecule<sup>88</sup> demonstrated that the dependence of the total energy of this compound on the angle between the O–P<sup>IV</sup>–C and P<sup>IV</sup>–C–C planes has a deep minimum corresponding to the *s-cis* conformation ( $\varphi = 0^\circ$ ) and a shallow minimum at  $\varphi = 180^\circ$  (*s-trans* conformation). In polar solvents, the *s-trans* conformation may become more stable, whereas the molecule adopts the *s-cis* conformation in the gas phase. More recent *ab initio* calculations for phosphorylated ethylenes CH<sub>2</sub>=CH–P(O)Cl<sub>2</sub>, CH<sub>2</sub>=CH–P(S)Cl<sub>2</sub>, CH<sub>2</sub>=CH–P(O)F<sub>2</sub>, CH<sub>2</sub>=CH–P(O)FMe, CH<sub>2</sub>=CH–P(O)Me<sub>2</sub> and CH<sub>2</sub>=CH–PCl<sub>2</sub> using the 4-31G basis set<sup>89,90</sup> confirmed the earlier conclusion that the *s-cis* conformation is favourable for these compounds. This conformation is also supported by the calculated dependences of the total energy (Fig. 3) and the parameters of the regression relation between the experimental and calculated ionisation potentials (IP) on the angle of internal rotation about the P–C bond. By contrast, calculations for dichlorovinylphosphonate and vinylphosphonic acid using the 6-31G\* basis set<sup>91</sup> and for some other derivatives of phosphonic acids (vinyl-, propenyl-, bromoalkenyl- and cyanoalkenylphosphonic acids and their diethyl esters) using the STO-3G basis set<sup>92</sup> gave two minima on the potential energy surface corresponding to the *s-cis* conformation, a distorted *s-trans-gauche* conformation

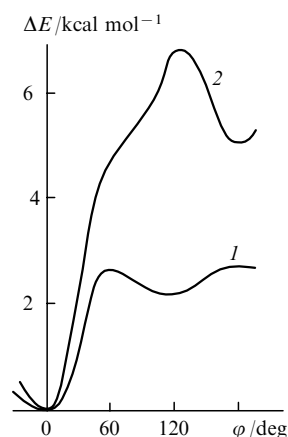


**Figure 3.** Dependence of the energies of the CH<sub>2</sub>=CHPCl<sub>2</sub> (1) and CH<sub>2</sub>=CHP(O)Cl (2) molecules on the torsion angle about the P–C bond.<sup>90</sup>

and two transition states with low barriers to rotation about the P–C(sp<sup>2</sup>) bond.

In the study,<sup>92</sup> the P=O bond in these compounds was demonstrated to be polarised and characterised by weak  $\pi$ -conjugation between the C=C and P=O groups. In the cited study, alkenylphosphonic acid derivatives were investigated by UV, IR, Raman and NMR (<sup>1</sup>H, <sup>31</sup>P, <sup>13</sup>C) spectroscopy, and it was concluded that the conformational equilibria were shifted toward the *s-cis* conformation [from 87% in the CH<sub>2</sub>=CH–P(O)(OH)<sub>2</sub> molecule to 99% in the MeCH=CH–P(O)Cl<sub>2</sub> molecule]. A distorted *s-trans-gauche* conformation was considered as the second most probable conformer. The energy difference between the conformers varied from 0.22 kcal mol<sup>–1</sup> in the *E* isomer of NC–CH=CH–P(O)(OMe)<sub>2</sub> to 2.81 kcal mol<sup>–1</sup> in the MeCH=CH–P(O)Cl<sub>2</sub> molecule.

The results of *ab initio* calculations for the CH<sub>2</sub>=CHPH<sub>2</sub>,<sup>88</sup> CH<sub>2</sub>=CHPF<sub>2</sub> (see Ref. 93) and CH<sub>2</sub>=CHPCl<sub>2</sub> molecules<sup>91,93</sup> are in complete agreement with experiment<sup>94</sup> (rotational spectra, the molecular constants and the dipole moment of vinylphosphine CH<sub>2</sub>=CHPH<sub>2</sub>) and indicate that these compounds adopt *s-cis* conformations. In these conformations, the lone electron pair of the phosphorus atom is parallel to the plane of the  $\pi$  system, hindering conjugation between these fragments. In the studies,<sup>91,93</sup> the form containing eclipsed C=C and P–Cl bonds was found as the minor conformation.

According to orbital models of donor-acceptor interactions (Fig. 4), the favourable conformation of vinyl derivatives of P<sup>III</sup> is determined by competition between the n(P)– $\pi^*(\text{PX}_2)$  and  $\pi(\text{C}=\text{C})$ – $\pi^*(\text{PX}_2)$  interactions. The former interaction stabilises the conjugated *gauche* conformation, whereas the latter stabilises the *cis* and *trans* conformations. In molecules containing electron-withdrawing substituents X at the P atom, the  $\pi(\text{C}=\text{C})$ – $\pi^*(\text{PX}_2)$  donor-acceptor interaction plays the major role, stabilises the *cis* conformation and is responsible for the  $\pi$ -acceptor character of the PX<sub>2</sub> fragment.<sup>93,95–97</sup>

A comparison of the vertical ionisation potentials of the EtPCl<sub>2</sub> [IP<sub>n(P)</sub> = 9.70, IP<sub>n(Cl)</sub> = 11.57 eV] and CH<sub>2</sub>=CHPCl<sub>2</sub> [IP<sub>n(P)</sub> = 9.84, IP <sub>$\pi(\text{C}=\text{C})$</sub>  = 10.86 and IP<sub>n(Cl)</sub> = 11.53 eV] molecules, which were determined from the photoelectron spectra,<sup>95</sup> also provides evidence that dichlorovinylphosphine adopts predominantly the *s-cis* conformation, in which there is no conjugation between the lone electron pair of the P atom and the  $\pi$  system of the C=C bond. In the electron-conjugated *s-trans* conformation, the first ionisation potential would be expected to decrease due to mixing of the n and  $\pi$  orbitals; however, an opposite situation is observed. Interestingly, theoretical conformational analysis of the related CH<sub>2</sub>=CHXMe molecules (X = O, S or Se) by *ab initio* methods including correlation energy at the MP2/

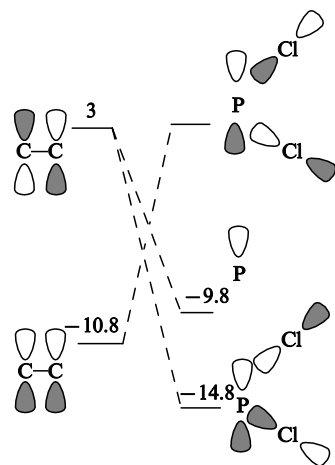


**Figure 4.** The key orbitals of dichlorovinylphosphine and their interactions in the *cis* conformation.<sup>95</sup> The calculated energies (eV) are given.

6-31G\* and MP2/6-311G\*\* levels of theory,<sup>98</sup> also predicted the *s-cis* conformation as the major one, characterised by a deep minimum in the energy curve.

The results of modern *ab initio* calculations (DFT/B3LYP/6-311++G\*\*) for the molecules  $\text{CH}_2=\text{CHP}(\text{O})\text{Cl}_2$  and  $\text{CH}_2=\text{CHP}(\text{O})\text{F}_2$  are virtually identical to the results of gas electron diffraction.<sup>88,93,99</sup> The calculations demonstrated that the *s-cis* conformation, in which the phosphoryl group eclipses the vinyl group, is stable at room temperature. It should be noted that the *gauche* rather than *s-trans* conformation (which was evident from the experimental data) was proposed<sup>99</sup> as the second possible form in the conformational equilibrium.

The mechanisms of electron conjugation between the vinyl and  $\text{PCl}_2$  fragments were considered in a study,<sup>90</sup> where the photoelectron spectra of phosphorylated ethylenes  $\text{Cl}_2\text{PCH}=\text{CH}_2$ ,  $\text{Cl}_2\text{P}(\text{O})\text{CH}=\text{CH}_2$  and  $\text{Cl}_2\text{P}(\text{S})\text{CH}=\text{CH}_2$  were analysed and *ab initio* calculations using the 4-31G basis set were carried out (see above). It was concluded that the *cis* and *trans* conformations of these compounds are stabilised by the  $\pi(\text{C}=\text{C})-\pi^*(\text{PCl}_2)$  and  $\pi^*(\text{C}=\text{C})-\pi(\text{PCl}_2)$  interactions involving the  $\pi$  system of the  $\text{C}=\text{C}$  double bond and the pseudo- $\pi$  orbitals of the  $\text{PCl}_2$  fragment. As a result of this interaction, the energies of the  $\pi$  and  $\pi^*$  orbitals of the vinyl fragment, unlike the energy of the  $\pi(\text{PCl}_2)$  orbital, depend only slightly on the angle of internal rotation about the  $\text{P}-\text{C}$  bond.

In another study,<sup>100</sup> the photoelectron spectroscopic data were compared with the results of calculations for phosphorylated allenes and ethylenes ( $\text{Me}_2\text{N})_2\text{P}(\text{O})\text{CH}=\text{C}=\text{CH}_2$ ,  $\text{Cl}_2\text{P}(\text{O})\text{CH}=\text{C}=\text{CH}_2$ ,  $\text{Cl}_2\text{P}(\text{O})\text{CH}=\text{C}=\text{CMe}_2$ ,  $(\text{MeO})_2\text{P}(\text{O})\text{CH}=\text{C}=\text{CH}_2$ ,  $(\text{MeO})_2\text{P}(\text{O})\text{CH}=\text{C}=\text{CMe}_2$ ,  $\text{Me}_2\text{P}(\text{O})\text{CH}=\text{C}=\text{CMe}_2$ ,  $\text{Cl}_2\text{P}(\text{O})\text{CH}=\text{CH}_2$  and  $\text{Cl}_2\text{P}(\text{S})\text{CH}=\text{CH}_2$ , which were performed using the 3G, 3G\*, 4-31G and 4-31G\* basis sets. It was demonstrated that at least the 4-31G split-valence basis set is required to achieve the proportionality of the calculated orbital energies  $\epsilon_m$  to the experimental ionisation potentials  $\text{IP}_m$  in phosphorylated allenes and alkenes. An increase in the energy of the  $\pi(\text{C}=\text{C})$  orbital in the molecules under consideration, compared to the energy of the same orbital in the ethylene molecule, is associated predominantly with the inductive effect of the  $\text{P}(\text{O})\text{Cl}_2$  and  $\text{P}(\text{S})\text{Cl}_2$  groups.

In polyfunctional alka-1,3-diene-2-phosphonates, coplanarity and consequently conjugation in the alka-1,3-diene fragment are disrupted.<sup>101</sup> This is evident from both experimental studies (IR and  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectroscopy) of these compounds and semiempirical CNDO/2 calculations. The energetically most favourable conformation was found to correspond to rotation about the central  $\text{C}-\text{C}$  bond in the 1,3-diene fragment of the

chain by a torsion angle of  $\varphi = 75^\circ$  (in fact, the *gauche* conformation). Hence, alkadienephosphonates containing a branched carbon skeleton should be considered as molecules with two isolated fragments, *viz.*, the chlorovinyl and vinylphosphonate groups. By contrast, 3-chlorobuta-1,3-dienephosphonates are electron-conjugated systems.

Experimental and theoretical conformational analysis of 2-phosphorus-substituted acrylonitriles by various methods (X-ray diffraction analysis, IR spectroscopy, dipole moments, quantum-chemical calculations) provides a detailed and non-

**Table 4.** Results of quantum-chemical calculations [DFT/B3LYP/6-31G(d)] of the relative energies and dipole moments of the possible conformers of  $\alpha$ -cyano- $\beta$ -furyl- $\beta$ -hydroxyvinylidiphenylphosphine oxide.<sup>102</sup>

| Z Isomer   |                                   |                | E Isomer   |                                   |                |
|------------|-----------------------------------|----------------|------------|-----------------------------------|----------------|
| conformers | $\Delta E$<br>(see <sup>a</sup> ) | $\mu/\text{D}$ | conformers | $\Delta E$<br>(see <sup>a</sup> ) | $\mu/\text{D}$ |
|            | 19.05                             | 9.30           |            | 22.60                             | 10.87          |
|            | 15.91                             | 8.32           |            | 16.91                             | 8.76           |
|            | 14.59                             | 8.76           |            | 22.78                             | 11.51          |
|            | 15.54                             | 7.39           |            | 20.08                             | 8.88           |
|            | 17.37                             | 6.53           |            | 17.30                             | 4.58           |
|            | 0.0                               | 0.48           |            | 12.75                             | 4.12           |
|            | 12.72                             | 5.56           |            | 12.87                             | 4.26           |
|            | 0.72                              | 1.08           |            | 11.81                             | 4.24           |

<sup>a</sup> In  $\text{kcal mol}^{-1}$ .



contradictory description of their structures in the individual state and solution.<sup>102</sup> Calculations using B3LYP/6-31G(d) hybrid density functional theory justified the favourability of the *Z-s-cis* arrangement of the hydroxy and diphenylenephosphine oxide substituents relative to the C=C bond in the molecules under consideration, the conformation being stabilised by intramolecular hydrogen bonding. Table 4 gives the relative energies and polarities of the possible conformers of  $\alpha$ -cyano- $\beta$ -furyl- $\beta$ -hydroxyvinylidiphenylphosphine oxide. Analysis of the relative energies of the geometric isomers provides unambiguous evidence that the *Z* configuration is favourable; the conformers with the C=C bond in the *s-cis* orientation with respect to the P=O (or P=S) bond correspond to the global energy minimum.

Quantum-chemical calculations of the polarities were carried out for phosphorus-containing acrylonitriles<sup>102</sup> (EtO)<sub>2</sub>P(O).C(CN)=C(OH)(2-Fu), Me(EtO)P(O)C(CN)=C(OH)(2-Fu), Ph<sub>2</sub>P(O)C(CN)=C(OH)(2-Fu) (where 2-Fu is the 2-furyl substituent) and also for Ph<sub>2</sub>P(O)C(CN)=C(OH)Me and Ph<sub>2</sub>P(S)C(CN)=C(OH)Me in benzene as the solvent used to determine the dipole moments of these compounds. In these calculations, the influence of the solvent was taken into account using the isodensity polarised continuum model (IPCM).<sup>103</sup> The calculated dipole moments do not differ significantly from their values in the gas phase and are in good agreement with the experimental values measured in solution. These results along with the spectroscopic data indicate that there are no strong interactions between the above compounds and benzene.

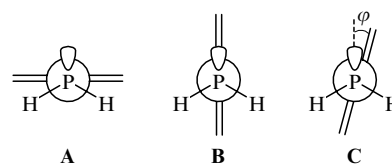
### 3. Internal rotation about the P—C(sp<sup>2</sup>)(carbonyl) bond

Data on rotations about the P—C(sp<sup>2</sup>)(carbonyl) bond are scarce in the literature. Experimental data on the structures of acylphosphine oxides and the corresponding phosphonates and aroylphosphines (dipole moments, <sup>13</sup>C NMR spectra) are indicative of a virtually ananameric equilibrium (*i.e.*, an equilibrium, in which one conformer is predominant) between the *s-cis* and *s-trans* conformations, the percentage of the latter form being as high as 90%–95%.<sup>5</sup> For other OPCs containing a P—C(sp<sup>2</sup>)(carbonyl) bond (triacylphosphines), *ab initio* and semiempirical calculations of the barriers to rotation about the P—C bond give similar estimates (~5 kcal mol<sup>-1</sup>).<sup>104</sup> The authors of the cited study believed that semiempirical calculations (CNDO/2) of the barriers to pyramidal inversion of the P<sup>III</sup> atom in these compounds gave a more reasonable estimate (14.4 kcal mol<sup>-1</sup>) than *ab initio* calculations with the minimum STO 3G basis set (28.9 kcal mol<sup>-1</sup>).

### 4. Internal rotation about the P—C(sp<sup>2</sup>)(phenyl) bond

The conformational state of OPCs containing P—Ph bonds have received the most attention. A review<sup>5</sup> has summarised considerable experimental data on the conformations of these compounds obtained by the above-mentioned physical methods. Simultaneously, researchers examined the possibility of conjugation between unsaturated fragments at the phosphorus atom and the lone electron pair of P<sup>III</sup>(3+) atoms or the P=Y bond (Y = O, S) of P<sup>IV</sup>(5+) compounds (the formal oxidation states of phosphorus are given in parentheses). Since questions about the relative orientations of the benzene ring and lone electron pair of the P atom, and of the benzene ring and P=Y bond are interrelated, they are generally considered simultaneously.

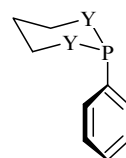
The structure of phenylphosphine PhPH<sub>2</sub> was studied<sup>105</sup> by gas electron diffraction and quantum chemistry (*ab initio* HF/6-31G\* and B3LYP/6-31G\* calculations). Calculations at the HF/6-31G\* level of theory predicted the bisecting conformation (**B**) for the PhPH<sub>2</sub> molecule characterised by the LEP—P—C—C torsion angle  $\varphi = 0^\circ$ , whereas calculations at the B3LYP/6-31G\* level predicted the skewed conformation (**C**) with the asymmetrically arranged phenyl substituent and angle  $\varphi = 20^\circ$ . Electron diffraction data were interpreted using the results of calculations by the HF/6-31G\* method, and some geometric parameters of the molecule were taken from the quantum-chemical data.



The results of numerous studies of phenylphosphine and its derivatives PhPXY by photoelectron spectroscopy using the data from semiempirical calculations were summarised in a monograph.<sup>106</sup> Photoelectron spectroscopy demonstrated that the lone electron pair of the phosphorus atom in the PhPCl<sub>2</sub> molecule lies in the plane of the phenyl group, *i.e.*, it is orthogonal to the orbitals of the benzene  $\pi$  system. Due to the absence of the  $n-\pi$  interaction, the photoelectron spectrum showed no splitting of the  $\pi$  levels of the arene fragment. However, this splitting was observed in the photoelectron spectrum of PhPH<sub>2</sub>, indicative of a considerable contribution of conformation **A**. It should be noted that if the spectra were interpreted in terms of the free internal rotation model about the P—C bond instead of the model of discrete conformers (which is conventionally used in the conformational analysis of OPCs), the theoretical spectrum and band splitting would also be consistent with experimental data.

By contrast, calculations using the Hartree–Fock method (HF/6-31G\*, HF/6-31G\*\* and HF/6-311G\*\*) for the PhPH<sub>2</sub> molecule gave the total energy minimum for the bisecting conformation **B** and the saddle point for structure **A** (the rotation barriers are 1.25, 1.06 and 1.06 kcal mol<sup>-1</sup>, respectively). Calculations including correlation energy at the B3LYP/6-31G\* and DFT/PBE/TZ2P levels of theory predicted the skewed structures **C** with  $\varphi$  angles of 20° and 45°, respectively, as the favourable conformations. Structures **A** and **B** correspond to saddle points on the potential energy surface with imaginary frequencies of 82 and 73 cm<sup>-1</sup>, respectively. The barriers to internal rotation are low and similar in height (~0.2 kcal mol<sup>-1</sup>). On the whole, aromatic derivatives of elements of row three of the Periodic Table (such as PhPH<sub>2</sub> or PhSH) are characterised by low barriers to internal rotation and high conformational flexibility. It is this factor that accounts in part for the contradictory experimental data.

In the above-cited review,<sup>7</sup> intramolecular electronic interactions in tri- and tetracoordinate phosphorus compounds were analysed on the basis of available structural data, and an example of the forced coplanar orientation of the lone electron pair of the P atom and the  $\pi$  orbitals of the phenyl group was given. In compounds containing 1,3,2-dioxaphosphine (Y = O) or 1,3,2-dithiaphosphine (Y = S) rings, strong 1,3-*syn*-axial interactions between the H atoms at positions 4 and 6 of the heterocycle and the *ortho*-H atoms of the axial phenyl group are responsible for the rotation of the arene ring by an angle of 90° with respect to the symmetry plane of the molecule in which the lone electron pair of the P atom lies. In this conformation,  $n,\pi$  conjugation is theoretically possible, but weak.



A systematic consideration of the steric and electronic characteristics of bonds involving P<sup>III</sup> and P<sup>IV</sup> demonstrated that specific orbital interactions between the arene fragment and the low-lying unoccupied  $\pi^*$  and  $\sigma^*$  orbitals of the bonds with phosphorus are of great importance. In a study,<sup>7</sup> an appropriate classification, in our opinion, of the structural features of OPCs was proposed in the context of the perturbation theory. The nature of the orbital effects discussed in this study is closely related to the conformational characteristics of the interacting orbitals. For example,  $n,\sigma^*$  hyperconjugation plays the major role in the case of a *trans* orientation of the lone electron pair and

polarised  $\sigma$  bond, the acceptor properties of which are most pronounced in the presence of destabilising n,n repulsion between the lone electron pairs of the adjacent heteroatoms involved ( $\alpha$  effect). In the case of a parallel orientation of the  $\pi$  orbitals of the benzene ring and pseudo- $\pi^*$  orbitals of the  $PX_2$  fragment, the n, $\sigma^*$  interaction in arylphosphines  $ArPX_2$  plays the major role and stabilises the bisecting conformation. The same structural features are observed in molecules containing P—O—Ar fragments.

A recent study<sup>107</sup> of the molecular structure of triphenylphosphine by gas electron diffraction and *ab initio* calculations at the HF/6-31G\* level of theory demonstrated that the  $Ph_3P$  molecule has  $C_3$  symmetry with a torsion angle  $\varphi$  of 32(3)°. The structure of the diphenylphosphine molecule  $Ph_2PH$  determined by gas electron diffraction and *ab initio* calculations at the same level of theory<sup>108</sup> is asymmetrical, the torsion angles at the P—C bonds being 65(7)° and 154(7)°.

It should be noted that the favourable structural factors are necessary but insufficient to account for the occurrence of p, $\pi$  interactions alone. Apparently, the assumption of the presence of these interactions with the  $P^{III}$  atoms in OPCs should be considered with caution taking into account the reasons stated in the debated papers<sup>109–111</sup> and analysis of this problem in the reviews.<sup>5,7</sup> In particular, the authors of the study<sup>112</sup> reasoned that UV spectroscopy is sometimes unsuitable for the detection of p, $\pi$  conjugation. Nevertheless, several examples<sup>7,113</sup> show that, in favourable molecular conformations, this conjugation can be revealed by quantum-chemical methods.

For example, *ab initio* calculations<sup>113</sup> at the HF/6-31G(d,p) level of theory of the geometry and electronic structures of triphenylphosphine, phenylphosphabicyclo[3.3.1]nonane and the [4.2.1]-isomer of the latter demonstrated that steric repulsion of the bicyclononane fragment causes the phenyl substituent at phosphorus to be located perpendicular to the lone electron pair (Fig. 5). This orientation is favourable for n, $\pi$  conjugation, which, in the authors' opinion, is responsible for high catalytic activity of both of the phosphorus-containing bicyclononanes. The sterically unhindered  $PhPH_2$  and  $Me_2PPh$  molecules do not adopt this conformation and, correspondingly, their catalytic activity is low.<sup>113</sup> The calculated geometric parameters of the molecules agree well with X-ray diffraction data.

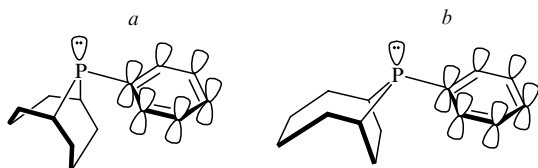


**Figure 5.** Stable conformations of phenylphosphabicyclo[3.3.1]nonane (a) and phenylphosphabicyclo[4.2.1]nonane (b).<sup>113</sup>

Semiempirical calculations,<sup>114</sup> where the angle of rotation of the  $PX_2$  group relative to the plane of the benzene ring was varied, also predicted the bisecting conformation as being the major one for the  $PhPF_2$ ,  $PhPCl_2$  and  $PhP(CN)_2$  molecules. However, the authors of this study suggested that there is an equilibrium between two of the conformations of  $PhPH_2$  and  $PhPMe_2$ , and an n, $\pi$  interaction can occur in one of these.

In an earlier study,<sup>115</sup> theoretical conformational analysis of the  $R_2PPh$  ( $R = H, F, Cl, Br, I, Me, Et, Pr^i, Bu^t$ ) and  $MeXPPh$  ( $X = H, F, Cl, Br$ ) molecules by the atom–atom potential method revealed flat minima in all conformational energy curves corresponding to the bisecting conformer. This provides evidence that the orientation of the Ph groups can be varied about the bisecting  $R_2P$  (or  $MePX$ ) plane within  $\pm 20^\circ$ , even in the case of di-*tert*-butylphenylphosphine. Therefore, the conformations of the above phenylphosphines do not rule out an insignificant p, $\pi$  interaction in these systems. Nevertheless, the conformations of aryl-substi-

tuted OPCs favourable for p, $\pi$  interactions (and, correspondingly, for the manifestation of these interactions in the spectra and properties) in this class of compounds are exceptions to this rule.

Semiempirical (CNDO/2, INDO, MINDO/3) calculations for the structures of diphenyl- and triphenylphosphines predicted the conformations that are unfavourable for conjugation between the lone electron pair of the phosphorus atom and the  $\pi$  system of the benzene ring.<sup>116</sup> Analysis of the results of semiempirical quantum-chemical calculations and spectroscopic characteristics (UV, IR, Raman) of *p*-carboxyphenyl-substituted dialkylphosphines and dialkylamines *p*- $HOOCC_6H_4EME_2$  ( $E = P, N$ ) showed that in the orthogonal conformation, the p, $\pi$  conjugation with the Ph fragment for a  $Me_2P$  group is half as strong as that observed for a  $Me_2N$  group, and, if the conformational equilibrium is not considered, this conjugation is weaker by a factor of 3–4.<sup>117</sup> Semiempirical (MNDO) and *ab initio* (HF, MP2) calculations for the  $RPCL_2$  ( $R = Me, ClCH_2, CF_3, CCl_3$ ) and  $ArPCL_2$  molecules and investigations of these compounds by  $^{35}Cl$  NQR spectroscopy led the authors of the study<sup>118</sup> to conclude that enhancement of steric interactions between the R and Cl substituents (the  $PCl_2$  group) and between the Ar and Cl at the  $P^{III}$  atom results in an increase in the s character of the lone electron pair of the chlorine atom. In a recent study,<sup>119</sup> the influence of the substituents on the structure of aromatic phosphines was investigated by the *ab initio* [MP2/6-311++G(U)B3LYP/6-31G(d)] method, and the P—X bond dissociation energies of *para*- and *meta*-substituted phenylphosphines *p*- $YC_6H_4PHX$  and *m*- $YC_6H_4PHX$  ( $X = H, F, Cl; Y = H, Me, NH_2, NMe_2, OMe, OH, SMe, etc.$ ) were evaluated.

Cyano derivatives of tri- and tetracoordinate phosphorus with one or two Ph substituents [ $PhP(CN)_2$ ,  $Ph_2PCN$ ,  $Ph(Et)PCN$ ,  $Ph_2P(O)CN$ ] were studied by the Kerr effect and dipole moment methods. These studies revealed structures in which the planes of the benzene rings virtually eclipse the lone electron pair of the phosphorus atom [ $PhP(CN)_2$ ,  $\varphi = 70^\circ$ ] or the phosphoryl group [ $Ph_2P(O)CN$ ,  $\varphi = 60^\circ$ ]. This excludes the possibility of efficient overlapping of the lone electron pair of the P atom with the  $\pi$  system of the benzene ring.<sup>120</sup> Therefore, it was experimentally demonstrated that the introduction of a strongly electron-withdrawing and small nitrile group directly at the phosphorus atom had no effect on the conformational behaviour of the phenyl fragments at the  $P^{III}$  and  $P^{IV}$  atoms and is not manifested in intramolecular electronic interactions involving these atoms. More recent<sup>121</sup> semiempirical (PM3) and *ab initio* (RHF/6-31G\*\*) calculations for the above-mentioned molecules also provided evidence that nearly-bisecting conformations are energetically favourable (Fig. 6).

The possibility of conjugation between the  $\pi$ -electron system and the lone electron pairs of  $P^{III}$  and  $P^{IV}$  atoms was actively discussed in the 1970s and 1980s. More recent studies did not confirm the initial assumption (which was made by many researchers) that trivalent phosphorus compounds, like nitrogen compounds, should be stabilised by p, $\pi$  conjugation. Tsvetkov and Kabachnik<sup>122</sup> analysed considerable experimental data and concluded that this conjugation in arylphosphines was inhibited. Later on,<sup>123</sup> dimethylphenylphosphine was studied by gas electron diffraction and IR and Raman spectroscopy. The authors of the cited study assumed the presence (along with that of an orthogonal conformer) of up to 30% of a conformer in which the mutual arrangement of the Ph group and the lone electron pair

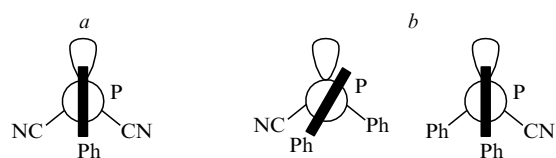


**Figure 6.** Newman projections of the stable conformers of dicyanophenylphosphine (a) and cyanodiphenylphosphine (b).<sup>121</sup>

of the  $P^{III}$  atom was favourable for conjugation. It was noted that the energy difference between these conformers was as small as  $0.40\text{--}0.63\text{ kcal mol}^{-1}$ , and the shape of the internal rotation potential was determined primarily by steric interactions. Compared to these interactions,  $p,\pi$  conjugation is substantially weaker, if existent at all. The same conclusion was reached in a study<sup>124</sup> based on the results of IR, X-ray fluorescence and Raman spectroscopy. Therefore, the following conclusion can be drawn from all the available data: both experimental methods and calculations demonstrate that conformations favourable for most  $P^{III}$  compounds containing one aryl substituent are those in which the aromatic ring is coplanar with the lone electron pair of the phosphorus atom, hindering  $p,\pi$  conjugation.

In monoaryl derivatives of  $P^{IV}(5+)$ , the arene ring is coplanar with the  $P=O$  and  $P=S$  bonds, which is favourable for its conjugation to the phosphorus-containing group. In contrast, steric interactions play a decisive role in diaryl- and triaryl-containing OPCs (regardless of the valence state of the phosphorus atom) and the least hindered conformations become favourable. This is evident from both experimental data and the results of *ab initio* calculations. Recall that calculations by the atom–atom potential method performed by Baranov, Dashevskii, Medved' and Kabachnik more than 20 years ago<sup>125, 126</sup> predicted, on the whole, the same conformational pattern.

Without discussing the role of d orbitals in the formation of bonds involving phosphorus in detail, we shall give several examples. Estimations of the contribution of d-orbital interactions in the  $Ph_2P(Y)C_6H_4OH-o$  molecules ( $Y = O, S$  or  $Se$ ) by semiempirical methods (CNDO/2, CNDO/C)<sup>127</sup> showed that the  $d(P) \leftarrow s,p(O,S,Se)$  charge transfers calculated from the overlap populations of phosphorus, sulfur and selenium AOs are substantially larger than the  $s,p(P) \rightarrow d(S,Se)$  back bonding. The occurrence of strong electronic interactions between the PY groups and aromatic fragments in these molecules was also confirmed by CNDO/C calculations of the electronic spectra of these compounds. However, in an earlier study,<sup>128</sup> where the electronic structures of selected OPCs containing phosphoryl groups were analysed by similar methods (CNDO/2 and INDO) and these data were compared with the results of *ab initio* calculations, it was inferred that the d orbitals played a negligible role in binding. Therefore, estimations of the contribution of d-AOs of P atoms to OPC bond systems by semiempirical methods often give contradictory results.

## 5. Internal rotation about P–O and P–S bonds

Experimental studies<sup>5, 129–152</sup> have demonstrated that internal rotation about P–O, P–S and P–Se single bonds in tri- and tetracoordinate phosphorus compounds (scarce data) is, in principle, similar to internal rotation about  $P-C(sp^3)$  bonds. However, there are substantial differences in their conformational behaviour due to anomeric  $n-\sigma^*$  interactions between the lone pairs of the heteroatoms (O, S, Se) and the antibonding orbitals of the adjacent P–X bonds involving the phosphorus atom.

By the mid-1980s, semiempirical quantum-chemical calculations had been carried out for a series of OPCs containing P–O and P–S bonds. A few publications on *ab initio* calculations were also reported (these studies are considered in other reviews<sup>5, 7</sup>). In most cases, the staggered *gauche* or *trans* conformations are favourable for acyclic OPCs regardless of the coordination of the phosphorus atom ( $P^{III}$  or  $P^{IV}$ ), the nature of the heteroatom bound to phosphorus and the number of internal rotation axes.<sup>5</sup> In the case of internal rotation about exocyclic P–X bonds ( $X = O, S, Se$ ), the staggered conformations of 1,3,2-dioxaphosphorinanes are also more stable, regardless of the nature of the heteroatom adjacent to the phosphorus.<sup>5, 27</sup> In solutions of 1,3,2-dioxaphospholanes, the general characteristic features are responsible for a *cis* orientation of irregular (*i.e.*, those having additional degrees of freedom associated with their own internal rotation) exocyclic substituents with respect to the lone electron pair of phosphorus atom or the  $P=O$  and  $P=S$  bonds.<sup>5</sup>

Exceptions to these rules are attributable to additional intramolecular interactions (hydrogen bonds, high dipole moments at the adjacent atoms, *etc.*).<sup>5</sup> In one review,<sup>153</sup> it was noted that  $P^{III}$  derivatives are characterised by stabilisation of one conformer, whereas an equilibrium between several rotamers is often observed for  $P^{IV}$  compounds. The differences in conformations of the molecules in the gas phase, liquid state (solution) and in crystals can be associated with crystal packing forces. In most examples, the conformation observed in crystal form is also present as one of the components of the conformational equilibrium in the liquid state and solution. However, this is not always the case, and the major conformers in solution can differ from the molecular conformation found in crystals.

### a. Molecules with one internal rotation axis

Semiempirical quantum-chemical methods predict that the staggered *gauche* and (or) *trans* conformations of  $MeOPF_2$  and  $MeOPCl_2$  molecules are favourable,<sup>154–156</sup> which is in agreement with the gas electron diffraction data and dipole moment measurements. The geometric parameters of difluoromethoxyphosphine calculated by *ab initio* methods<sup>157</sup> agree well with the corresponding experimental parameters. Semiempirical calculations (CNDO/2) for thio derivatives of trivalent phosphorus acids, such as  $Cl_2PSMe$ ,  $Et_2PSMe$ ,  $MeP(SMe)_2$  and  $P(SET)_3$ , revealed a conformational equilibrium between the staggered synclinal and antiperiplanar conformations resulting from rotation about the P–S bond.<sup>156, 158</sup> This is consistent with the experimental dipole moment and Kerr constant data as well as with the vibrational spectra of these compounds.<sup>5</sup>

At least four staggered *gauche* and *trans* conformations were found for dichloropropyl and dichloroisopropyl thiophosphites  $Pr^n-S-PCl_2$  and  $Pr^i-S-PCl_2$  by Raman spectroscopy and quantum-chemical calculations.<sup>159</sup> In this case, as in the case of rotation about the  $P-C(sp^3)$  bonds (see Section II.1), only one conformer with the lone pair of the P atom in the *trans* orientation with respect to the C–S bond is present in crystals, whereas in the liquid state and solution, rotation about the P–S, S–C and C–C bonds leads to dynamic equilibrium between synclinal and antiperiplanar conformations. It was also noted that variation in length and branching of the alkyl substituent at sulfur in a series of thiophosphites  $RS-PCl_2$  ( $R$  is alkyl) does not lead to a qualitative change in barriers to internal rotation about the P–S bond, *i.e.*, the conformation with a *trans*-R–S bond relative to the lone pair of the P atom remains energetically favourable for all members of the series.

Several studies have been devoted to *ab initio* calculations of the structures of fluorophosphinates  $R'(F)P(O)OR$ , where  $R = Me, Pr^i, CH(Me)Bu^i$ , cyclo- $C_6H_{11}$  and  $R' = Me, Et$ .<sup>160, 161</sup> Calculations at all the levels of theory used in these studies [RHF/6-31G(d), MP2/6-31G(d), B3LYP/6-31(d), 3-21G\*] revealed one stable staggered conformer in which the O–C(R) bond is perpendicular to the P–F bond due to the anomeric effect. Figure 7 shows the potential energy curve for internal rotation about the P–O(R) bond in these molecules. The  $^{31}P$  and  $^{13}C$  NMR spectra of  $Me(F)P(O)OMe$  are also indicative of the occurrence of one stable conformer.<sup>160</sup> (In the cited study, the earlier interpretation of electron diffraction data was corrected.)

It should be noted that *ab initio* calculations of the molecular structures of methyl hypophosphite  $H_2P(O)OMe$ , dimethyl phosphite  $HP(O)(OMe)_2$  and trimethyl phosphite using different basis sets (STO-3G\*, 3-21G\* and 4-31G\*) gave different results.<sup>162</sup> The relative energies of stable conformers resulting from internal rotation about the P–O bond and the changes in the dipole moments of the methyl hypophosphite and dimethyl phosphite molecules depending on the  $O=P-O-Me$  torsion angle were calculated using the STO-3G\* basis set. These calculations showed that there was a conformational equilibrium between two forms, with the *cis* conformation predominating. Calculations using alternative basis sets predicted that the *trans* conformation was more stable. It was noted that the energy difference

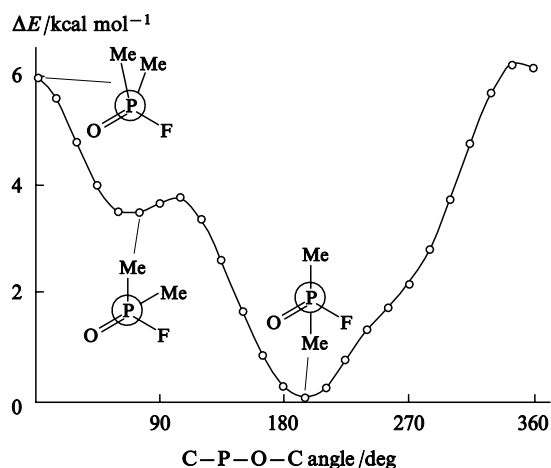


**Figure 7.** The curve of the potential energy of rotation about the P–O bond (directed perpendicular to the plane of the page) for the MeOP(O)FMe compound.<sup>160</sup>

The geometric parameters were fully optimised at the B3LYP/6-31G\* level of theory, except for the C–P–O–C torsion angle.

$\Delta E$  between the conformers was insignificant ( $0.08 \text{ kcal mol}^{-1}$  for methyl hypophosphite and dimethyl phosphite and  $0.9 \text{ kcal mol}^{-1}$  for trimethyl phosphite). *Ab initio* calculations (RHF/6-31G\*) for the MeOP(CN)<sub>2</sub> and MeP(O)(CN)<sub>2</sub> molecules, which were carried out<sup>163</sup> to study the tautomeric and conformational stability of these compounds, revealed a deep minimum for the *trans* configuration of Me–O–P–LEP in dicyanomethoxyphosphine (Fig. 8). In contrast, three minima corresponding to the staggered *gauche* and *trans* conformations of dicyanomethylphosphine oxide are observed in the potential curve.

Analogous results were obtained for dicyanomethoxyphosphine in the study,<sup>121</sup> where the *trans*-Me–O–P–LEP structure was demonstrated to be the favourable conformation with the lowest energy, regardless of the method used for calculation (PM3, RHF/6-31G\*\*). This conclusion is in complete agreement

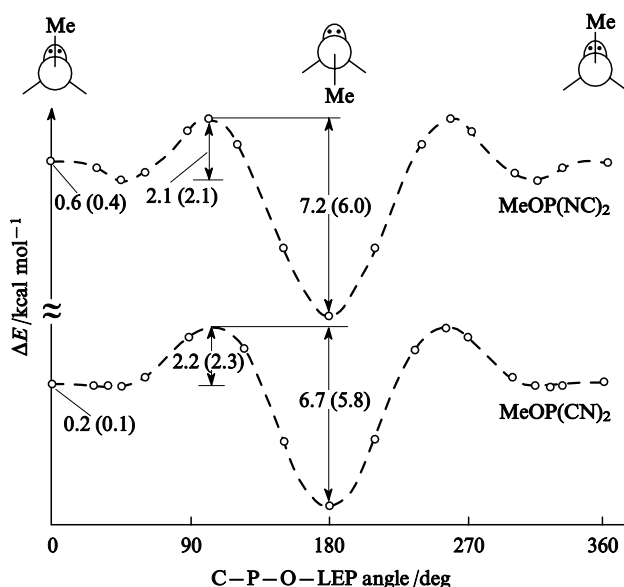


**Figure 8.** Potential curves of the internal rotation about the P–O bond and barriers to transition for the MeOP(CN)<sub>2</sub> and MeOP(NC)<sub>2</sub> molecules calculated by the MP2/6-31G\* method.

The potential barriers calculated at the RHF/6-31G\* level<sup>164</sup> are given in parentheses.

with experimental data<sup>165</sup> and with the results of other *ab initio* calculations,<sup>164</sup> including electron correlation (MP2 = FULL/6-31G\*). In the latter case, a deep minimum was found in the potential curve of internal rotation, corresponding to the *trans* arrangement of the MeO group with respect to the lone pair of the P atom.

It should be emphasised that the *trans* conformer appeared to be favourable for MeOP(CN)<sub>2</sub> regardless of the quantum-chemical method used [PM3 and 6-31G\*\*,<sup>121</sup> 6-31G\* and MP2 = FULL/6-31G\* (see Ref. 164)]. Stabilisation of the *trans* conformation of this compound is, apparently, associated with two factors acting in the same direction, *viz.*, Coulombic attraction between the oppositely directed P → CN and Me → O dipoles and the *gauche* effect. Apparently, due to the presence of the polar P–CN fragment with a large charge separation, interactions between the polar bonds play a major role in the stabilisation of conformations. The staggered *gauche* and *trans* conformations also result from rotation about the P–O bonds in phosphonite (MeO)<sub>2</sub>PCN and phosphonate (MeO)<sub>2</sub>P(O)CN.<sup>121</sup> Therefore, in some cases the favourable conformations with respect to the P–O bond can be transferred to related OPC molecules containing two or three identical internal rotation axes.

Somewhat unexpected results were obtained<sup>166</sup> in *ab initio* calculations of the molecular structure, conformational stability, vibrational frequencies and intensities of the absorption bands in the IR and Raman spectra of methyl dimethylphosphinite Me<sub>2</sub>POMe. Internal rotation about the P–O bond gives rise to two favourable conformers with the lone electron pair of the P atom in ‘nearly *cis*’ and ‘nearly *trans*’ orientations relative to the methyl group, the *cisoid* structure being more stable by more than  $1.5 \text{ kcal mol}^{-1}$ . Similar results were obtained in photoelectron spectroscopy and semiempirical quantum-chemical calculations (MNDO and INDO) for the Me<sub>2</sub>P–XMe compounds, where X = S or Se (and their arsenic analogues).<sup>167</sup> For these compounds, intermediate conformations with the  $\varphi$  angle varying between 0° and 180° rather than the ideal *cis* or *trans* conformations are stabilised. A study of the molecular structures of Me<sub>2</sub>PSMe and Ph<sub>2</sub>PSet by photoelectron spectroscopy in combination with quantum chemistry (CNDO/2 and *ab initio* calculations using various basis sets from 3G to 6-31G)<sup>168</sup> also led the authors to conclude that dimethyl methylthiophosphinite adopts a distorted (toward *cis*) *gauche* conformation with a torsion angle of 32°.

Semiempirical calculations demonstrated that methyl di(thio-methyl) phosphonite MeP(SMe)<sub>2</sub> with two internal rotation axes also adopts an ‘intermediate’ favourable conformation, in which the Me–P–S–Me torsion angles have similar values (17° and 14°).<sup>168</sup> If the photoelectron spectrum of this compound is modelled by an equilibrium between two conformations, the *gt* conformation with torsion angles of –45° and 180°, should be included. This is in complete agreement with the results of calculations using the HF/6-31G\*\* and DFT methods at the B3LYP/6-31G\*\* and PBE/TZ2P levels of theory (Table 5). The conformational equilibrium of phenyl di(thioethyl) phosphonite, which also has two internal rotation axes about the P–S bond, always includes the *g*<sub>1</sub>*g*<sub>2</sub> conformation, in agreement with the earlier experimental data.<sup>168</sup>

The existence of distorted conformations of OPCs in the case of a flat potential energy curve for the internal rotation about the P–O bond was demonstrated in principle by semiempirical quantum-chemical calculations performed by Gorenstein *et al.*<sup>169</sup> in the 1970s.

*Ab initio* calculations for the methyl phosphinate Me<sub>2</sub>P(O)OMe, dimethyl phosphite HP(O)(OMe)<sub>2</sub> and dimethyl phosphonates MeP(O)(OMe)<sub>2</sub>, (MeO)<sub>2</sub>P(O)CH<sub>2</sub>OH and (MeO)<sub>2</sub>P(O)CH(OH)CMe<sub>2</sub>CH<sub>2</sub>NMe<sub>2</sub> (HF/6-31G\*\*, B3LYP/6-31G\* and DFT/PBE/TZ2P), performed by one of the authors of this review, showed that, regardless of the number of P–O bonds (one or two) in these compounds and the basis set used in calculations, *gauche* (one internal rotation axis) or *gauche,gauche*

**Table 5.** Relative energies ( $\Delta E/\text{kcal mol}^{-1}$ ) of the stable conformers of the  $\text{P}(\text{OMe})_3$ ,  $\text{Me}_2\text{PSMe}$ ,  $\text{MeP}(\text{SMe})_2$  and  $\text{P}(\text{SMe})_3$  molecules (HF/6-31G\*\* and DFT methods at the B3LYP/6-31G\*\* and PBE/TZ2P levels of theory).<sup>a</sup>

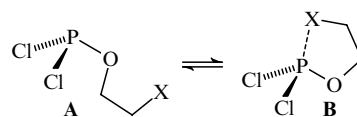
| Conformer                                    | Calculation method |       |      |
|----------------------------------------------|--------------------|-------|------|
|                                              | HF                 | B3LYP | PBE  |
| <b><math>\text{P}(\text{OMe})_3</math></b>   |                    |       |      |
| <i>ggt</i>                                   | 0.00               | 0.00  | 0.00 |
| <i>gtt</i>                                   | 1.38               | 1.39  | 1.77 |
| <i>ttt</i>                                   | 5.75               | 5.75  | 5.29 |
| <b><math>\text{Me}_2\text{PSMe}</math></b>   |                    |       |      |
| <i>c</i>                                     | 0.00               | 0.00  | 0.00 |
| <i>t</i>                                     | 0.93               | 0.84  | 1.12 |
| <b><math>\text{MeP}(\text{SMe})_2</math></b> |                    |       |      |
| <i>gt</i>                                    | 0.00               | 0.00  | 0.00 |
| <i>gg</i>                                    | 1.09               | 0.84  | 0.56 |
| <i>tt</i>                                    | 4.68               | 4.06  | 4.42 |
| <b><math>\text{P}(\text{SMe})_3</math></b>   |                    |       |      |
| <i>-ggt</i>                                  | 0.02               | 0.00  | 0.00 |
| <i>ggt</i>                                   | 0.00               | 0.32  | 0.51 |
| <i>ggg</i>                                   | 0.59               | 1.09  | 0.99 |
| <i>gtt</i>                                   | 2.89               | 2.38  | 1.53 |

<sup>a</sup> V V Zverev, unpublished data.

(two internal rotation axes) conformations are the most favourable rotamers. These conformations are characterised by energy minima in the potential curves, in complete agreement with the experimental data.

In contrast, *ab initio* HF/6-31G\*\* calculations<sup>170</sup> and calculations including electron correlation (see Tables 1 and 2) for phosphorus acids  $\text{H}_2\text{POH}$ ,  $\text{H}_2\text{P}(\text{O})\text{OH}$  and  $\text{H}_2\text{P}(\text{S})\text{OH}$  led to three different situations. The eclipsed *cis* and *trans* conformations were found for  $\text{H}_2\text{POH}$ , the staggered *gauche* and *trans* conformations were revealed for  $\text{H}_2\text{P}(\text{O})\text{SH}$ , whereas the energy difference between the *cis* and *gauche* conformations of  $\text{H}_2\text{P}(\text{S})\text{OH}$  is negligibly small. In the vicinity of *cis*–*gauche* conformations, the potential energy surface resembles a plateau. Unlike the neutral  $\text{H}_2\text{POH}$  molecule, the most favourable conformation of the radical cation of this compound is *gauche*. The inclusion of the solvent effect in calculations using the SCRf HF/6-31G\*\* method was demonstrated to lead to the elongation of the  $\text{P}=\text{O}$  bond and slight changes in the geometric parameters.<sup>170</sup> The calculated energies of the rearrangement of the molecule and solvation shell upon ionisation are slightly higher than the experimental values.

An analysis of normal vibrations in the IR and Raman spectra of phosphorodichloridates  $\text{R}(\text{CH}_2)_2\text{O}-\text{PCl}_2$  ( $\text{R} = \text{Et}, \text{OMe}, \text{Cl}, \text{SCN}$ ) and molecular mechanics calculations<sup>171–173</sup> demonstrated that the *anti* (*trans*) and *gauche* conformers with respect to the  $\text{P}-\text{O}$  and  $\text{C}-\text{O}$  bonds are favourable for alkoxy groups. The energy differences between these conformations are small (0.9  $\text{kcal mol}^{-1}$  for the  $\text{P}-\text{O}$  bond and 0.8  $\text{kcal mol}^{-1}$  for the  $\text{C}-\text{O}$  bond). In the liquid state, *gauche* conformations are favourable. At low temperatures, for  $\text{R} = \text{Cl}$ , these conformations are frozen out and the *trans* conformer becomes the most stable. In the liquid state, all compounds are characterised by a conformational equilibrium between the *gauche* conformation (A) and ‘bent’ conformation (B). In various studies,<sup>171–173</sup> it has been suggested that there is an additional intramolecular interaction between the phosphorus and oxygen (sulfur, chlorine) atoms in the latter conformer.



## b. Molecules with two and three internal rotation axes

Semiempirical [MNDO and CNDO/2(s,p,d)] calculations of dialkyl phosphites  $(\text{RO})_2\text{P}(\text{O})\text{H}$  ( $\text{R} = \text{Me}, \text{Et}, \text{Pr}, \text{Bu}, \text{C}_5\text{H}_{11}, \text{C}_6\text{H}_{13}$ ) substantiated the fact that the staggered *gauche* and *trans* conformations are energetically favourable, regardless of the method used.<sup>174</sup> Interestingly, a very small energy difference between the major conformer and the second most energetically favourable conformer (0.06 eV) was obtained in all approximations. An analogous conclusion about stability of the staggered *gauche*, *gauche* (*gg*) and *trans*, *gauche* (*tg*) conformations was drawn in an earlier experimental study of dimethyl phosphite and its deuterated analogue.<sup>175</sup> These conformations were evident from vibrational spectra measured at different temperatures, in different aggregation states and in solvents of different polarity and concentration, and were supported by force constant calculations.

Similar results were obtained by semiempirical calculations for trialkyl phosphate molecules<sup>176, 177</sup> (an equilibrium mixture of  $\text{C}_3$  and  $\text{C}_1$  rotamers). The conformational equilibrium was also evident from photoelectron spectra. In the cited study, a new assignment of the bands in the spectra was made and the ionisation potentials were refined. In continuation of these studies, the first five ionisation potentials were determined by mathematical processing, and the conformational inhomogeneity of samples was found to influence the photoelectron spectra of trimethyl and triethyl phosphates.<sup>178</sup> In the spectra of more complex phosphates, the contributions of different conformers became indistinguishable because of overlapping of the bands corresponding to the  $n_\sigma$  and  $\sigma$  orbitals of similar energies.

The conformational equilibrium between rotamers of trimethyl phosphate with  $\text{C}_3$ ,  $\text{C}_1$  and  $\text{C}_s$  symmetry corresponding to three minima on the potential energy surface (PES) was found in the study<sup>179</sup> with the use of *ab initio* methods (6-31G\* and 6-31G\*\* basis sets). The energy of the conformer with  $\text{C}_1$  symmetry is higher than that with  $\text{C}_3$  symmetry by 0.56  $\text{kcal mol}^{-1}$ , and the energy of the  $\text{C}_s$  conformer is higher than that of the  $\text{C}_3$  conformer by 1.43  $\text{kcal mol}^{-1}$ . The study of triethyl phosphate<sup>180</sup> by the semiempirical AM1 method and IR spectroscopy revealed two conformers with  $\text{C}_1$  symmetry.

Theoretical conformational analysis was carried out for a wide range of tetravalent phosphorus compounds containing one, two or three  $\text{P}-\text{O}$  rotation axes:  $\text{H}_2\text{P}(\text{O})\text{OH}$ ,  $\text{HP}(\text{O})(\text{OH})_2$ ,  $(\text{HO})_3\text{PO}$ ,  $\text{MeP}(\text{O})(\text{OH})_2$ ,  $\text{HP}(\text{O})(\text{OMe})_2$ ,  $\text{Me}_2\text{P}(\text{O})\text{OMe}$ ,  $\text{Me}_3\text{P}(\text{O})$ ,  $\text{MeP}(\text{O})(\text{OMe})_2$  and  $(\text{MeO})_3\text{PO}$ .<sup>181, 182</sup> In the study,<sup>181</sup> the authors used the molecular mechanics method (MM3) and parameters chosen from the results of *ab initio* calculations of the conformations of several phosphates (HF/6-31G\*\*). Figure 9 shows the plots of the relative energies of dimethyl phosphinate and trimethyl phosphate vs. the angle of rotation about the  $\text{P}-\text{O}$  bond. The *gauche* and *trans* conformations appeared to be favourable for these esters, whereas the *cis* conformation was favourable for dimethylphosphinic acid.

The possibility of  $\text{P}^{\text{IV}}$  acids adopting eclipsed conformations was also discussed above. It should be noted that the *cis* conformation of dimethylphosphinic acid and analogous compounds was found only in calculations by the Hartree–Fock method, whereas calculations by the MP2, MP4 and DFT methods using the correlation energy density functional predicted that the lowest energy corresponds to the staggered *gauche* structures, and the saddle point on the potential energy surface corresponds to the *cis* conformation (see Table 2). The parametrisation of the MM3 force field on the basis of *ab initio* calculations at the RHF/6-31G\* level of theory includes all the errors of the latter method. Here we are dealing with the relative energies of the conformations rather

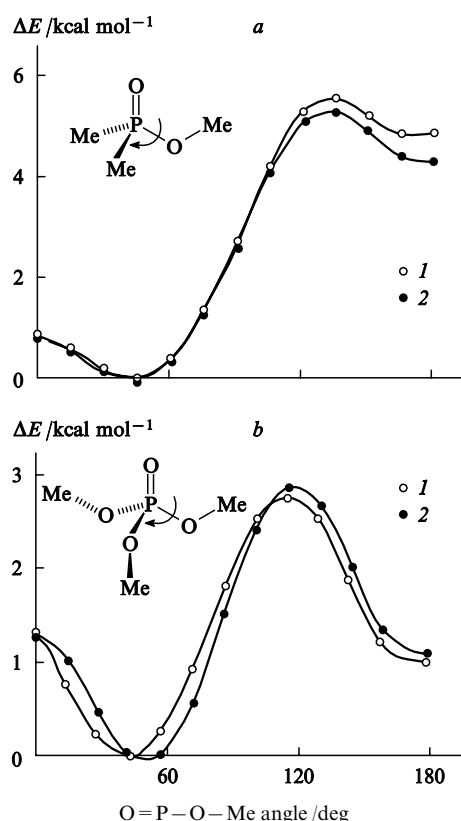


**Figure 9.** Rotation profiles [HF/6-31G\*\* (1) and MM3 parameterised from the results of HF/6-31G\*\* calculations (2)] for the O=P–O–Me fragment in methyl dimethylphosphinate (a) and trimethyl phosphate (b).<sup>181</sup>

than with a considerable deformation of the overall calculated potential surface.

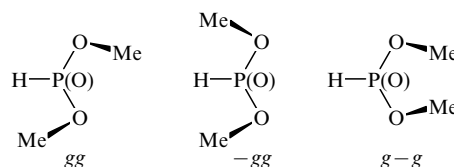
*Ab initio* MP2/6-31 + G\* and MP2/6-31G\* calculations for the methyl phosphinate, dimethyl phosphonate, trimethyl phosphate and hypophosphorous, phosphorous and phosphoric acids revealed<sup>182</sup> the global minimum in the energy curve for R–O–P=O torsion angles of 35–58° corresponding to the *gauche* conformation (in some cases, the conformation is slightly distorted towards the *cis* conformation). Analogous results were obtained for P<sup>IV</sup> compounds at other levels of theory (see Tables 2 and 6). Phosphorous and phosphoric acids are characterised by the presence of a second minimum at 180° (a *trans* conformation). The barrier to rotation about the P–O bond was estimated at 5 kcal mol<sup>–1</sup>. Calculations using the molecular mechanics method including interactions of the lone electron pairs for dialkyl phosphites (RO)<sub>2</sub>P(O)H demonstrated that these molecules can adopt at least two stable conformations of similar energy,<sup>184</sup> one of which is the above-mentioned *gauche* conformation distorted toward the *cis* conformation.

Conformational analysis of dimethyl phosphite in aqueous solution by the DFT method<sup>185</sup> demonstrated that solvent reorganisation plays an important role in the conformational

equilibrium between the *gauche,gauche* and *gauche,trans* conformations favourable for these compounds. In these calculations, the solvent was taken into account by the isodensity polarised continuum model (IPCM). Conformational analysis of this compound in the pure liquid state (dielectric permeability  $\epsilon = 34.3$ ) and in carbon tetrachloride by the *ab initio* self-consistent reaction field (SCRf) method with a fixed cavity, in which the solute is embedded, at the HF/6-31G\*\* level of theory, also showed that solvent reorganisation plays an important role in the equilibrium between the above-mentioned conformations (Table 6). The molar fractions of the conformers of dimethyl phosphite in polar solvents calculated by the SCRf method are equal to their empirical values and account for the kinetic data of this compound's homolytic reactions.<sup>183</sup>

The results of theoretical studies of the conformations of the HP(O)(OMe)<sub>2</sub> molecule by the Hartree–Fock method were compared with the results obtained using density functional theory (see Table 6).<sup>77,183</sup>

Calculations of the conformations of HP(O)(OMe)<sub>2</sub>, MeP(O)(OMe)<sub>2</sub> and C<sub>60</sub>C(CO<sub>2</sub>Me)[P(O)(OMe)<sub>2</sub>] using the PM3 method predicted that the –*gg* orientation of the methoxy groups relative to the P=O bond (which is directed perpendicular to the plane of the figure) corresponds to the most stable conformation.



The –*gt* and *tt* conformers are less stable, and their energies are lower than that of the –*gg* conformation by 2 and 4 kcal mol<sup>–1</sup>, respectively. However, *ab initio* calculations at HF/6-31G\* and MP2/6-31G\* levels and by the density functional theory with two different exchange-correlation functionals for HP(O)(OMe)<sub>2</sub> demonstrated that the *gg* rather than –*gg* conformation is most stable, whereas the energies of the less stable –*gt* and *gt* conformers are lower than that of the *gg* by ~2 kcal mol<sup>–1</sup>. Analogous results were obtained for MeP(O)(OMe)<sub>2</sub>. Analysis of the potential energy surfaces for the (MeO)<sub>2</sub>P(O)H and MeP(O)(OMe)<sub>2</sub> molecules showed<sup>77</sup> that the *gg* and –*gg* structures correspond to stationary points, but only one of these points is a local minimum (–*gg* according to calculations by the PM3 method and *gg* according to calculations by *ab initio* and DFT methods), whereas the second conformation is characterised by a saddle point (*gg* and –*gg* according to calculations by the PM3 and *ab initio* methods, respectively).

Semiempirical calculations (AM1, PM3) for *O,O*-di(isopropyl) isoxazolinophosphonate, in combination with the dipole moment method, demonstrated the favourability of the staggered *gauche* and *trans* conformations.<sup>186</sup> These recent results agree well with the experimental and calculated data reported in the preceding review.<sup>5</sup>

Examination of the photoelectron spectra and electronic structures of (MeO)<sub>3</sub>P, (MeO)<sub>2</sub>PNCO, MeOP(NCO)<sub>2</sub> and P(NCO)<sub>3</sub> by *ab initio* methods using the STO-3G basis set<sup>187</sup> showed an increase in the first ionisation potential corresponding to the n(P) orbital and in the second ionisation potential corre-

**Table 6.** Relative energies (kcal mol<sup>–1</sup>) and torsion angles OPOC(1) ( $\varphi_1$ ) and OPOC(2) ( $\varphi_2$ ) (deg) of different conformers of the dimethyl phosphite molecule HP(O)(OMe)<sub>2</sub> in the gas phase and in a solution with a dielectric permeability of  $\epsilon = 34.3$ .<sup>77,183</sup>

| Conformer   | HF/6-31G*  |             |             | HF/6-31G* $\epsilon$ |             |             | MP2/6-31G* |             |             | B3LYP/6-31G* |             |             | PBE/TZ2P   |             |             |
|-------------|------------|-------------|-------------|----------------------|-------------|-------------|------------|-------------|-------------|--------------|-------------|-------------|------------|-------------|-------------|
|             | $\Delta E$ | $\varphi_1$ | $\varphi_2$ | $\Delta E$           | $\varphi_1$ | $\varphi_2$ | $\Delta E$ | $\varphi_1$ | $\varphi_2$ | $\Delta E$   | $\varphi_1$ | $\varphi_2$ | $\Delta E$ | $\varphi_1$ | $\varphi_2$ |
| <i>gg</i>   | 0.00       | 30          | 51          | 0.09                 | 30          | 60          | 0.00       | 31          | 58          | 0.00         | 30          | 55          | 0.00       | 31          | 49          |
| – <i>gt</i> | 1.91       | –32         | 179         | 0.00                 | –44         | 178         | 1.76       | –40         | 177         | 1.71         | –36         | –179        | 1.89       | –38         | 177         |
| <i>gt</i>   | 2.39       | 27          | 173         | 0.77                 | 45          | 173         | 2.68       | 35          | 172         | 2.48         | 30          | 176         | 2.39       | 42          | 168         |

sponding to the  $n(\text{O})$  orbital, which is gradually transformed into  $\pi(\text{NCO})$  in a series from trimethyl phosphite to triisocyanatophosphine. The non-additive change in the first ionisation potential in this series of compounds, which was noted by the authors of the cited study, is attributable to the fact that the isocyanate group initially replaces the *gauche*-methoxy group on going from trimethyl phosphite to dimethyl isocyanatophosphonite and then replaces the *trans*-methoxy group on going to methyl diisocyanatophosphinite and triisocyanatophosphine. The results of *ab initio* calculations for the  $(\text{MeO})_3\text{P}$  and  $(\text{MeS})_n\text{PMe}_{3-n}$  molecules performed in this study (see Table 5) are consistent with the earlier experimental data (the Kerr effect, dipole moments, vibrational spectroscopy, gas electron diffraction).

Investigation of selenophosphate  $(\text{MeO})_3\text{P}=\text{Se}$  by the DFT method (6-311 + G\*\*) and temperature-dependent vibrational spectroscopy revealed an equilibrium between conformations<sup>188</sup> of  $C_3$  and  $C_1$  symmetry. Calculations by the DFT method with the 6-31G\* basis set for the dicharged dimethyl diphosphate anion<sup>189</sup> demonstrated that staggered conformations resulting from rotation about its P–O bonds are favourable for this anion, the synclinal (*sc*) conformation being more stable than the antiperiplanar (*ap*) conformation due to the anomeric effect.

Vibrational spectroscopy (IR and Raman) and *ab initio* calculations (HF/6-31G\*) revealed<sup>190</sup> the staggered *gauche* and *trans* conformations of the modified oligonucleotide chains  $[\text{MeOCH}_2-\text{P}(\text{O})\text{OMe}]_n$ ; the experimental results were in good agreement with theoretical data. Orbital interactions in the stable and metastable conformations of the dimethyl phosphate anion  $(\text{MeO})_2\text{P}(\text{O})\text{O}^-$  were considered, and the favourability of the staggered *gauche*, *gauche* and *trans*, *gauche* conformations was accounted for by stereoelectronic effects.<sup>191</sup> The key geometric parameters of phosphoric acid derivatives were determined by *ab initio* methods [HF/6-31G\*\*, B3LYP/6-31G(d), EDF1/6-31 + G(d), B3LYP/6-31 + G(d,p)].<sup>192, 193</sup> For the  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{C}(\text{O})\text{X}$  compounds (X = Me, Ph, OEt,  $\text{NEt}_2$ , SEt), the results of the calculations were compared with experimental spectroscopic data (IR and  $^{13}\text{C}$  NMR).

Investigation of the vibrational spectra and conformations of phosphorus dithio acids by the molecular mechanics method<sup>194</sup> showed that the conformational equilibrium is shifted to the *trans* and *gauche* conformations of *O,O*-dimethyl dithiophosphate due to rotation about the P–O bonds. For *O,O*-diethyl dithiophosphate, only the *gauche* orientation of the C–O bonds (in the ethoxy substituents) relative to the P=S group was found. The

crystals of the former compound are composed of two staggered conformers, whereas the latter compound is conformationally homogeneous in the solid state.

Experimental and theoretical conformational analysis of silyl, germyl and stannyl derivatives of *O,O*-dialkyl dithiophosphates gave interesting results.<sup>195</sup> Photoelectron spectroscopy and calculations (*ab initio*, MNDO and PM3) for  $(\text{RO})_2\text{P}(\text{S})\text{S}-\text{EMe}_3$  (R = Me, Et, Pr<sup>i</sup>; E = Si, Ge, Sn) demonstrated that the *gauche* and *trans* conformations of the E–S–P=S fragments are favourable. This conclusion is consistent with the results of the earlier experimental conformational studies of acyclic derivatives of phosphorus dithio acids and *O,O*-dialkyl *S*-triethylstannyldithiophosphates (dipole moments, the Kerr effect, vibrational spectra).<sup>196–198</sup>

Therefore, semiempirical methods and most *ab initio* methods provide evidence for a threefold barrier to rotation about the P–O bond in OPCs, which is consistent with experimental data on the staggered synclinal and antiperiplanar conformations. It should be noted that this principal fact is virtually independent of the coordination state of the phosphorus atom, the number of internal rotation axes of the molecule and the nature of the substituents at the P atom. The conformational behaviour of various molecules differs primarily in the presence or absence of a conformational equilibrium between staggered conformations. For some molecules, synclinal conformations (+*sc* or –*sc*) are stabilised, whereas antiperiplanar (*ap*) conformations are stable for other molecules. In the presence of two or more internal rotation axes, the conformational equilibrium between two or several energetically favourable and least sterically hindered staggered conformers is, as a rule, observed.

Intramolecular electronic interactions in OPCs have been studied most thoroughly by theoretical methods for tri- and tetracoordinate phosphorus cyanides. The relative contributions of the interactions between the cyano group, on the one hand, and the lone electron pair of the phosphorus atom and the phosphoryl group, on the other hand, to stabilisation of the conformers of phosphorus cyanides were examined.<sup>121</sup> Unlike the  $n, \pi$  conjugation between the lone pair of the phosphorus atom and the benzene ring, this interaction in the P–C $\equiv$ N system is sterically unhindered. Figure 10 shows the correlation diagram of the energies of the frontier MOs for favourable conformations of the  $\text{MeO}-\text{P}(\text{CN})_2$  (*t*),  $\text{Ph}-\text{P}(\text{CN})_2$  (*c*),  $\text{Ph}_2\text{P}(\text{O})\text{CN}$  (–*gc*) and  $(\text{MeO})_2\text{P}(\text{O})\text{CN}$  (*g-g*) molecules and the hydrocyanic acid molecule. In the favourable *trans* conformation of  $\text{MeO}-\text{P}(\text{CN})_2$ , the

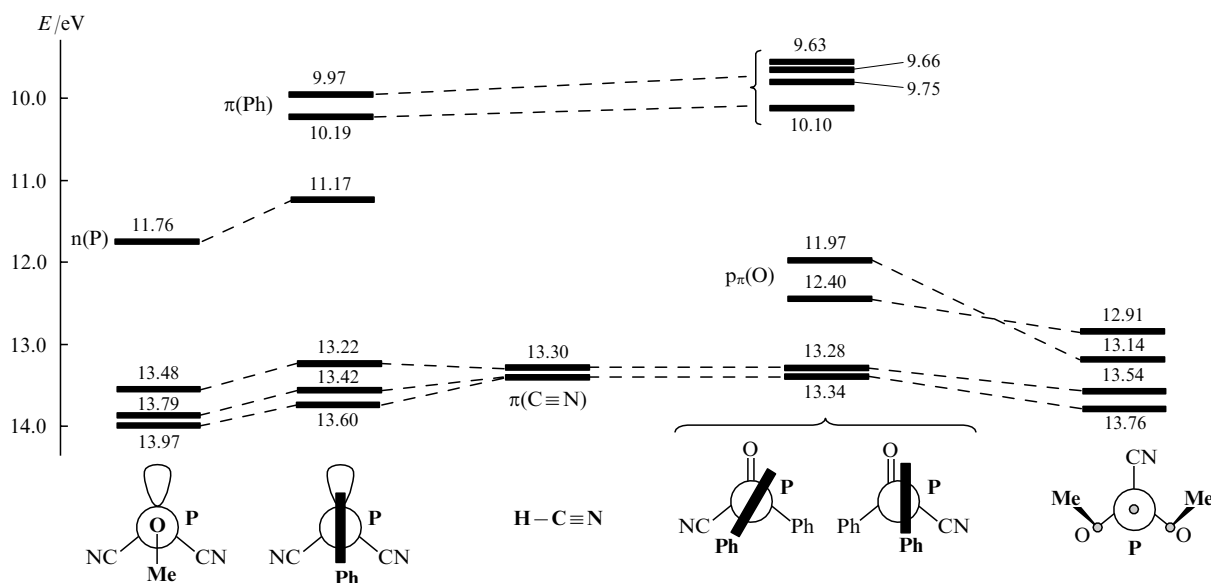


Figure 10. Correlation diagram of the HOMO energies for the stable conformations of phosphorus cyanides and HCN.<sup>121</sup>



highest occupied molecular orbital (HOMO), which is predominantly  $n(\text{P})$  in character, is additionally stabilised by the  $n(\text{P})-\sigma^*(\text{O}-\text{C})$  hyperconjugation interaction, absent in the eclipsed structure of  $\text{Ph}-\text{P}(\text{CN})_2$ . This is also evident from a decrease in the effective charge on the phosphorus atom from 1.05 in methoxydicyanophosphine to 0.79 in phenyl dicyanophosphine. Analysis of the energies and compositions of the frontier MOs showed that interactions between the  $n(\text{P})$  and  $\pi(\text{C}\equiv\text{N})$  orbitals are absent in  $\text{MeO}-\text{P}(\text{CN})_2$  and  $\text{Ph}-\text{P}(\text{CN})_2$ , and the interactions between the  $p_\pi(\text{O})$  and  $\pi(\text{C}\equiv\text{N})$  orbitals are absent in  $\text{Ph}_2\text{P}(\text{O})\text{CN}$  and  $(\text{MeO})_2\text{P}(\text{O})\text{CN}$ . In addition, all of the above-mentioned favourable conformations are characterised by a low population of  $d_{\pi^*}$ -AOs on the phosphorus atom, which indicates that there are no interactions between these orbitals and the orbitals of the substituents with suitable symmetry. Therefore, it can be concluded that interactions between the cyano group and the lone pair of the phosphorus atom, its  $d$  orbitals or the phosphoryl group make no contribution to stabilisation of the favourable conformers of phosphorus cyanides. Apparently, the nitrile group in the  $\text{P}-\text{CN}$  fragment behaves predominantly as a  $\sigma$  acceptor and does not exhibit  $\pi$ -acceptor properties.

The relationship between the conformations of OPCs and their reactivity has been studied in detail by photoelectron spectroscopy. At the Arbuzov Institute of Organic and Physical Chemistry (Kazan, Russia), the ionisation potentials of about 170 various organic uniconordinate, dicoordinate and tricoordinate phosphorus compounds (which comprise about one-half of all the data published in the literature) were determined by photoelectron spectroscopy in combination with quantum-chemical calculations.<sup>106</sup> The relationships between the ionisation potentials and the molecular structures, in particular, the bond and torsion angles, were revealed.

The ionisation potentials of the favourable and less stable conformations of selected OPCs are given in Table 7. The dependence of conformation on ionisation potential was found, and the regression relationship between the vertical ionisation potentials and the molecular orbital energies, calculated by varying the geometric parameters, was optimised:<sup>106, 168</sup>

$$\text{IP}_m = a\varepsilon_m + b,$$

where  $\varepsilon_m$  are the energies of the highest occupied orbitals.<sup>90, 97, 168, 187</sup> For the molecules under study, the conformations predicted by optimisation of the total energy of the molecule and the regression relationship were similar, but the latter approach was less sensitive to the calculation method.

In the publication,<sup>168</sup> a procedure was described for theoretical simulation of the photoelectron spectra of systems consisting of two conformers. The molecular orbital energies scaled from the experimental ionisation potentials of favourable conformers and their regression relationships can also be used to estimate the ionisation potentials of unstable conformations. The latter are not detected by photoelectron spectroscopy. However, in specific cases, these values can determine the reactivity of molecules.

## 6. Internal rotation about P–N and P–P bonds

Experimental and selected calculated data on the conformations and barriers to internal rotation about P–N bonds published before 1982 were summarised in a review.<sup>5</sup> The results of semi-empirical and *ab initio* calculations for OPCs with P–N bonds were analysed in several studies.<sup>199–207</sup> Apparently, this is in part attributable to the complexity of the systems under consideration because of internal rotation about this bond often being accompanied by a change in the configuration at the nitrogen atom. For example, it was noted<sup>208</sup> that topomerisation in aminophosphines is a complex process involving simultaneous rotation about the P–N bond and possible inversion of configuration at the N atom.

Substituents at the  $\text{N}(\text{sp}^3)$  atom increase the height of the barrier to internal rotation due to destabilising steric repulsions in its pyramidal environment. On the contrary, substituents at the P atom decrease this barrier because they induce the pyramidal

**Table 7.** Ionisation potentials and relative energies of stable conformers of organophosphorus compounds.<sup>90, 97, 168, 187</sup>

| Compound                               | Basis set | Conformer      | $\Delta E$<br>(see <sup>a</sup> ) | IP <sub>1</sub> /<br>eV | $r$ (see <sup>b</sup> ) |
|----------------------------------------|-----------|----------------|-----------------------------------|-------------------------|-------------------------|
| PhPH <sub>2</sub>                      | 3-21G*    | A <sup>c</sup> | 1.25                              | 8.88                    | 0.999                   |
|                                        |           | B <sup>c</sup> | 0.00                              | 9.66                    | 0.987                   |
| F <sub>2</sub> P(O)CH=CH <sub>2</sub>  | 6-31G*    | <i>c</i>       | 0.00                              | 11.58                   | 0.977                   |
|                                        |           | <i>t</i>       | 1.95                              | 11.46                   | 0.902                   |
| Cl <sub>2</sub> P(O)CH=CH <sub>2</sub> | 4-31G     | <i>c</i>       | 0.00                              | 11.24                   | 0.996                   |
|                                        |           | <i>t</i>       | 4.80                              | 11.12                   | 0.986                   |
| Me <sub>2</sub> POMe                   | 6-31G**   | <i>g</i>       | 0.00                              | 8.78                    | 0.994                   |
|                                        |           | <i>t</i>       | 1.57                              | 8.97                    | 0.991                   |
| Cl <sub>2</sub> PMe                    | 6-31G**   | <i>t</i>       | 0.00                              | 10.26                   | 0.997                   |
|                                        |           | <i>g</i>       | 3.81                              | 10.14                   | 0.992                   |
| Me <sub>2</sub> PSMe                   | CNDO/2    | <i>g</i>       | 0.00                              | 8.60                    | 0.997                   |
|                                        | 6-31G**   | <i>c</i>       | 0.00                              | 8.60                    | 0.992                   |
|                                        | 6-31G**   | <i>t</i>       | 0.93                              | 8.81                    | 0.966                   |
| Cl <sub>2</sub> PSMe                   | 6-31G**   | <i>t</i>       | 0.00                              | 9.75                    | 0.984                   |
|                                        |           | <i>g</i>       | 1.75                              | 9.32                    | 0.981                   |
|                                        |           | <i>c</i>       | 0.00                              | 9.84                    | 0.994                   |
| Cl <sub>2</sub> PCH=CH <sub>2</sub>    | 4-31G     | <i>g</i>       | 2.03                              | 10.03                   | 0.943                   |
|                                        |           | <i>c</i>       | 0.00                              | 9.84                    | 0.994                   |
| P(OMe) <sub>3</sub>                    | 3G        | <i>ggt</i>     | 0.00                              | 9.18                    | 0.993                   |
|                                        | 6-31G**   | <i>ggt</i>     | 0.00                              | 9.18                    | 0.973                   |
| HP(O)(OMe) <sub>2</sub>                | 6-31G*    | <i>gg</i>      | 0.00                              | 11.10                   | 0.998                   |
|                                        |           | <i>–gt</i>     | 1.93                              | 11.15                   | 0.995                   |
|                                        |           | <i>gt</i>      | 1.94                              | 11.08                   | 0.995                   |
| MeP(O)(OMe) <sub>2</sub>               | 6-31G*    | <i>gg</i>      | 0.00                              | 10.53                   | 0.994                   |
|                                        |           | <i>–gt</i>     | 2.64                              | 10.55                   | 0.986                   |

<sup>a</sup> In kcal mol<sup>–1</sup>.

<sup>b</sup>  $r$  is the correlation coefficient of the regression equation  $\text{IP} = a\varepsilon + b$ , where  $\varepsilon$  are the energies of the highest occupied molecular orbitals.

<sup>c</sup> A and B are respectively the conjugated and bisecting conformations of phenylphosphine.

configuration of the nitrogen atom. *Ab initio* calculations demonstrated<sup>208</sup> that a change in the torsion angle of the  $\text{LEP}-\text{N}-\text{P}-\text{LEP}$  fragment from 90° to 180° leads to a change in the configuration at the nitrogen atom from trigonal-planar to pyramidal with close to tetrahedral bond angles. Rotation of the amide group about the P–N bond is hindered, and the barrier height was estimated<sup>202</sup> to be approximately 6.5 kcal mol<sup>–1</sup>. The complexity of the equilibrium set of configurations results in an ambiguous interpretation of the photoelectron spectra of phosphoramidates.<sup>201</sup>

*Ab initio* calculations performed in recent years have provided an essential supplement to our knowledge about internal rotation about P–N bonds. For acid amides of Group V elements,  $\text{E}(\text{NMe}_2)_3$  ( $\text{E} = \text{As}, \text{Sb}, \text{P}$ ), a comparative study of the structures and favourable conformations was performed by electron diffraction and quantum-chemical methods.<sup>209</sup> The structural parameters are intended for use in compiling electronic databases, calculating the physicochemical properties of molecules and constructing a theory of reactivities for this class of compounds.

The use of the results of *ab initio* quantum-chemical calculations (HF/6-31G\*) and spectroscopic data for the interpretation of electron diffraction data made it possible to determine the geometric parameters and force fields for two stable rotamers of the  $\text{Me}_2\text{N}-\text{PCl}_2$  molecule: *gauche* ( $C_1$  symmetry) and *trans* ( $C_s$  symmetry).<sup>210</sup> For the energetically much more favourable *gauche* conformer, the vibrational spectra of undeuterated and completely deuterated isotopomers of  $\text{Me}_2\text{N}-\text{PCl}_2$  were reliably interpreted for the first time in the cited study. Gas electron diffraction data were analysed and the equilibrium geometric parameters of the molecules evaluated, taking into account the non-linear kinematic effect in first-order perturbation theory, which led to the conclusion that the  $\text{Me}_2\text{N}$  group has a non-planar equilibrium configuration.

In the study,<sup>211</sup> the effects of the electronic and steric factors on the structures of mono-, di- and triaminophosphines and dialkylaminophosphines were investigated by *ab initio* methods, providing evidence that the orthogonal conformation of the LEP–P–N–LEP fragment ( $\varphi = \pm 90^\circ$ ) is energetically more favourable. The *anti* conformation ( $\varphi = 180^\circ$ ) can occur as a minor structure. Tris(dimethylamino)phosphine can adopt a *syn* conformation. Therefore, the structures of the aminophosphines considered in the cited study were determined by interactions between the lone electron pairs of the phosphorus and nitrogen atoms, the hybridisation of the nitrogen atom and the steric requirements of the substituents.

It should be noted that the structure of the tris(dimethylamino)phosphine molecule has been debated for three decades and studied many times by gas electron diffraction using semiempirical and *ab initio* calculations.<sup>200, 203, 204</sup> *Ab initio* calculations revealed two stable conformations with  $C_3$  and  $C_s$  symmetry, the latter being more stable by 7 kcal mol<sup>-1</sup>. The electron diffraction study demonstrated that two of the NMe<sub>2</sub> groups in the  $C_s$  conformation are oriented so that the lone electron pairs of the nitrogen atoms [N(2) and N(3) in Fig. 11] are approximately perpendicular to the lone electron pair of the P atom, and the lone pair of the third NMe<sub>2</sub> fragment is positioned antiparallel with respect to the lone pair of the P atom. The environment of the N atom in the third fragment is essentially pyramidal (the sum of the bond angles is 337°), whereas two other nitrogen atoms have a flattened configuration (the sum of the bond angles is 353°). In the study,<sup>203</sup> it was hypothesised that the equilibrium  $C_s$ -symmetric structure is stabilised due to the anomeric effect, *i.e.*, due to overlapping of the lone electron pairs of the N(2) and N(3) atoms with the antibonding  $\sigma^*$  orbital of the P–N(1) bond (Fig. 11). The cited study has summed up the discussion and probably proposed an adequate model for this complicated conformational system.

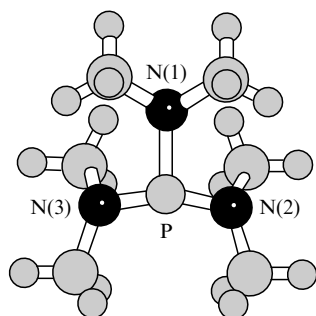


**Figure 11.** Perspective model of the  $C_s$ -symmetric conformation of the P(NMe<sub>2</sub>)<sub>3</sub> molecule based on the results of gas electron diffraction and *ab initio* calculations.<sup>203</sup>

Data on internal rotation about P–P bonds are scarce. *Ab initio* calculations for the 1,1-difluorophosphine (H<sub>2</sub>P–PF<sub>2</sub>) molecule revealed<sup>212</sup> the existence of the staggered *trans* and *gauche* conformations, separated by a barrier of 0.9 kcal mol<sup>-1</sup>. Previously, the *trans* and *gauche* conformers of the Me<sub>2</sub>P–PMe<sub>2</sub> molecule had been detected by photoelectron spectroscopy by varying the temperature from 20 to –252 °C.<sup>213</sup>

### III. Conclusion

Modern quantum chemistry combined with the results of physicochemical methods of investigation provides a reliable theoretical basis for many general chemical features in terms of orbitals and electronic configurations.<sup>214</sup> Moreover, modern aspects of the theory, such as the structures of metastable intermediate particles, the compositions and geometries of molecular associates, the shapes of potential surfaces, *etc.*, give impetus to experimental

investigations and the development of new concepts.<sup>¶</sup> However, a search for stable conformers of molecules, analysis of their relative stabilities and examination of the shapes of their barriers to internal rotation are complicated physicochemical problems, which remain, in many respects, unresolved.

In recent years, the molecular structures of OPCs have been re-investigated more thoroughly by various experimental methods (gas electron diffraction, vibrational and photoelectron spectroscopy, the dipole moment method, *etc.*) and quantum-chemical calculations. The results of calculations using extended basis sets including correlation effects are in some respects similar to the results of high-precision experiments; they also require generalisation and explanation in terms of approximate models and theories. The main aim of each systematic conformational study is to draw generalisations which have predictive capabilities and allow one to exclude steps that give unambiguous and predictable results. An important problem is to reveal the general and specific features in the body of data and determine their place in general chemical theory.

It can be stated that experimental and theoretical results obtained by the conformational analysis of relatively simple OPCs (for example, OPCs containing one internal rotation axis) adequately describe sets of conformers resulting from internal rotation about P–C, P–O and P–S bonds. The data considered in this review demonstrate that the staggered *gauche* and *trans* conformations are favourable for OPCs, which is also true for molecules of classical organic compounds. The occurrence of eclipsed conformations is attributable to the structural features of particular molecules and these require special theoretical analysis.

The structures of more complex compounds with several internal rotation axes (particularly, if these axes belong to different atoms) cannot necessarily be unambiguously determined, even using physical methods combined with calculations. The spatial and electronic structures of polyfunctional OPCs (in which intramolecular interactions can give rise to unusual conformations) and OPCs containing P in low coordination states were poorly studied. Experimental and theoretical data on these compounds are scarce. Quantum-chemical studies of OPCs in solution are few in number. In addition to the above-considered publications on the theoretical conformational analysis of phosphorus-substituted acrylonitriles<sup>102</sup> and studies of a number of the simplest phosphorus compounds and their radical cations by *ab initio* self-consistent reaction field calculations,<sup>170</sup> several investigations also dealt with the conformational composition and reactivity of dimethyl phosphite in the gas phase and solvents of varying polarity<sup>183</sup> and with the conformational composition and spin properties of iminoxyl radicals containing the phosphine oxide substituent.<sup>216, 217</sup>

When using calculated data, it should be remembered that semiempirical quantum-chemical methods, which, on the whole, correctly reproduce the structures and conformations of organic molecules, can give large errors in their estimates of the geometric parameters and relative stabilities of OPCs. With certain exceptions, this is also true for *ab initio* calculations. In Section II.5, it was demonstrated that calculations for the H<sub>2</sub>P(O)OH molecule by the Hartree–Fock method using the rather large 6-31G\*\* basis set predicted the eclipsed *cis* conformation; however, this result is reproduced in the single-determinant approximation only for particular basis sets, whereas various modes of inclusion of electron correlation always predict a skewed conformation. On the other hand, transition structures on potential energy surfaces (saddle points with one imaginary frequency), *i.e.*, the peaks of the

<sup>¶</sup> In a recent theoretical study,<sup>215</sup> it was stated that the staggered conformation of the ethane molecule, which has been studied many times by various methods is, contrary to popular opinion, determined by superconjugation of the C–H bonds rather than by steric repulsions between hydrogen atoms.

barriers to internal rotation, generally correspond to the  $C_s$ -symmetric *cis* conformations for P–O and P–S bonds. Nevertheless, for H<sub>2</sub>POH, H<sub>2</sub>PSH and some other molecules, conformations with the eclipsed lone electron pair of the phosphorus atom are predicted at several levels of theory.

The relative stabilities of the *gauche* and *trans* conformations of the X<sub>2</sub>PCH=CH<sub>2</sub> or X<sub>2</sub>POMe molecules are, apparently, determined from competition between the  $n(\text{P})-\pi^*(\text{PX}_2)$  and  $\pi(\text{C}=\text{C})-\pi^*(\text{PX}_2)$  donor–acceptor interactions (see Fig. 4). In molecules containing electron-withdrawing PX<sub>2</sub> groups, the  $\pi(\text{C}=\text{C})-\pi^*(\text{PX}_2)$  donor–acceptor interactions stabilise the *trans* conformation. Compounds H<sub>2</sub>POH, H<sub>2</sub>PCH=CH<sub>2</sub> and H<sub>2</sub>PPh belong to an intermediate type, in which competitive interactions are of similar magnitudes and the conformers have similar energies. Calculations by the Hartree–Fock method using the 3-21G\*, 6-311G\*\* and 6-311(2d,2p) basis sets demonstrated that the *trans* conformation of these molecules is more stable, whereas calculations with the 6-31G\*, 6-31G\*\*, 6-31+G\* and 6-31+G\*\* basis sets predicted the *cis* conformation as the more stable. A further extension of the basis set up to 6-311++(3d,3p) results in a zero energy difference between the conformers. Calculations including of electron correlation at different levels of theory predict the *cis* conformation as the favourable one; however, an extension of the basis set decreases the energy difference between the *cis* and *trans* conformers.

These data suggest that investigations of the relative stabilities of conformers with similar energies and the correct treatment of eclipsed conformations requires the use of quantum-chemical methods at the maximum possible levels of theory with inclusion of electron correlations at the MP2, B3LYP or PBE level (see Tables 1, 2 and 6). However, the principal limitations of the model of discrete conformers are manifested in compounds with low barriers to internal rotation. Examples of these limitations encountered in the conformational analysis of the PhPH<sub>2</sub> molecule were considered in Section II.4.

The predictive capabilities of quantum chemistry and its role in modern conformational analysis are still debated.<sup>218</sup> In Scerri's opinion,<sup>219</sup> quantum theory often simulates and interprets (although at a very high level) experimental data (for example, spectroscopic characteristics and geometric parameters of the molecules) rather than gives predictions. At the same time, it was noted that the reliability of quantum-chemical predictions increases.<sup>218</sup> For example, a review<sup>220</sup> where the use of various versions of the Gaussian package for describing ion-molecular processes was considered, gave examples of the refinement of experimental data using the results of quantum-chemical calculations, which made it possible to reveal and eliminate errors in the measurements. The direct relationship between the quantum-chemical theory and conformational analysis of OPCs is clearly demonstrated by the evolution of views on the structure of the Cl<sub>2</sub>POMe molecule discussed in the study.<sup>221</sup> In the period from 1974 to 1994, the initial views on the *cis* conformation of this molecule were revised first in favour of the *gauche* conformer and then in favour of the *trans* conformer, which is sterically hindered but stabilised by electronic factors, according to calculated data.

On the whole, conformational analysis of organoelement compounds is in its infancy. A general system for determining the conformations of such compounds, which could allow one to reveal the characteristic features of internal rotation about any chemical bond in an arbitrary environment, so far is only qualitatively developed. For many organoelement compounds, conformational data are lacking, often for objective reasons (instability of compounds, the impossibility of preparing their solutions, etc.). However, experimental and theoretical studies are opening up new possibilities for the development of conformational analysis as a necessary step in routes to the synthesis of compounds possessing specified physical, chemical and biological properties, to explain of the reactivities of such compounds and to elucidate their reaction mechanisms.

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<sup>h</sup> — *J. Organomet. Chem. (Engl. Transl.)*

<sup>i</sup> — *Dokl. Chem. (Engl. Transl.)*

# The use of selective methods of heteronuclear NMR spectroscopy in studies of multicomponent systems<sup>†</sup>

Yu E Chernysh, V A Volynkin, V T Panyushkin, V I Kondakov, M S Korobov, G S Borodkin

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**Abstract.** Some important aspects of the use of selective methods in NMR spectroscopy for interpreting the spectra of complex multicomponent systems, measuring the spin–spin coupling constants and determining the structure of compounds are discussed. Procedures for recording selective spectra and the application of selective radiofrequency pulses together with magnetic field gradient pulses are described. Practical methods for suppression of water signals in the study of biological samples are considered. The bibliography includes 198 references.

## I. Introduction

NMR spectroscopy belongs to the most efficient methods of investigation of the liquid, solid and liquid-crystalline states of matter.<sup>1</sup> Correctly interpreted NMR spectra give a clear picture of the molecular conformations, internuclear and intermolecular distances, angles and bond properties and information on the molecular dynamics. Usually, the most significant information is extracted from three main parameters of an NMR spectrum, namely, the chemical shift, spin–spin coupling constant and nuclear spin relaxation rate.<sup>2–6</sup> However, these parameters cannot always be measured immediately from the spectrum. This is due to low sensitivity of NMR spectroscopy owing to very small transition energy differences ( $\sim 10^{-6}$  eV) between nuclear energy levels and to the low natural abundance and gyromagnetic ratios of many nuclei. Often, these factors act in line with one another.

Yet another problem consists of the overlap of resonance signals, which is particularly typical of the spectra of large molecules and complex systems. As an example, let us compare resonances of two widely used nuclei, <sup>1</sup>H and <sup>13</sup>C. <sup>1</sup>H NMR spectroscopy is characterised by higher sensitivity due to both high natural abundance of the <sup>1</sup>H isotope (99.98%) and high gyromagnetic ratio [26.75 rad (s T)<sup>−1</sup>]. However, the width of the <sup>1</sup>H NMR spectrum is about 20 ppm while signals of most organic compounds are observed in an interval of around 8 ppm. <sup>13</sup>C resonances are observed in a much wider region of chemical shifts (200 ppm), signals being relatively well-resolved. However, the natural abundance of this isotope is low (1.1% of the total content of carbon isotopes) and its gyromagnetic ratio is low (0.25 of the gyromagnetic ratio of the <sup>1</sup>H isotope). Therefore, <sup>13</sup>C NMR spectroscopy is less sensitive. Using higher magnetic fields allows the sensitivity and resolution to be enhanced. However, <sup>1</sup>H NMR spectra of complex samples (*e.g.*, biological liquids and tissue extracts) remain overcrowded even at a frequency of 800 MHz,<sup>7</sup> such ultrahigh-field systems being too expensive. An alternative approach to enhancement of the sensitivity and spectral resolution is based on design of new pulse sequences for selective detection of particular signals.

At present, NMR methodology concerns not only the known and continuously revisable two-dimensional (2D) and three-dimensional (3D) pulse methods but also two more avenues. One of them is associated with the use of selective radiofrequency (RF) pulses<sup>8–10</sup> while the other employs pulsed magnetic field gradients (PFG), which improve the spectra by selecting appropriate coherent superpositions of different states of the nuclear spin system (from this point on, coherences).<sup>11–13</sup> Both methods, their advantages and drawbacks have been well documented.<sup>8–13</sup> Often, methods based on the use of selective RF pulses only are complicated by artifacts arising from long pulse durations. To suppress unwanted responses, phase cycling is needed. Experiments with selective pulses require a skilled operator; interpretation of the resulting spectrum is often unobvious and therefore the corresponding techniques are of limited use. In the case of PFG, no phase cycling is needed and the duration of experiments is

**Yu E Chernysh, M S Korobov, G S Borodkin** Institute of Physical and Organic Chemistry of the Rostov State University, prosp. Stachki 194/2, 344090 Rostov-on-Don, Russian Federation. Fax (7-8632) 43 46 67, tel. (7-8632) 43 38 94, e-mail: nmr@ipoc.rsu.ru

**V A Volynkin, V T Panyushkin** Kuban State University, Stavropolskaya ul. 149, 350040 Krasnodar, Russian Federation. Fax (7-8612) 69 95 70, tel. (7-8612) 69 95 74, e-mail: vva@chem.kubsu.ru (V A Volynkin), Panyushkin@chem.kubsu.ru (V T Panyushkin)

**V I Kondakov** Grodno State Agrarian University, ul. Tereshkovoi 28, 230008 Grodno, Belarus. Fax (37-5152) 77 01 68, tel. (37-5152) 72 00 24, e-mail: Vlad.Kondakov@mail.ru

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shortened by a factor of nearly five. The most promising approaches combine both these methods.<sup>14, 15</sup>

Combining selective RF pulses and pulsed field gradients began only recently but this gave good results.

## II. Selective pulses

The function of selective pulses<sup>8–10</sup> is to excite or invert certain resonances, either singlets or multiplets (sometimes, these can be subspectra within the same spectrum or single lines within a multiplet). The structure of organic compounds is determined using selective pulses, which allow the dimension of the problem to be reduced from 3D to 2D or from 2D to 1D in one experiment and necessary information to be obtained during a shorter time period with a rather high resolution.

Three general problems arise when using selective pulses. The first problem is associated with a rather long duration of such pulses, which is three orders of magnitude longer than the duration of non-selective ‘hard’ pulses. The selectivity obtained nearly equals the inverse pulse duration. For instance, excitation of a multiplet of spectral width 50 Hz requires a selective pulse of about ~20 ms long to be applied. Eagerness for selectivity enhancement can lead to considerable relaxation loss within the pulse sequence.

The second problem concerns the shape of the selective pulse profile. An ‘ideal pulse’ must have a rectangular envelope uniformly filled with the carrier radiofrequency. In the framework of the consecutive response theory the excitation profile can be calculated using the direct Fourier transform of the pulse shape from the frequency domain to the time domain and *vice versa*. However, the consecutive response theory is valid only for very weak excitation; therefore, the shape design of new selective pulses, which is usually performed using iterative methods, must involve an experimental stage. The most widely used shaped pulses are shown in Fig. 1. Application of a rectangular, Gaussian and sinc-type pulse creates a sinc-type, Gaussian and rectangular excitation profile, respectively.

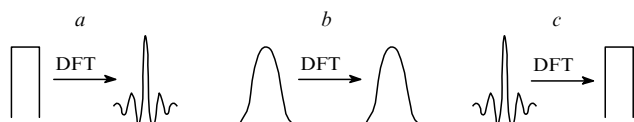


**Figure 1.** RF pulse shapes and corresponding excitation profiles. Pulse: rectangular (a), Gaussian (b) and sinc (c); DFT stands for direct Fourier transform.

The third problem is concerned with the phase change of the selective pulse. Unfortunately, the excitation phase varies within the chosen width of a selective pulse. Therefore, excitation of a multiplet by a selective pulse can lead to a complex spectral pattern, because first-order phase correction is impossible. Pulse sequence designers mostly aim their efforts at generating short selective pulses with a constant phase and a smooth envelope within the semicircle. However, this problem has no exact solution and therefore it is necessary to find approximate solutions.

In principle, it is possible to determine the excitation profile and the phase change of the pulses employed. This requires a successive variation of the repetition frequency of a selective pulse in the frequency region of interest; however, the procedure is very time-consuming. Hwang and Shaka<sup>16</sup> reported an experiment with pulsed magnetic field gradients employed to ‘visualise’ the shape of a selective excitation pulse (Fig. 2). The pulse sequence used is inappropriate for solving structural chemical tasks; however, it exhibits many features of widely used pulse sequences. Experiments were carried out with the spin echo gradient sequence. When the selective pulse is on, a magnetic field gradient is applied to reproduce the image of the frequency distribution,

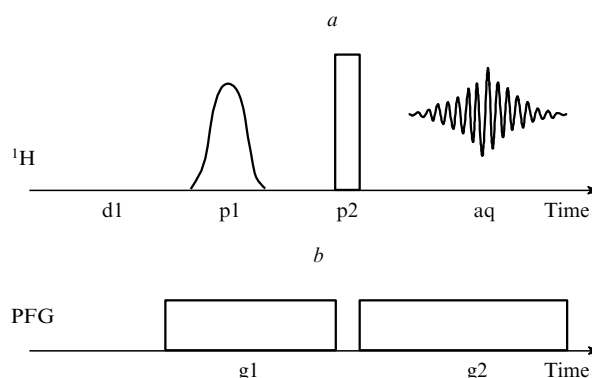


**Figure 2.** The RF pulse sequence (a) and PFG sequence (b) used for determination of the excitation profiles of 90° pulses. d1 is the relaxation delay, p1 is the selective 90° pulse, p2 is the 180° pulse, g1 and g2 are the rectangular pulse gradients and aq is the acquisition time.

which is read out during the data acquisition time, *i.e.*, during the last time interval.

The phases of the 90° Gaussian and sinc pulses change their signs, whereas the semi-Gaussian pulse has good phase characteristics and a good excitation profile for the *x*-magnetisation only. BURP<sup>15</sup> (Band-selective Uniform Response Pure-phase Pulses) type pulses are characterised by a very good phase mode. These ‘soft’ pulses are designed for refocussing the magnetisation trajectory in such a way that the natural divergence between the fast and slow components of the magnetisation vector is corrected. These pulses transfer the magnetisation to the +*y* axis in the whole range of resonance offsets, *i.e.*, shifts of the resonances from zero.

A 180° Gaussian pulse provides a good selectivity and phase mode due to the action of a REBURP (Refocused Band-selective Uniform Response Pure-phase) composite pulse. It should be noted that old spectrometers having no envelope shape storage modules can operate with modern pulses that can be programmed using the DANTE (Delays Alternating with Nutation for Tailored Excitation) sequence.<sup>17, 18</sup>

Prior to using selective pulses, the operator has to calibrate the excitation profiles. A detailed description of calibration procedures was reported by Braun *et al.*<sup>19</sup> The procedures are much like those used in the calibration of ‘hard’ pulses. The main difference is that determination of the duration of the 180° pulse only requires damping of the RF power. One should keep in mind that damping ‘operates’ in the logarithmic scale. Therefore, experiments with old instruments, which have no software for matching the initial phases of pulses within the same pulse sequence, require a check of either the phase of the selective 90° RF pulse or, at least, the phase of the 90° pulses with the phases of ‘hard’ 90° pulses at the same power. If both pulses are applied within the same pulse sequence, the difference in the corresponding phase programme must be set every time.

## III. Pulsed magnetic field gradients ‡

Selection of coherences using pulsed magnetic field gradients has been studied in detail.<sup>11–13</sup> The field gradient applied along the *z* axis causes a *z*-dependence of the resonance frequencies and thus the phase dependence of the magnetisation (Fig. 3). If the gradient

‡ The abbreviations of the NMR techniques employing pulsed magnetic field gradients are as follows: GRASP (Gradient Accelerated Spectroscopy) and ge (gradient enhanced). It is more appropriate to use the gs (gradient selection) abbreviation, which has been commonly accepted. Actually, the magnetic field gradients ‘select’ desired and ‘ignore’ undesired coherences; therefore, this term seems to be the best to reflect the essence of all the known gradient experiments.



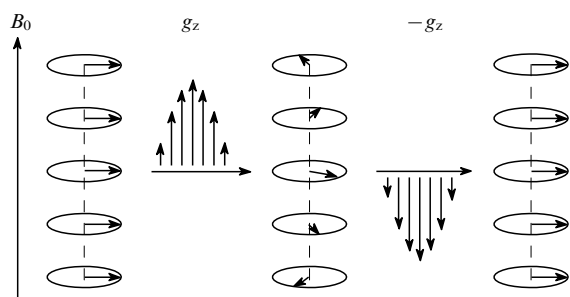


**Figure 3.** The action of pulsed magnetic field gradient. Application of the gradient  $g_z$  causes dephasing, which is rephased by applying the gradient  $-g_z$ .

pulse has a limited intensity and duration, switching it off will be followed by precession of identical spins at their initial frequencies with the gradient-set phases. A signal detected at this stage will at best have the shape of a broadened absorption signal. Applying the second field gradient pulse of the opposite sign will result in a conventional NMR spectrum. Therefore, dephasing caused by the first gradient can be rephased by applying the second gradient, which is identical to the first one but has the opposite sign.

Practical implementation of this principle offers great prospects. Dephasing and rephasing depend on the gyromagnetic ratio and coherence orders at the instant of application of the gradient pulse; therefore, one can readily select coherences by changing their orders between the gradients set by the RF pulses. If selective RF pulses are applied between two gradients, only the coherences created by these pulses contribute to the resulting signal.

The use of magnetic field gradient pulses can be best considered using the coherence transfer diagram, which is based on the shift operators  $I^+$  and  $I^-$ . From the expression

$$I_x = \frac{1}{2}(I^+ + I^-) \quad (1)$$

it can be seen that the excitation by a  $90^\circ$  pulse can cause both a decrease and an increase in the coherence level (Fig. 4).

In performing a theoretical description it is assumed that the NMR spectrometers set the  $I^-$  level. Therefore, the RF pulses for detection using a pulse sequence must be chosen in such a way that the coherence trajectory arrives at this level. Here, the field gradient pulses must be distributed in a fashion that excludes other possible trajectories. To select the desired coherence, the following condition must be met:

$$\sum_{i=1} p_i \gamma_i g_i \geq 0, \quad (2)$$

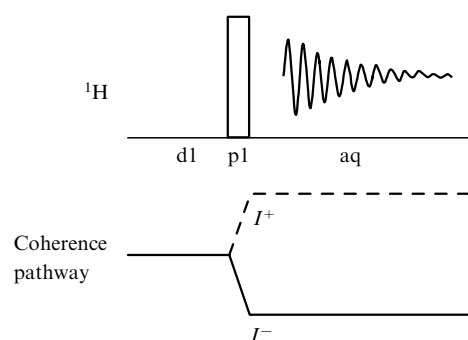


**Figure 4.** Coherence pathway diagram for the excitation by a single RF pulse.

where  $p_i$  is the order of the  $i$ th coherence, a  $\gamma_i$  is the effective gyromagnetic coefficient, which exists during the action of  $i$ th pulse gradient  $g_i$ . All gradient pulses are assumed to have the same duration and shape.

Figure 5 presents a typical result of the gradient strength measurements using the pulse sequence shown in Fig. 6. The possibility of using the field gradient pulses depends on the degree of improvement of the spectrometer hardware.

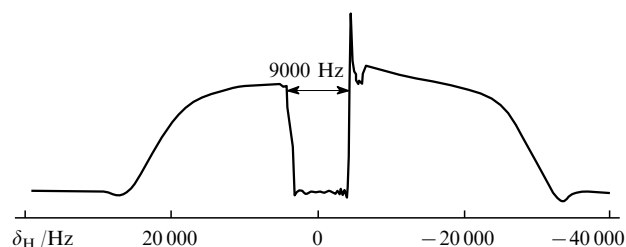


**Figure 5.** Results of measurements of the magnetic field gradient strength in a water sample (a Teflon disk of diameter 2 mm was placed at the centre of the sample);<sup>18</sup>  $\delta_H$  is the chemical shift of protons.

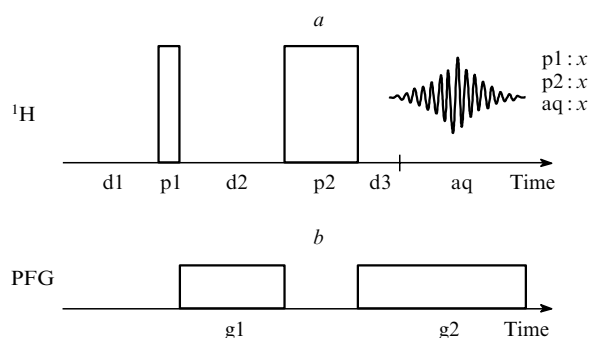


**Figure 6.** The RF pulse sequence (a) and PFG sequence (b) used for determination of the magnetic field gradient strength. For notations, see Fig. 2.

#### IV. Selective methods with inverse detection

Usually, the function of selective methods is to determine the structure of organic compounds. Below we will consider only the  $^{13}\text{C}-^1\text{H}$  groups (though other groups, *e.g.*,  $\text{NH}$ ,  $\text{NH}_2$  and  $\text{NH}_3$  can also be considered). There are five main types of spin systems, namely, those of methyl ( $^{13}\text{CH}_3$ ), methylene ( $^{13}\text{CH}_2$ ) and methyne ( $^{13}\text{CH}$ ) groups, quaternary  $^{13}\text{C}$  atoms and all protons attached to  $^{12}\text{C}$ , O, N, *etc.* rather than  $^{13}\text{C}$ . The multiplicity of the  $^{13}\text{C}$  resonances depends on the number of attached protons. Because of this, particular  $^{13}\text{CH}_n$  groups are characterised by different precession rates of scalar coupling, possible highest orders of multiquantum coherences and corresponding angles and phases of RF pulses. These features are used in spectral editing for selective detection of  $^1\text{H}$  and  $^{13}\text{C}$  signals. At present, spectral editing is used in  $^{13}\text{C}$  NMR spectroscopy as a routine technique for assignment of C, CH,  $\text{CH}_2$  and  $\text{CH}_3$  signals.

Pulse methods comprise the APT (Attached Proton Test),<sup>20–23</sup> SEMUT (Subspectral Editing Using a Multiple-Quantum Trap),<sup>24,25</sup> RELAY (Relayed Correlation Spectroscopy),<sup>26,27</sup> INEPT (Insensitive Nuclei Enhanced by Polarisation Transfer),<sup>28,29</sup> DEPT (Distortionless Enhancement by Polarisation Transfer)<sup>30–32</sup> and PENDANT (Polarisation Enhancement During Attached Nucleus Testing)<sup>33</sup> techniques. An important role in spectral editing is played by various  $J$  precession effects in  $\text{CH}_n$  groups. For instance, in the INEPT

experiments the signal intensities of different  $\text{CH}_n$  groups depend on time and  $J$  precession angle, which is proportional to the number,  $n$ , of attached protons. In the case of the DEPT pulse sequence spectral editing is performed using specific angles of the coherence transfer pulses that are applied on double-quantum and zero-quantum coherences containing a total of  $n + 1$  spins.

In these methods, the magnetisation is transferred from  $^1\text{H}$  to  $^{13}\text{C}$  and theoretically the sensitivity of the  $^{13}\text{C}$  nuclei must increase by a factor of four<sup>2</sup> due to both pre-saturation of  $^1\text{H}$ -coherences<sup>21,22</sup> and the use of different pulse sequences.<sup>26–33</sup> In addition, the pulse sequences creating the transfer of  $^1\text{H}$ -polarisation are used in 2D heteronuclear correlation experiments,<sup>34</sup> in which the proton and carbon signals are in the  $F_1$  and  $F_2$  dimensions, respectively.

A large number of communications on the use of heteronuclear filtering for simplification of  $^1\text{H}$  NMR spectra has been reported in the last decade.<sup>35–50</sup> One of these methods is known as inverse detection NMR spectroscopy or NMR spectroscopy with proton detection. It is characterised by high sensitivity, because of the use of  $^1\text{H}$  nuclei with high gyromagnetic ratio for both coherence creation and detection.<sup>4</sup>

Heteronuclear single-quantum or multiquantum coherences are incorporated in the middle of most of the pulse sequences based on the INEPT and DEPT with inverse signal detection (inverse DEPT and inverse INEPT).<sup>35–37</sup>

The RELAY pulse sequence<sup>38</sup> uses two  $90^\circ$  ( $^1\text{H}$ ) pulses for selective excitation of  $^{13}\text{CH}_n$  group coherences.<sup>26,27</sup>

Using specific methods, one can easily obtain  $^1\text{H}$  NMR subspectra of  $^{13}\text{CH}_2$  ( $^{13}\text{CH}$  or  $^{13}\text{CH}_3$ ) groups only. Obtaining the spectrum of  $^{13}\text{CH}$  groups is a non-trivial task because the  $^{13}\text{CH}$  and  $^{13}\text{CH}_3$  spin systems have the same phases. A method for recording selective spectra of  $^{13}\text{CH}_n$  groups with minimum phase and intensity distortions was proposed.<sup>46</sup> It is based on the principle of Quantum Filtering of Maximum Order (MAXY).<sup>43–47</sup> In the MAXY experiments the spin systems of  $^{13}\text{CH}_n$  groups are excited to corresponding maximum possible (for a given group) order of heteronuclear multiquantum coherence (second order for  $^{13}\text{CH}$ , third order for  $^{13}\text{CH}_2$  and fourth order for  $^{13}\text{CH}_3$ ). This provides the possibility of selective observation of signals of one, two or all three groups. Selectivity can be achieved by using both phase cycling and pulsed field gradients.

## 1. DEPT and INEPT experiments

The possibility of editing the spin system in the DEPT and INEPT experiments is attained by using a corresponding angle for one pulse in the DEPT sequence or the precession angle  $\pi J\tau$  ( $J$  is the spin–spin coupling constant and  $\tau$  is the time interval between pulses) of the heteronuclear coupling in the INEPT experiments. The pulse angles ( $\psi = \beta$ , DEPT) and precession angles ( $\psi = \pi J\tau$ , INEPT) affect the signal intensities of different  $^{13}\text{CH}_n$  groups. The signal intensity depends on  $\sin(\psi)$  for  $^{13}\text{CH}$ , on  $\sin(2\psi)$  for  $^{13}\text{CH}_2$  and on  $(3/4)(\sin 3\psi + \sin \psi)$  for  $^{13}\text{CH}_3$ . Analogous principles are implemented in the DEPT and INEPT methods with inverse detection.

By specifying the delays and pulse angles and using the inverse-DEPT or inverse-INEPT sequences, a number of spectra are obtained. Then, by subtracting (adding) the spectra one gets the edited spectra of  $^{13}\text{CH}_n$  groups; however, the signal intensities become distorted (Table 1).

In the inverse-DEPT sequence (Fig. 7), the  $\beta_y$  pulse is applied to heteronuclear zero-quantum and double-quantum coherences  $2S_yI_x$  ( $^{13}\text{CH}$ ),  $4S_xI_xI_z$  ( $^{13}\text{CH}_2$ ) and  $8S_yI_xI_zI_z$  ( $^{13}\text{CH}_3$ ) and the products of the operators, which remain the same as before application of the  $\beta_y$  pulse, contribute to the signals observed.

The dependences of the signal intensities of the groups mentioned above are as follows:

for  $^{13}\text{CH}$  groups

$$2S_yI_x \xrightarrow{\beta_y} 2S_yI_x \cos \beta, \quad (3)$$

**Table 1.** Combination of NMR spectra for obtaining  $^1\text{H}$  subspectra of individual  $^{13}\text{CH}_n$  groups using the inverse DEPT sequence with the pulse angles  $\beta = 60^\circ$  (I),  $120^\circ$  (II) and  $180^\circ$  (III).<sup>35–37</sup>

| Spin system        | Signal intensity (rel.u.) |       |      | Combination                                       | Intensity ratio | Number of runs |
|--------------------|---------------------------|-------|------|---------------------------------------------------|-----------------|----------------|
|                    | I                         | II    | III  |                                                   |                 |                |
| $^{13}\text{CH}$   | 0.5                       | −0.5  | −1.0 | $0.111(\text{I}) - \text{II} - 0.555(\text{III})$ | 1.0             | 3              |
| $^{13}\text{CH}_2$ | −1.0                      | −1.0  | 2.0  | $\text{I} + \text{II}$                            | 2.0             | 2              |
| $^{13}\text{CH}_3$ | −1.875                    | 1.875 | −3.0 | $\text{I} + 0.5 \text{ III}$                      | 3.3             | 2              |

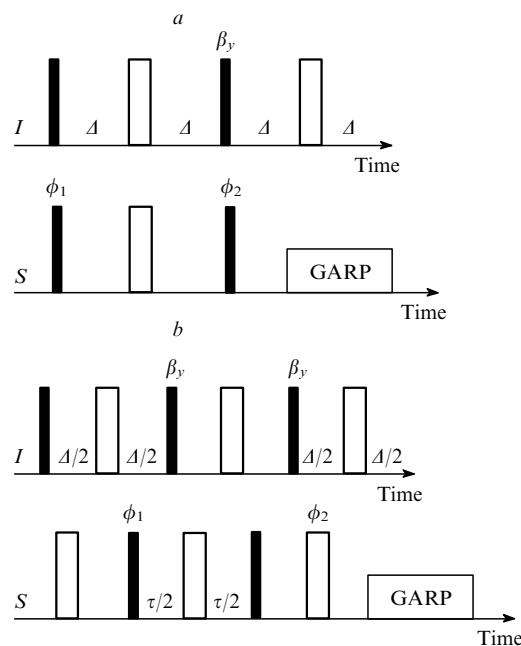


**Figure 7.** The inverse DEPT (a) and inverse INEPT (b) pulse sequences.  $I$  and  $S$  are the spins of a coupled system  $IS$ ;  $\Delta$  are the time intervals between pulses;  $\beta_y$  is the pulse applied along the  $y$  axis;  $\phi_1$  and  $\phi_2$  are the flip angles for the first and second pulse, respectively; GARP are the Globally-optimised, Alternating-phase Rectangular Pulses for Broad-band Decoupling.

Here and in Figs 9–14, 16, 18, 20–22, 24, 26 and 27 the filled and open rectangles denote the  $90^\circ$  and  $180^\circ$  pulses, respectively.

for  $^{13}\text{CH}_2$  groups

$$4S_xI_xI_z \xrightarrow{\beta_y} 4S_xI_xI_z \cos 2\beta,$$

and for  $^{13}\text{CH}_3$  groups

$$-8S_yI_xI_zI_z \xrightarrow{\beta_y} -2S_yI_xI_zI_z(3\cos 3\beta + \cos \beta).$$

When using the inverse-INEPT sequence and the spin–spin interaction Hamiltonian in the form  $\pi J_{IS}\tau(2S_yI_z)$  ( $J_{IS}$  is the spin–spin coupling constant between nuclei with the spins  $I$  and  $S$ ), intensity modulation occurs during the interval  $\tau$  in the middle of the pulse sequence. The expressions for the signals observed before and after the evolution of the system caused by the spin–spin interaction have the form:

for  $^{13}\text{CH}$

$$2S_yI_x \xrightarrow{\pi J_{IS}\tau(2S_yI_z)} 2S_yI_z \cos \psi, \quad (4)$$

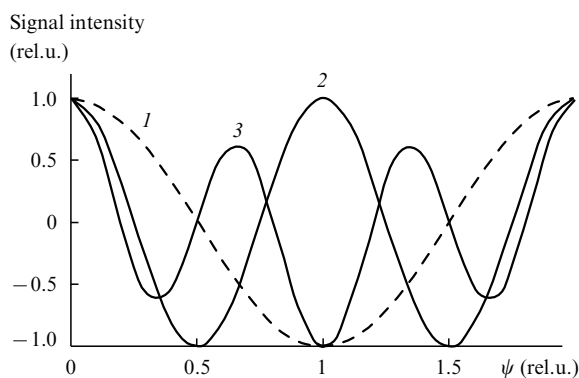


**Figure 8.**  $^{13}\text{CH}$  (1),  $^{13}\text{CH}_2$  (2) and  $^{13}\text{CH}_3$  (3) signal intensities plotted vs. pulse angle  $\beta$  (inverse DEPT) (1), evolution time  $\tau$  (inverse INEPT) (2) and pulse phase  $\phi_2$  (MAXY) (3).

for  $^{13}\text{CH}_2$

$$2 S_y I_z \xrightarrow{\pi J \tau (2 S_y I_z)} 2 S_y I_z \cos 2\psi,$$

and for  $^{13}\text{CH}_3$

$$2 S_y I_x \xrightarrow{\pi J \tau (2 S_y I_x)} 2 S_y I_x \frac{1}{4} (\cos 3\psi + \cos \psi).$$

Figure 8 presents the signal intensities of different spin systems plotted vs. the relative pulse angle ( $\psi = \beta$ , inverse-DEPT), evolution time ( $\psi = \tau$ , inverse-INEPT) and pulse phase ( $\psi = \phi_2$ , MAXY). Signals of the  $^{13}\text{CH}$ ,  $^{13}\text{CH}_2$  and  $^{13}\text{CH}_3$  groups can be separated using the  $60^\circ$ ,  $120^\circ$  and  $180^\circ$  pulses, respectively (inverse-DEPT), or the evolution times equal to  $1/3J$ ,  $2/3J$  and  $1/J$ , respectively (inverse-INEPT).

## 2. Selective experiments based on the MAXY sequence

The MAXY sequence (Fig. 9a) includes excitation of the spin ( $^{13}\text{CH}_n$ ) systems to the maximum possible quantum order using the following pulse scheme:  $90_x^\circ(I) - \Delta - 90_x^\circ(S) 180_x^\circ(I) - \Delta - 90_x^\circ(I)$  (where  $\Delta = 1/2J$ ).<sup>46, 47</sup>

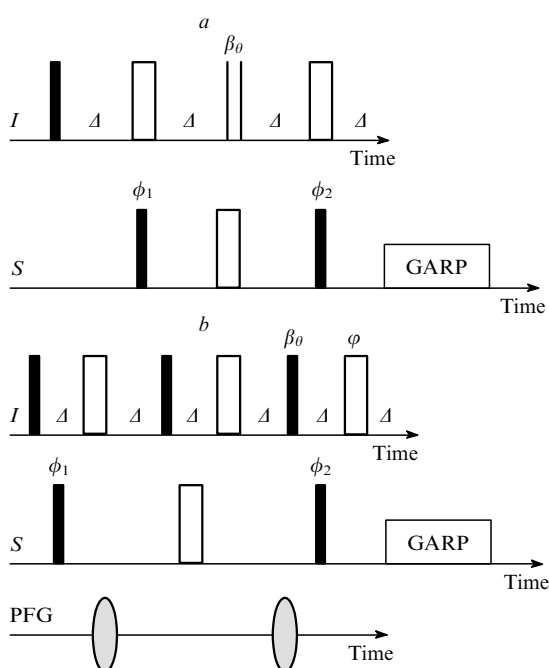


**Figure 9.** MAXY pulse sequence without (a) and with PFG (b).

Since the maximum possible quantum level of each different spin system is different, it is possible to convert all transitions, or any transition, to observable  $^1\text{H}$  single-quantum coherence. Spectral editing can be achieved by using multiple-quantum proton read pulses with different phases ( $\theta$ ) as in, e.g., the RELAY sequence<sup>26, 27</sup> or different flip angles ( $\beta$ ) as in the DEPT sequence.<sup>30, 31</sup> But it is also possible to use simply  $pmx$ - or  $\pm y$ -phases (i.e., phases associated with the positive or negative direction of the pulses along the coordinate axes) because this provides the highest signal intensity.

### a. Spectral selection using phase cycling

When using a sequence of  $90_\theta^\circ(I) - \Delta - 90_{\phi_2}^\circ(S) 180_\phi^\circ(I) - \Delta$  ( $\phi = \theta/2$ ) all multiple-quantum coherences can be converted to observable magnetisation:<sup>47</sup>

$$+ 2 I_x S_y \xrightarrow{90_\theta^\circ(I) - \Delta - 180_\phi^\circ(I) 90_{\phi_2}^\circ(S) - \Delta} I_y \cos \theta, \quad (5)$$

for  $^{13}\text{CH}_2$

$$+ 2 I_x I_y S_x \xrightarrow{90_\theta^\circ(I) - \Delta - 180_\phi^\circ(I) 90_{\phi_2}^\circ(S) - \Delta} I_y \cos 2\theta,$$

and for  $^{13}\text{CH}_3$

$$- 8 I_x I_y I_z S_y \xrightarrow{90_\theta^\circ(I) - \Delta - 180_\phi^\circ(I) 90_{\phi_2}^\circ(S) - \Delta} (1/4) I_y (3 \cos 3\theta + \cos \theta).$$

The pulse  $90^\circ(I_\theta)$  converts part of the magnetisation to zero-quantum and double-quantum coherences with intensities proportional to  $\cos n\theta$ . The expression for a  $^{13}\text{CH}_3$  group contains two terms proportional to  $\cos 3\theta$  and  $\cos \theta$  with intensity ratios of 3 : 1, respectively, and which correspond to the  $^1\text{H}$  triple-quantum coherence of  $8 I_x I_y I_z$ . The desired resonances can be selected by phase cycling the  $90^\circ(\theta)$  pulse with  $\theta = 180^\circ/n$ , where  $n$  is the number of attached protons. An advantage in this procedure is that resonances of protons not bound to  $^{13}\text{C}$  can be better suppressed by further cycling of the receiver phase. The phase cycling programmes for selection of  $^{13}\text{CH}_2$  and  $^{13}\text{CH}_3$  resonances via  $^1\text{H}$  double-quantum and triple-quantum coherences are listed in Table 2.

**Table 2.** Phase cycling programmes for selective observation of  $^{13}\text{CH}_2$  and  $^{13}\text{CH}_3$  resonances with the MAXY sequence.

| Phase    | For $^{13}\text{CH}_2$                                                           | Phase    | For $^{13}\text{CH}_3$                                                                  |
|----------|----------------------------------------------------------------------------------|----------|-----------------------------------------------------------------------------------------|
| $\phi_1$ | $0^\circ, 180^\circ$                                                             | $\phi_1$ | $0^\circ, 180^\circ$                                                                    |
| $\phi_2$ | $0^\circ, 0^\circ, 180^\circ, 180^\circ$                                         | $\phi_2$ | $0^\circ, 0^\circ, 180^\circ, 180^\circ$                                                |
| $\theta$ | $(0^\circ)_4, (90^\circ)_4, (180^\circ)_4, (270^\circ)_4$                        | $\theta$ | $(0^\circ)_4, (60^\circ)_4, (120^\circ)_4, (180^\circ)_4, (240^\circ)_4, (300^\circ)_4$ |
| $\phi$   | $(0^\circ)_4, (45^\circ)_4, (90^\circ)_4, (135^\circ)_4$                         | $\phi$   | $(0^\circ)_4, (30^\circ)_4, (60^\circ)_4, (90^\circ)_4, (120^\circ)_4, (150^\circ)_4$   |
| $\phi_n$ | $0^\circ, 180^\circ, 180^\circ, 0^\circ, 180^\circ, 0^\circ, 0^\circ, 180^\circ$ | $\phi_r$ | $0^\circ, 180^\circ, 180^\circ, 0^\circ, 180^\circ, 0^\circ, 0^\circ, 180^\circ$        |

**Note.** The subscripts denote the numbers of cycles.

It is interesting that mathematical expressions for the observable signals for the inverse-DEPT, inverse-INEPT and MAXY sequences have the same form [see Eqns (4) and Fig. 8].

It is possible to obtain subspectra of the  $\text{CH}_3$  and  $\text{CH}_2$  groups by choosing appropriate  $\phi$  values (see Table 2). This can be done by phase cycling in the MAXY experiments because the variable is the read pulse phase ( $\theta$ ). When using inverse-DEPT and inverse-INEPT methods, the variables are the pulse flip angles and times, respectively, and the task becomes much more complicated.

**Table 3.** Combination of NMR spectra for obtaining  $^1\text{H}$  subspectra of individual  $^{13}\text{CH}_n$  groups using the MAXY sequence with the pulse angles  $\beta = 0^\circ$  (I),  $90^\circ$  (II),  $270^\circ$  (III).<sup>43–47</sup>

| Spin system        | Signal intensity (rel. u.) |    |     |          |          | Combination of spectra | Intensity ratio | Number of runs |
|--------------------|----------------------------|----|-----|----------|----------|------------------------|-----------------|----------------|
|                    | I                          | II | III | II + III | II – III |                        |                 |                |
| $^{13}\text{CH}$   | 1                          | 1  | 1   | 1        | 0        | I                      | 1.0             | 1              |
| $^{13}\text{CH}_2$ | 0                          | 2  | –2  | 0        | 2        | II – III               | 2.0             | 1              |
| $^{13}\text{CH}_3$ | 0                          | 3  | 3   | 3        | 0        | II + III – I           | 3.0             | 2              |

**b. Spectral selection using a  $\beta_x(I)$  pulse**

If a  $\beta(I)$  pulse is applied along the  $x$  axis, it will convert part of the magnetisation heteronuclear zero-quantum and double-quantum coherence, which is then transferred to  $I$ -spin single-quantum coherence by the pulse following a delay  $\Delta$ . The data acquisition starts after a delay of  $\Delta$  and results in in-phase (correct) absorption lineshapes for all spins with the intensities proportional to  $\sin\beta$  (for  $^{13}\text{CH}_2$ ) or  $\sin^2\beta$  (for  $^{13}\text{CH}_3$ ); the exception is the  $^{13}\text{CH}$  group, which is not affected by the  $\beta_x(I)$  pulse:

for  $^{13}\text{CH}$

$$+ 2 I_x S_y \xrightarrow{\beta_x(I)} + 2 I_x S_y \xrightarrow{\Delta - 180^\circ_x(I) 90^\circ_x(S) - \Delta} + I_y, \quad (6)$$

for  $^{13}\text{CH}_2$

$$+ 4 I_x I_y S_x \xrightarrow{\beta_x(I)} + 4 I_x I_z S_z \sin\beta \xrightarrow{\Delta - 180^\circ_x(I) 90^\circ_x(S) - \Delta} + I_y \sin\beta,$$

for  $^{13}\text{CH}_3$

$$- 8 I_x I_y I_z S_y \xrightarrow{\beta_x(I)} - 8 I_x I_z S_z \sin^2\beta \xrightarrow{\Delta - 180^\circ_x(I) 90^\circ_x(S) - \Delta} + I_y \sin^2\beta.$$

When studying the dependence of the signal intensities on the pulse flip angle ( $\beta_x$ ), the flip angles of  $0^\circ$ ,  $180^\circ$ ,  $90^\circ$  and  $270^\circ$  are particularly interesting because at these angles the intensities reach extrema, which can be used for spectral editing. If a  $0^\circ$  or  $180^\circ$   $^1\text{H}$  read pulse is used, only  $^{13}\text{CH}$  resonances can be observed. The efficiency of suppression of  $^{13}\text{CH}_2$  and  $^{13}\text{CH}_3$  signals is very high, because these groups are in the multiple-quantum coherence states and all protons not bound to  $^{13}\text{C}$  will have only longitudinal magnetisation.

A  $90^\circ$  or  $270^\circ$   $^1\text{H}$  read pulse will convert the coherence of  $^{13}\text{CH}_2$  and  $^{13}\text{CH}_3$  groups to heteronuclear zero-quantum and double-quantum coherences and thus make it possible to get the true intensity (for  $\beta = 90^\circ$ , all signals in the spectrum are positive, whereas for  $\beta = 270^\circ$ , only  $^{13}\text{CH}_2$  signals are negative). This provides a way to edit the spectra by phase cycling, because the  $90^\circ$  and  $270^\circ$  flip angles are equivalent to a  $90^\circ$  pulse with phases of  $x$  and  $-x$  directions. As a result, if the receiver phase is shifted (subtraction of spectra), one gets the subspectrum of  $^{13}\text{CH}_2$  groups only; otherwise if the receiver phase is fixed (addition of spectra), the subspectrum of  $^{13}\text{CH}$  and  $^{13}\text{CH}_3$  groups together is observed.

**c. Spectral selection using a  $\beta_y(I)$  pulse**

Yet another method of obtaining the  $^{13}\text{CH}$  and  $^{13}\text{CH}_2$  subspectra involves the use of a  $\beta(I)$  read pulse applied only along the  $y$  axis. The effect of such a pulse is shown in Eqns (7):

for  $^{13}\text{CH}$

$$+ 2 I_x S_y \xrightarrow{\beta_y(I)} + 2 I_x S_y \xrightarrow{\Delta - 180^\circ_x(I) 90^\circ_x(S) - \Delta} + I_y \cos\beta, \quad (7)$$

for  $^{13}\text{CH}_2$

$$+ 4 I_x I_y S_x \xrightarrow{\beta_y(I)} + 4 I_x I_z S_z \sin\beta \xrightarrow{\Delta - 180^\circ_x(I) 90^\circ_x(S) - \Delta} + I_y \sin\beta,$$

for  $^{13}\text{CH}_3$

$$\begin{aligned} - 8 I_x I_y I_z S_y \xrightarrow{\beta_y(I)} - 8 I_y I_z S_z \sin\beta \xrightarrow{\Delta - 180^\circ_x(I) 90^\circ_x(S) - \Delta} \\ \longrightarrow + 8 I_y I_z S_z \sin\beta. \end{aligned}$$

Note that the coherence of  $^{13}\text{CH}_3$  groups cannot be converted to observable magnetisation by a read pulse applied along the  $y$  axis.

The intensities of  $^{13}\text{CH}$  and  $^{13}\text{CH}_2$  group resonances vary in proportion to  $\cos\beta$  and  $\sin\beta$ , respectively. Therefore, a  $90^\circ$  pulse along the  $y$  axis allows the subspectrum of the  $^{13}\text{CH}_2$  group to be selected. The editing scheme for MAXY  $^1\text{H}$  NMR spectra using spectrum addition or subtraction with  $\beta$  pulses is given in Table 3.

**d. The use of pulsed magnetic field gradients**

An advantage of the MAXY method over the inverse-DEPT and inverse-INEPT techniques is that selective detection of resonance signals can be achieved using pulsed magnetic field gradients.<sup>46–50</sup> This was shown to provide enhanced performance in many pulse sequences. In the MAXY experiments, the spin systems  $^{13}\text{CH}_n$  are excited to their highest possible quantum levels. In this case it is possible to observe subspectra of individual  $^{13}\text{CH}_n$  groups using PFG because the phase of the multiple-quantum coherence is proportional to the quantum order of the coherence. The quantum orders of all  $^{13}\text{CH}_n$  systems are the same in both the inverse-DEPT and inverse-INEPT experiments; therefore, pulsed magnetic field gradients cannot be used for selective detection. The PFG-MAXY pulse sequence is shown in Fig. 9b. Here, two pulses are used, with the first one applied during the first  $\Delta$  delay period and the second one applied immediately after the last  $90^\circ(S)$  transfer pulse, the field gradients having the values of  $g_1$  and  $g_2$ , respectively. The overall effect of the action of the PFGs can be written as follows:

for  $^{13}\text{CH}$

$$A_1 = \frac{1}{2} \cos[\pi(\gamma_H + \gamma_C)g_1\delta + \pi\gamma_H g_2\delta],$$

for  $^{13}\text{CH}_2$

$$A_2 = \frac{1}{2} \cos[\pi(2\gamma_H + \gamma_C)g_1\delta + \pi\gamma_H g_2\delta],$$

and for  $^{13}\text{CH}_3$

$$\begin{aligned} A_3 = \frac{3}{8} \cos[\pi(3\gamma_H + \gamma_C)g_1\delta + \pi\gamma_H g_2\delta] + \\ + \frac{1}{8} \cos[\pi(\gamma_H + \gamma_C)g_1\delta + \pi\gamma_H g_2\delta], \end{aligned}$$

where  $g$  and  $\delta$  are the gradient strength and duration of the PFG pulse, respectively. The first gradient pulse usually causes a phase shift proportional to the quantum order ( $n\gamma_H + \gamma_C$ ), where  $n$  is the number of attached protons in the  $^{13}\text{CH}_n$  groups. The effect of the first gradient pulse can be compensated by the second gradient pulse. By choosing an appropriate strength for the second gradient it is possible to selectively detect individual spin systems. When the same gradient shape and duration are used, the gradient strengths must be as follows:

for  $^{13}\text{CH}$

$$g_2 : g_1 = (\gamma_H + \gamma_C) : \gamma_H = -5 : 4, \quad (8)$$

for  $^{13}\text{CH}_2$

$$g_2 : g_1 = (2\gamma_H + \gamma_C) : \gamma_H = -9 : 4,$$

and for  $^{13}\text{CH}_3$

$$g_2:g_1 = (3\gamma_{\text{H}} + \gamma_{\text{C}}):\gamma_{\text{H}} = -13:4.$$

Selective detection using PFG is accompanied by a 50% decrease in signal intensity. Moreover, any molecular self-diffusion processes can cause a signal attenuation on the multiple-quantum coherence, which is proportional to the square of the quantum order.<sup>51</sup>

The application of the MAXY method can be useful in the case of complex NMR spectra, *e.g.*, those of peptides or proteins, or biological fluids and tissue extracts. A general problem in the NMR studies of such objects is the overlap of signals (often, even if a very high magnetic field strength was used). Generally, the assignment of most spectral lines requires an extensive use of 2D NMR spectroscopy methods.<sup>7</sup> As an initial stage in the line assignment procedure before carrying out time-consuming 2D NMR experiments, it is useful to determine which lines correspond to  $^{13}\text{CH}$ ,  $^{13}\text{CH}_2$  and  $^{13}\text{CH}_3$  groups. The NMR spectra can be essentially simplified by suppression of water signals. This approach facilitates both signal assignment and structural studies of complex molecules.

### 3. MAXY-Based selective 2D NMR methods

Two-dimensional correlation NMR spectroscopy is a modern method used for signal assignment in the NMR spectra. It is based on a general approach in which the magnetisation is transferred from one spin to another through spin–spin coupling, chemical exchange or cross-relaxation. In the case of  $^1\text{H}$ – $^1\text{H}$  correlations, especially for macromolecules, signal overlap can present a serious problem and thus limit the application of the technique. A possible solution to such problem is to use the editing capabilities of the RELAY,<sup>23,24</sup> INEPT<sup>25,26</sup> and DEPT<sup>27–29</sup> methods in the experiments on heteronuclear correlation<sup>36,41,46,48,52</sup> and homonuclear correlation.<sup>34,37–39,44–47</sup> Signal overlap can be reduced owing to multiplicity selection and enhanced resolution of the 2D NMR spectra.

2D MAXY-Based pulse sequences are shown in Fig. 10.<sup>44</sup> In the time axis, the increment time ( $t_1$ ) is placed at the centre, at the position where the  $^{13}\text{CH}_n$  spin systems are in their highest quantum states. The  $180^\circ$  ( $^{13}\text{C}$ ) pulse in the middle of the evolution period interchanges the quantum order and refocusses the  $^{13}\text{C}$  chemical shift evolution in such a way that only  $^1\text{H}$  chemical shifts have single-quantum coherence (SQ) for  $^{13}\text{CH}$ , pure double-quantum coherence (DQ) for  $^{13}\text{CH}_2$  and both triple-quantum (TQ) and single-quantum coherences for  $^{13}\text{CH}_3$  groups.

A composite  $180^\circ$  ( $^{13}\text{C}$ ) pulse can be utilised for suppression of undesired resonances in the  $^{13}\text{C}$  spectral region, especially in the case of molecules containing aromatic and aliphatic carbon atoms. Thus, at the end of period  $t_1$ , the intensities of observable signals will be proportional to:<sup>44</sup>

$$-2 I_x S_y \cos(2\pi\delta t_1) \Pi \cos(\pi J_j t_1)$$

for  $^{13}\text{CH}$ ,

$$-4 I_x I_y S_x \cos(4\pi\delta t_1) \Pi \cos(2\pi J_j t_1)$$

for  $^{13}\text{CH}_2$ , and

$$+2 I_x I_y S_y [3\cos(6\pi\delta t_1) + \cos(2\pi\delta t_1)] \Pi \cos^3(\pi J_j t_1) \text{ for } ^{13}\text{CH}_3.$$

Here  $\delta$  represents the proton chemical shifts,  $J_j$  is the  $j$ th spin–spin coupling constant and  $\Pi \cos(\pi J_j t_1)$  represents passive  $^1\text{H}$ – $^1\text{H}$  couplings evolving during  $t_1$ . It should be noted that the precession frequency of the  $^{13}\text{CH}_n$  groups is proportional to the number,  $n$ , of the attached protons. Selective detection of the subspectra of the individual  $^{13}\text{CH}_n$  groups can be achieved using the same technique as that used in the 1D experiments. Moreover, with a suitable acquisition mode, such as TPPI (Time-proportional Phase Incrementation),<sup>51</sup> it is possible to separate resonances from different  $^{13}\text{CH}_n$  groups.<sup>44</sup>

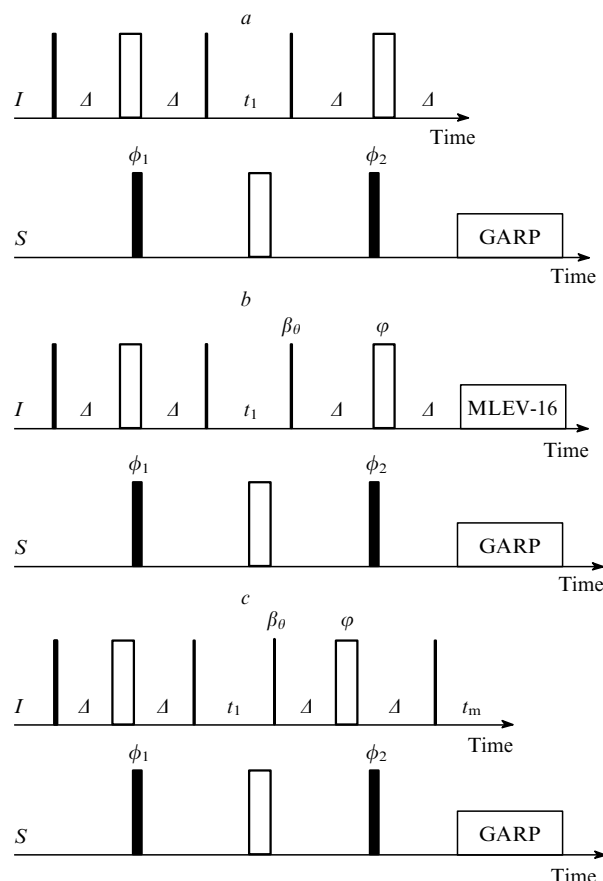


**Figure 10.** Pulse sequences based on 2D MAXY. 2D MAXY–COSY (Correlation Spectroscopy) (a), 2D MAXY–TOCSY (Total Correlation Spectroscopy) (b) and 2D MAXY–NOESY (Nuclear Overhauser Effect and Exchange Spectroscopy) (c). MLEV-16 stands for M Levitt's Composite pulse Decoupling Sequence;  $t_1$  is the increment time and  $t_m$  is the mixing time.

**Coherence separation using TPPI.** The TPPI method is widely used in phase-sensitive 2D experiments to achieve quadrature detection in the  $F_1$  dimension.<sup>51</sup> In the 2D MAXY experiments, TPPI acquisition is achieved by increasing the phase of the mixing pulses  $90^\circ\phi$  ( $^1\text{H}$ ) and  $180^\circ\phi$  ( $^1\text{H}$ ) with an increment of  $90^\circ$  and  $45^\circ$ , respectively, starting from  $0^\circ$  for the non-selective experiment. The increase in the mixing pulse phase by  $90^\circ$  shifts the phase by  $-90^\circ$  for SQ, by  $-180^\circ$  for DQ and by  $-270^\circ$  ( $+90^\circ$ ) for TQ, which is equivalent to the carrier frequency change<sup>4</sup> for the corresponding coherence. Thus, any quantum coherence can be separated and labelled by its carrier frequency or the number of protons in the  $^{13}\text{CH}_n$  groups. These changes can be seen after each phase increment (Table 4).

The  $90^\circ$  increment of the phase  $2\pi\delta t_1$  causes the functions  $\cos(2\pi\delta t_1)$  and  $\sin(2\pi\delta t_1)$  of the  $^1\text{H}$  single-quantum and triple-quantum coherences to be observed in alternating experiments with different sign cycling ( $++--$  for SQ and  $+-+ -$  for TQ) corresponding to the  $-90^\circ$  and  $+90^\circ$  phase changes. Those of homonuclear double-quantum coherences of the  $^{13}\text{CH}_2$  systems are always  $\cos(2\pi\delta t_1)$  terms with the signs  $(+ - + -)$  because of the  $180^\circ$  phase change in frequency. The signals of the  $^1\text{H}$  protons not attached to  $^{13}\text{C}$  are unaffected by the TPPI scheme. After appropriate Fourier transformation, the single-quantum coherence peaks of  $^{13}\text{CH}$  and  $^{13}\text{CH}_3$  groups appear along a  $45^\circ$  diagonal and the triple-quantum signals appear along a  $-71.56^\circ$  line in the  $F_1$  dimension. The peaks corresponding to the double-quantum and zero-quantum coherences appear at

$$\omega' = |\omega_1 + \omega_2|,$$

**Table 4.** Change in the quantum coherence on phase change.

| Spin system                   | Phase 0°                                                               | Phase 90°                                                              | Phase 180°                                                             | Phase 270°                                                             |
|-------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|
| <sup>13</sup> CH              | + $I_y \cos(2\pi\delta t_1)$                                           | + $I_y \sin(2\pi\delta t_1)$                                           | - $I_y \cos(2\pi\delta t_1)$                                           | - $I_y \sin(2\pi\delta t_1)$                                           |
| <sup>13</sup> CH <sub>2</sub> | + $(I_{1y} + I_{2y}) \cos[2\pi(\delta_1 + \delta_2)t_1]$               | - $(I_{1y} + I_{2y}) \cos[2\pi(\delta_1 + \delta_2)t_1]$               | + $(I_{1y} + I_{2y}) \cos[2\pi(\delta_1 + \delta_2)t_1]$               | - $(I_{1y} + I_{2y}) \cos[2\pi(\delta_1 + \delta_2)t_1]$               |
| <sup>13</sup> CH <sub>3</sub> | + $(9/4)I_y \cos(6\pi\delta t_1)$<br>+ $(3/4)I_y \cos(2\pi\delta t_1)$ | - $(9/4)I_y \sin(6\pi\delta t_1)$<br>+ $(3/4)I_y \sin(2\pi\delta t_1)$ | - $(9/4)I_y \cos(6\pi\delta t_1)$<br>- $(3/4)I_y \cos(2\pi\delta t_1)$ | + $(9/4)I_y \sin(6\pi\delta t_1)$<br>- $(3/4)I_y \sin(2\pi\delta t_1)$ |

( $\omega_1$  and  $\omega_2$  are the chemical shift frequencies of the single-quantum coherences) with respect to the carrier frequency at the highest and lowest positions in the  $F_1$  spectral window. Therefore, the complete spectrum is divided into four parts in the  $F_1$  dimension. The upper part is the DQ COSY-spectrum of <sup>13</sup>CH<sub>2</sub> protons, the middle part is the COSY-spectrum of <sup>13</sup>CH and <sup>13</sup>CH<sub>3</sub> protons and the lower part is the TQ COSY-spectrum of <sup>13</sup>CH<sub>3</sub> protons and any unsuppressed resonances of XH<sub>n</sub> (X ≠ <sup>13</sup>C) groups (ZQ-spectrum) lying along the bottom line in the  $F_1$  dimension. The positions of <sup>13</sup>CH<sub>2</sub> and XH<sub>n</sub> signals can be exchanged by decreasing the phase of the 90°(<sup>1</sup>H) pulse and increasing the phase of the 180°(<sup>1</sup>H) pulse with 45° and 90° increments, respectively. Generally, this leads to an increase in the observable signal in proportion to  $I_y \cos(m\pi) \cos(n2\pi\delta t_1 - nm\pi/2)$ , where  $m$  is the number of phase increments. For selective measurements, the TPPI scheme can be applied to the 90°(<sup>1</sup>H) and 180°(<sup>1</sup>H) pulses with phase increments of 90°/ $n$  and 90°/2*n*, respectively.

**MAXY-TOCSY.** The magnetisation transfer from a spin ( $I_i$ ) to its coupling partners  $I_j$  can be achieved by the homonuclear Hartmann-Hahn mechanism.<sup>51, 53–58</sup> This can be done with ease by adding a TOCSY magnetisation transfer step before the data acquisition.<sup>44</sup>

**MAXY-NOESY.** When a 90°(<sup>1</sup>H)- $t_m$ -90°(<sup>1</sup>H) scheme is inserted before data acquisition, it is possible to obtain cross-peaks due to nuclear Overhauser effect (NOE) or chemical exchange.<sup>44</sup> For a <sup>12</sup>C-<sup>1</sup>H<sub>A</sub>-<sup>13</sup>C-<sup>1</sup>H<sub>B</sub> spin system, the first pulse will convert the coherence to longitudinal magnetisation as  $I_{zB}$  and  $I_{zA} \cos(\omega t_1)$ , respectively. The NOE magnetisation transfer occurs during the mixing of different states of the coupled spin system. The final 90°(<sup>1</sup>H) pulse re-establishes the single-quantum coherence of spin  $I$ . The observed NOE cross-peak corresponding to coherence transfer from the H<sub>B</sub> proton to the H<sub>A</sub> proton is defined as

$$I_A = I \cos(\omega_B t_1) \frac{\sigma_{AB}}{(\lambda_1 - \lambda_2) [\exp(-\lambda_1 t_m) - \exp(-\lambda_2 t_m)]},$$

where  $\lambda_{1,2} = (1/2)\{(R_A + R_B) \pm [(R_A - R_B)^2 + 4\sigma_{AB}\sigma_{BA}]^{1/2}\}$ ,  $\sigma_{AB}$  and  $\sigma_{BA}$  are the cross-relaxation rates from spin A to spin B (AB) and from spin B to spin A (BA), respectively,  $R$  is the longitudinal relaxation rate including all terms except for the cross-relaxation rate  $\sigma_{AB}$ . To calculate the maximum possible NOE, one must differentiate this equation with respect to  $t_m$ . Suppose that

$$R_A = R_B = 2\sigma_{AB} = 2\sigma_{BA},$$

$$\lambda_1 = 3\sigma,$$

$$\lambda_2 = \sigma.$$

Then one gets

$$t_m(\max) = \frac{\ln 3}{2\sigma} \approx 1.1 T_1.$$

If

$$\frac{\sigma_{AB}}{\lambda_1 - \lambda_2} = 0.5,$$

the maximum NOE enhancement is

$$I_{\text{cross}}(\max) = -0.19 I_{zB}(t_1).$$

The MAXY-TOCSY and MAXY-NOESY spectra can provide information on the type of the spin system provided that two spins are involved in a dipole-dipole coupling.

#### 4. Selective $J$ -resolved 1D NMR spectroscopy.

##### MAXY-JRES

Using  $J$ -resolved NMR spectroscopy, it is possible to separate the chemical shifts and the spin-spin coupling constants into the  $F_1$  and  $F_2$  dimensions, respectively,<sup>3, 59</sup> and thus obtain a broadband-decoupled 1D NMR spectrum from the projection on the  $F_2$  dimension. However, for complex samples (e.g., biological fluids<sup>60, 61</sup>), the method is of limited use because of strong overlap of NMR resonances. Procedures used for spectral resolution enhancement and lineshape improvement include pseudo-echo-weighting,<sup>62</sup> 'time-reversal'<sup>63</sup> and other techniques,<sup>64, 65</sup> specific data processing<sup>65, 66</sup> and the 3D JRES-COSY NMR spectroscopy<sup>67, 68</sup> (here, JRES stands for J Relay Selective). The MAXY approach can be successfully employed for obtaining individual JRES-spectra of <sup>13</sup>CH, <sup>13</sup>CH<sub>2</sub> and <sup>13</sup>CH<sub>3</sub> groups.<sup>45</sup> The MAXY-JRES pulse sequence is shown in Fig. 11. An advantage of the MAXY technique is the possibility of using magnetic field gradient pulses for separation of the subspectra of CH<sub>n</sub> groups. The gradient strength ratios,  $g_1 : g_2 : g_3 : g_4$ , are as follows:

Nonselective <sup>13</sup>CH + <sup>13</sup>CH<sub>3</sub>    <sup>13</sup>CH    <sup>13</sup>CH<sub>2</sub>    <sup>13</sup>CH<sub>3</sub>  
tive spectrum

1 : 1 : 4 : 5    1 : (-1) : 2 : 4    1 : (-1) : 2 : 4    1 : (-1) : 2 : 6    1 : (-1) : 2 : 8

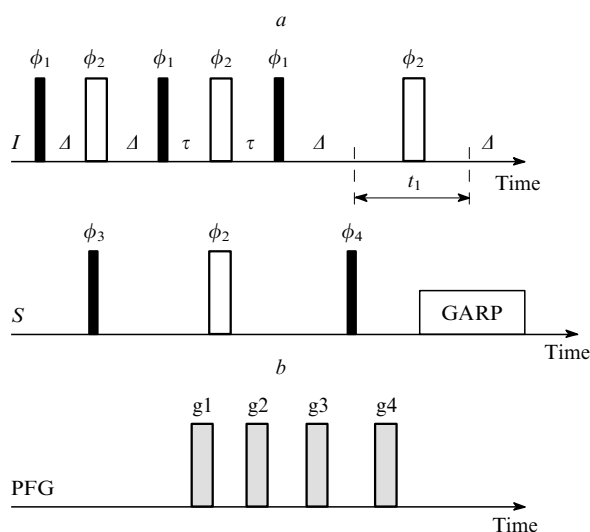


**Figure 11.** The RF pulse sequence (a) and PFG sequence (b) in the MAXY-JRES experiments.

The delay  $\Delta$  is  $1/(2 J_{CH})$ ;  $\tau$  is the short delay for compensation of the pulse phase,  $t_1$  is the increase in the magnetisation evolution time. The pulse phase cycling scheme is as follows:  $\phi_1 = 0^\circ$ ;  $\phi_2 = 90^\circ$ ;  $\phi_3 = 0^\circ, 180^\circ$ ;  $\phi_4 = 0^\circ, 0^\circ, 180^\circ, 180^\circ$ .

The selective spectrum of a  $^{13}\text{CH}_n$  group can also be obtained using the phase cycling scheme.

## 5. 2D correlation NMR spectroscopy of geminal protons

Using a 2D method, which shows correlations only between geminal protons of methylene groups, it is possible to simplify both a COSY spectrum and signal assignment.<sup>37, 38, 44, 47</sup> Two pulse sequences were reported,<sup>37</sup> named gem-COSY-MQ (Fig. 12a) and gem-COSY-PT (Fig. 12b) and based on the inverse-DEPT-90 (see Ref. 31) and inverse-INEPT-1/(2 $J_{\text{CH}}$ ) (see Ref. 33) techniques, respectively. The techniques were modified in such a fashion that the  $\text{H} \rightarrow ^{13}\text{C} \rightarrow \text{H}$  magnetisation transfer was restricted to one-bond couplings. For a spin system  $I_1-S-I_2$ , the initial  $90^\circ(I)$  excitation pulse creates negative magnetisation along the  $y$ -axis of the  $I_1$  spin ( $-I_{1y}$ ) in both pulse sequences.<sup>37</sup> After the evolution and mixing periods, the expressions for the observable signals are as follows:

gem-COSY-MQ

$$\sigma = -I_{2y}\cos(2\pi\delta_1 t_1)\cos(\pi J_{12} t_1)\Pi\cos(\pi J_{1j} t_1) + 2I_{1x}I_{2z}\cos(2\pi\delta_1 t_1)\sin(\pi J_{12} t_1)\Pi\cos(\pi J_{1j} t_1), \quad (9)$$

gem-COSY-PT

$$\sigma = -I_{2x}\cos(2\pi\delta_1 t_1)\cos(\pi J_{12} t_1)\Pi\cos(\pi J_{1j} t_1) - 2I_{1z}I_{2y}\cos(2\pi\delta_1 t_1)\sin(\pi J_{12} t_1)\Pi\cos(\pi J_{1j} t_1) \quad (10)$$

( $\sigma$  is the density operator). Equation (10) describes the double magnetisation transfer  $I_1 \rightarrow S \rightarrow I_2$ , which gives rise to a cross-peak equivalent to an analogous peak in the COSY spectrum, except that it has an in-phase doublet pattern ( $J_{12}$ ) in both frequency dimensions. Equation (10) describes the magnetisation back-transfer  $I_1 \rightarrow S \rightarrow I_1$ , which gives rise to a double diagonal

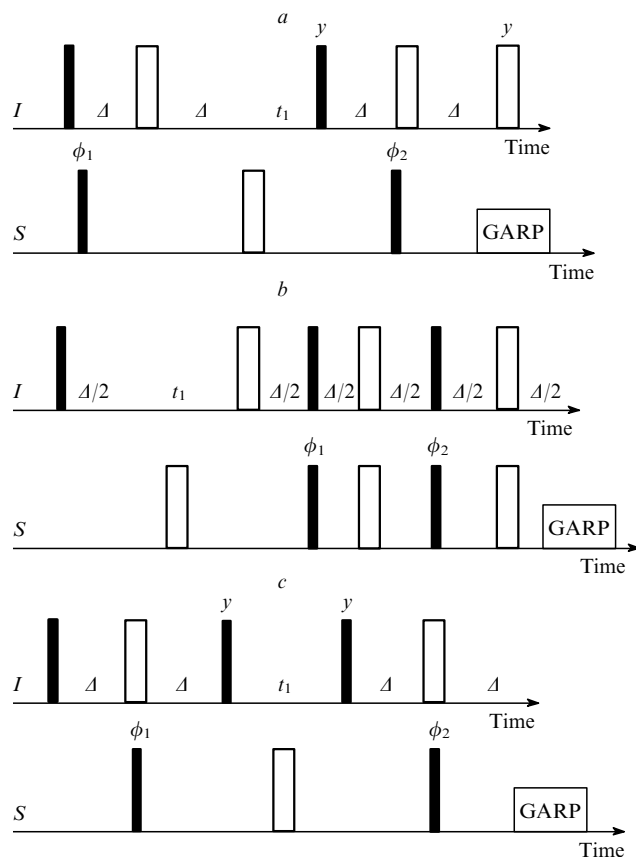


**Figure 12.** gem-COSY-MQ (a), gem-COSY-PT (Polarisation Transfer) (b) and gem-COSY (c) pulse sequences based on the MAXY sequence.

dispersion peak with antiphase splitting ( $J_{12}$ ). Passive  $^1\text{H}-^1\text{H}$  coupling described by the term  $\Pi\cos(\pi J_{1j} t_1)$  has the same meaning as in conventional correlation spectroscopy.<sup>37</sup> An alternative method of obtaining gem-COSY spectra involves modification of the 2D MAXY pulse sequence (Fig. 12c).<sup>44, 47</sup> If a  $90_x(^1\text{H})-\Delta-90_x(^{13}\text{C})180_x(^1\text{H})-\Delta-90_y(^1\text{H})$  is used, the  $^{13}\text{CH}_n$  spin systems will be excited to the second maximum possible quantum order ( $n$  for  $^{13}\text{CH}_n$  or  $n-1$  for  $^1\text{H}$ ) as shown below:

for  $^{13}\text{CH}$

$$I_z \rightarrow +2I_z S_y \text{ (SQ)},$$

for  $^{13}\text{CH}_2$

$$I_{1z} \rightarrow -4I_{1z}I_{2x}S_x \text{ (DQ)},$$

for  $^{13}\text{CH}_3$

$$I_z \rightarrow -8I_xI_xI_zS_y \text{ (TQ)}.$$

The modification of the MAXY pulse sequence is that the second  $90_y(^1\text{H})$  pulse is applied along the  $y$  axis; therefore, the spin- $I_1$  coherence is transferred to  $I_2$  during the preparation period. At the end of the coherence evolution time, we get:

for  $^{13}\text{CH}$  (SQ)

$$+2I_z S_y,$$

for  $^{13}\text{CH}_2$  (DQ)

$$4I_{1z}I_{2y}S_x\cos(2\pi\delta_2 t_1)\cos(\pi J_{12} t_1) \cdot \Pi\cos(\pi J_{1j} t_1) + 2I_{2y}S_x\cos(2\pi\delta_2 t_1)\sin(\pi J_{12} t_1),$$

for  $^{13}\text{CH}_3$  (TQ)

$$-8I_yI_yI_zS_y\sin^2(2\pi\delta_2 t_1)\Pi\cos^2(\pi J_{1j} t_1).$$

After the mixing scheme  $90_x(^1\text{H})-\Delta-90_x(^{13}\text{C})-180_x(^1\text{H})-\Delta$ , the observable single-quantum coherence is:

$$+I_y \text{ for } ^{13}\text{CH},$$

$$+I_{1y}\cos(2\pi\delta_2 t_1)\cos(\pi J_{12} t_1)\Pi\cos(\pi J_{1j} t_1) - 2I_zI_{2x}\cos(2\pi\delta_2 t_1)\sin(\pi J_{12} t_1) \text{ for } ^{13}\text{CH}_2$$

and

$$-(1/2)I_y[\cos(4\pi\delta_2 t_1) + 1]\Pi\cos^2(\pi J_{1j} t_1) \text{ for } ^{13}\text{CH}_3.$$

Signals of  $^{13}\text{CH}$  groups appear in the zero-frequency region along the bottom line in the  $F_1$  dimension and signals of a  $^{13}\text{CH}_3$  group will appear as two peaks corresponding to double-quantum and zero-quantum coherences with the same initial intensity in the  $F_1$  dimension. For  $^{13}\text{CH}_2$  groups, the first term describes the  $I_1 \rightarrow I_2 S(t_1) \rightarrow I_1(t_2)$  transfer, which gives rise to a cross-peak equivalent to that in a conventional COSY spectrum with the exception that multiplets are in-phase in both measurements. The second term describes the  $I_1 \rightarrow I_2 S(t_1) \rightarrow I_2(t_2)$  transfer responsible for the appearance of diagonal peaks with dispersion doublet lineshapes. If the phase of the last  $90_y(^1\text{H})$  pulse alternates about the  $x$  axis, the sign of the  $\text{CH}_2$  cross-peak is the same, whereas the signs of the peaks of other groups are altered. This offers yet another way of obtaining diagonal peak suppressed gem-COSY spectra, as in the 2D MAXY NMR spectrum.

The TOCSY and NOESY transfers can also be used in the gem-COSY experiments. The MAXY method provides a better suppression of diagonal peaks compared to the original MQ method. Proton signals of  $^{13}\text{CH}$ ,  $^{13}\text{CH}_2$  and  $^{13}\text{CH}_3$  groups are observed separately in different parts of the spectrum.  $^{13}\text{CH}_2$  group protons give a normal gem-COSY spectrum.  $^{13}\text{CH}_3$  proton signals appear at the right lower region of the spectrum.  $^{13}\text{CH}$  proton peaks are along the bottom line of the spectrum together with zero-quantum coherence correlation of  $^{13}\text{CH}_3$  protons. 2D correlation NMR spectroscopy of geminal protons appeared to be useful for analysis of the spectra of large molecules<sup>47</sup> and provides an alternative method of editing  $^1\text{H}$  NMR spectra.



## 6. Spin–spin coupling constants measurement using MAXY-based experiments

The spin–spin coupling constant is one of the most important parameters in NMR spectroscopy and has been widely used in conformational analysis of complex molecules and in structural modelling.<sup>2, 4, 69–74</sup>

For the first-order spectra of symmetrical systems the spin–spin coupling constants can be measured directly in the NMR spectrum. However, in the case of complex molecules, line assignment is very difficult because of signal overlap.

Using the MAXY method, it is possible to obtain 2D NMR subspectra of individual  $^{13}\text{CH}_n$  groups or separate the spectra into different spectral regions according to the number,  $n$ , of the protons bonded to  $^{13}\text{C}$ , thus resulting in appreciable reduction of signal overlap. For instance, the 2D MAXY technique was used to determine the spin–spin coupling constants in the neurotensin molecule.<sup>75</sup> Although neurotensin is a relatively short peptide, proton signals in its  $^1\text{H}$  NMR spectrum are strongly overlapped, especially in the low-frequency region. The use of the 2D MAXY method with correlation of only  $^{13}\text{CH}_2$  groups permits resolution enhancement of most overlapped peaks including the  $\beta$ -proton peaks.

## V. Measurements of self-diffusion coefficients

At present, self-diffusion coefficients are very often measured using the pulsed magnetic field gradient technique according to Stejskal and Tanner.<sup>76</sup>

Once the Longitudinal Eddy Current Delay (LED) pulse sequence was designed and the concept of diffusion-ordered spectroscopy proposed, it became possible to determine the diffusion coefficients associated with each resonance signal in the high-resolution NMR spectrum. Therefore, researchers expressed increased interest in measuring diffusion coefficients using NMR spectroscopy.<sup>77–87</sup> The diffusion coefficients thus determined were used in, *e.g.*, experimental studies on the vesicle size distribution in phospholipids,<sup>82</sup> molecular mass distribution in polymers,<sup>83</sup> in analysing complex mixtures of cell extracts,<sup>85</sup> protein association,<sup>86</sup> aggregation of insulin molecules<sup>87</sup> and protein binding with drugs.<sup>88–107</sup> Editing 1D and 2D NMR spectra of biological fluids, based on differences in the molecular diffusion coefficients and relaxation times, is possible using the DIRE (Diffusion Relaxation) and DETOCY (Delay TOCSY) techniques<sup>108</sup> and improved 2D methods of the HETCOR (Heteronuclear Correlation Spectroscopy), COSY and NOESY types.<sup>109–111</sup>

In an original PFG–SE (Pulsed Field Gradient Spin Echo) experiment, signal attenuation can be written as follows<sup>76</sup>

$$\ln \frac{A(g)}{A(0)} = -\gamma^2 D \left[ \frac{2g_0^2 \tau^3}{3} + gg_0 \delta \left( \frac{3\tau^2}{2} - \frac{\delta^2}{6} \right) + g^2 \delta^2 \left( \Delta - \frac{\delta}{3} \right) \right] - \frac{2\tau}{T_2}. \quad (11)$$

Here  $A(g)$  and  $A(0)$  are the signal intensities in the presence and in the absence of PFG,  $\gamma$  is the magnetogyric ratio for a given spin,  $D$  is the diffusion coefficient,  $g_0$  is the steady magnetic field gradient,  $g$  and  $\delta$  are the strength and duration of the rectangular gradient pulse,  $\Delta$  is the time interval between the starting points of two gradient pulses (diffusion time),  $2\tau$  is the time at which spin echo occurs and  $T_2$  is the transverse relaxation time. If

$$g_0^2 = \tau^3 \ll g^2 \delta^2 \Delta,$$

Eqn (11) is simplified

$$\ln \frac{A(g)}{A(0)} = -\gamma^2 D g^2 \delta^2 \left( \Delta - \frac{\delta}{3} \right) - \frac{2\tau}{T_2}. \quad (12)$$

This equation is known as the Stejskal–Tanner equation for diffusion coefficient measurement.

Having obtained a number of spectra using different gradient strengths and plotted  $\ln A$  vs.  $\gamma^2 g^2 \delta^2 (\Delta - \delta/3)$ , one gets a straight line with the slope equal to the self-diffusion coefficient. In order to determine the exact  $D$  values, one must attenuate the NMR signal. This can be achieved using a wide range of gradient pulses. For slowly diffusing particles the gradient strength can be of the order of 1000 to 2000 mT m<sup>−1</sup>.

Alternating eddy flows that can be induced in a sample under study in the course of experiments complicate exact detection of the NMR signal.<sup>112</sup> It is also possible to obtain the same range of  $\gamma^2 g^2 \delta^2 (\Delta - \delta/3)$  values using small gradients with compensation of alternating eddy flows owing to longer diffusion time.<sup>113, 114</sup> However, this can lead to a decrease in sensitivity due to spin relaxation.<sup>113</sup>

Another way of increasing gradient strength is to use the dependence of the dephasing/rephasing of gradient pulses on the quantum order of the spin systems affected<sup>115</sup> by the gradients during the multiple-quantum sequence. In this case the effective magnetogyric ratio  $\gamma_{\text{ef}}$  is the sum of the values,  $\gamma$ , of the spins involved in coherence. For a homonuclear double-quantum sequence one has  $\gamma_{\text{ef}} = 2\gamma$ ; therefore, the gradient strength is doubled while the measurable diffusion coefficient decreases by a factor of four.<sup>116–120</sup> Diffusion spread of longitudinal spin orders  $2I_z I_z$  and  $4I_z I_z I_z$  normal to the gradient direction was studied.<sup>118, 119</sup> It was shown that the effective magnetogyric ratios are equal to  $2\gamma$  and 0 for the  $2I_z I_z$  system and to  $3\gamma$  and  $\gamma$  for the  $4I_z I_z I_z$  system.

The MAXY method was modified<sup>43–46, 121–123</sup> to determine diffusion-induced changes in the maximum quantum order of the spin operator  $8I_x I_y I_z S_y$  for the  $^{13}\text{C}^1\text{H}_3$  ( $SI_3$ ) spin system. This system is characterised by four magnetogyric ratios, namely,  $(3\gamma_{\text{H}} + \gamma_{\text{C}})$ ,  $(3\gamma_{\text{H}} - \gamma_{\text{C}})$ ,  $(\gamma_{\text{H}} + \gamma_{\text{C}})$  and  $(\gamma_{\text{H}} - \gamma_{\text{C}})$ , corresponding to four multiple-quantum levels composed of possible combinations of individual spin states. The multiple-quantum coherences (each of them can be obtained individually using pulsed field gradients) can be converted to observable single-quantum coherences. Diffusion-induced changes in each coherence can also be measured individually.<sup>43–46</sup>

An original technique<sup>124</sup> permits reduction of the duration of the 3D NMR experiments; the corresponding pulse sequence is given in Fig. 13. The modification of the MAXY sequence consists of addition of a diffusion time and diffusion gradient

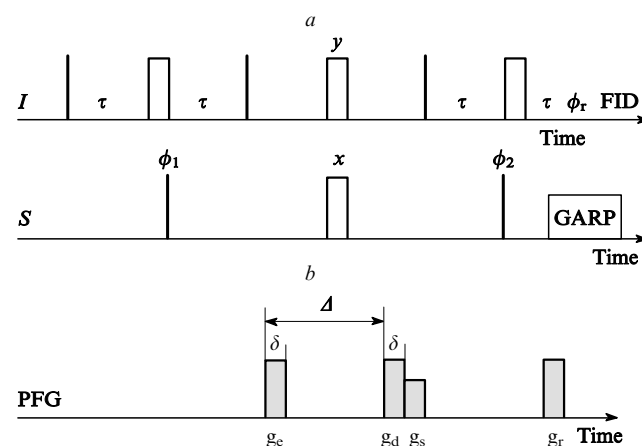


**Figure 13.** The RF pulse sequence (a) and PFG sequence (b) used in the modified MAXY diffusion coefficient measurement technique.

The pulse phases in the rotating frame are along the  $x$  axis until otherwise specified, *i.e.*,  $\phi_1 = x$ ,  $x$ ,  $x$ ,  $-x$ ,  $-x$ ;  $\phi_2 = -y$ ,  $y$ ,  $y$ ,  $-y$ . The delay time  $\tau$  is 3.85 ms, the time interval  $\Delta$  is set to 50 ms; FID stands for Free Induction Decay. For notations  $g_c$ ,  $g_d$ ,  $g_s$  and  $g_r$ , see text.

pulses (encoding gradient  $g_e$  and decoding gradient  $g_d$ ). The coherence-selective and read pulse strengths ( $g_s$  and  $g_r$ , respectively) are chosen according to the desired quantum order and fixed. The interval  $\tau$  is set to  $1/(2^1 J_{SI})$ ; this delay period is too short for significant homonuclear  $J$  precession to occur.<sup>125</sup>

This pulse sequence was used in the diffusion coefficient measurements in studies of D,L-alanine.<sup>126</sup>

Most diffusion coefficient measurement techniques<sup>127</sup> are comparatively time-consuming because they include either a series of NMR experiments or a 2D DOSY (Diffusion-Order Spectroscopy) experiment. A 1D DOSY method<sup>128</sup> for the determination of diffusion coefficients in a single experiment (scan) involves spatial variation of the parameters of a conventional STE (Stimulated Echo) pulse sequence<sup>78</sup> in such a manner that all the scans necessary for the determination of diffusion coefficient could be performed simultaneously in different regions of the sample. The spectrum is recorded in the presence of a weak read gradient and therefore the lineshape contains the necessary information. For well-resolved spectra with high signal-to-noise ratio the method allows the duration of the experiment to be shortened by an order of magnitude (to 1 s), which is important in studies of those samples whose state rapidly changes with time.

Diffusion, relaxation and the spin–spin coupling precession directly affect the accuracy of measurements of coefficients. The larger the  $\Delta$  value, the smaller the gradient strength or duration; however, signal attenuation due to transverse relaxation  $\exp(-\Delta/T_2^*)$  leads to a decrease in the signal-to-noise ratio. To compensate for the loss of sensitivity, it is necessary to obtain a larger number of spectra, which increases the duration of the experiment.

Thus, methods based on the MAXY sequence can be successfully implemented on spectrometers with low gradient strength and low magnetic field for measuring small diffusion coefficients (in macromolecules and molecular ensembles). Signal attenuation due to self-diffusion can be observed simultaneously for all coherences using 2D NMR spectroscopy or for a certain coherence using magnetic field gradient pulses. In the case of systems with natural abundance of  $^{13}\text{C}$  the sensitivity of such methods is

low. However, they can be suitable for measuring the diffusion coefficients of  $^{13}\text{C}$ -labelled molecules in complex mixtures such as biological fluids or cell extracts.

Now consider again Eqn (11). If the condition  $g_0^2 \tau^3 \ll g^2 \delta^2 \Delta$  is not met, the effect of the steady gradient must be accounted for. There are two factors that have a negative effect on the accuracy of measurements; these are the steady gradient and thermal convection. The steady gradient is due to inhomogeneity of the static magnetic field in the sample, which can be eliminated using the spin echo technique.<sup>88–90</sup> This approach is widely used in transverse relaxation time measurements. Thermal convection particularly manifests itself if experiments are carried out at high temperatures.

To obtain reliable values of metabolite diffusion coefficients in biological fluids, the diffusion coefficients must be measured at physiological temperature.<sup>80,81</sup> Since in most NMR spectrometers the temperature is maintained with an upstream gas (nitrogen or air) flow, a temperature gradient is created in the sample, which is responsible for the onset of convection flow. In addition, time-dependent temperature gradients are created when the gradient pulses are switched on and off.

Problems associated with convection were analysed by Carr and Purcell<sup>91</sup> in the early studies of the spin echo effect and diffusion. In the multiple spin-echo gradient experiments carried out in the presence of convection flows the amplitudes of the even echo signals are larger than those of the odd signals. This is due to the fact that the effect of thermal convection during the odd echo is compensated for during the even echo. Therefore, the simplest method is to measure only the even echo signals. This approach was implemented in the PFG–STE method and its versions involving doubling of the pulse sequence.<sup>93,94</sup> It should be noted that the diffusion gradients in the PFG–STE pulse sequence and its versions, such as LED, act for coherence selection, as in gradient enhanced NMR spectroscopy.

The use of coherence-selective gradients causes the sensitivity of the method to be halved. Doubling the STE and LED sequences again halves the sensitivity so it totally decreases by a factor of four. This is equivalent to shortening of the transverse relaxation

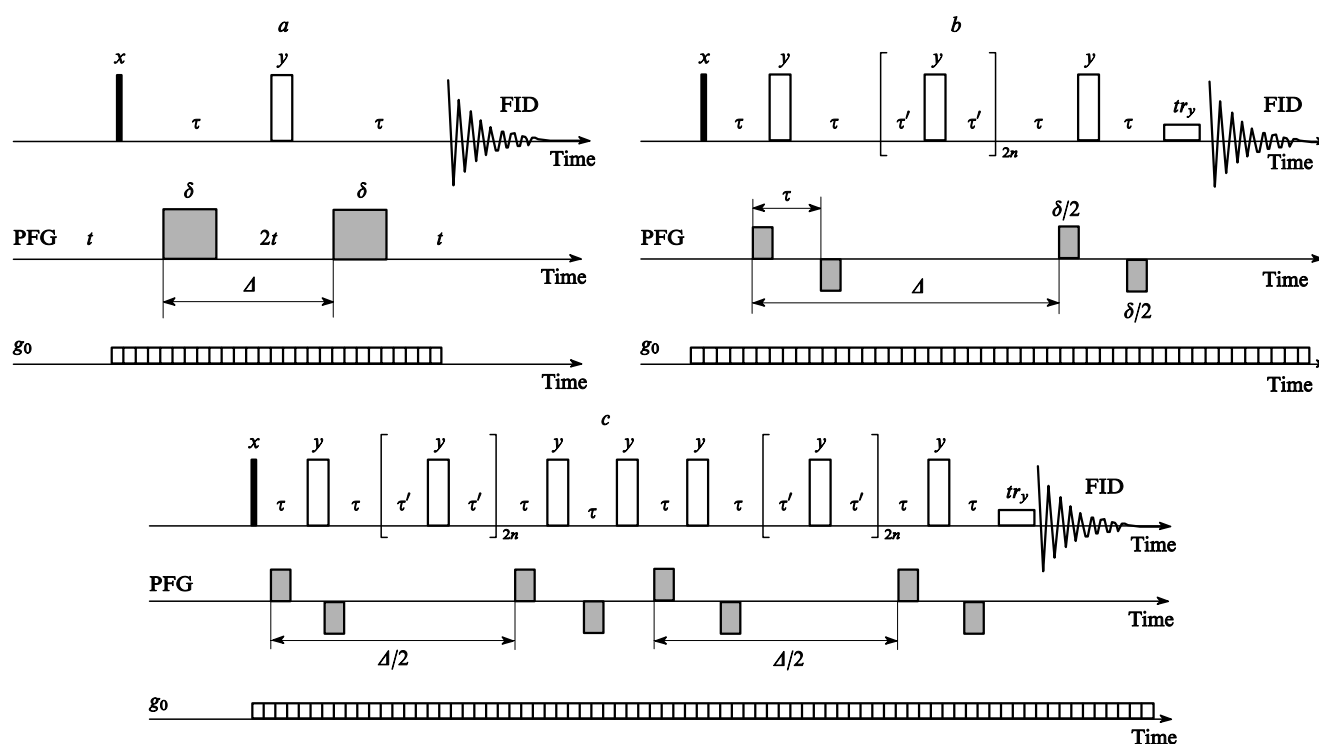


**Figure 14.** The RF pulse sequences and the PFG sequences used in the spin-echo (SE) methods for diffusion coefficient measurements (a), MSE (Multiple Spin Echo) (b) and DMSE (c).

time by a factor of  $1.4 T_2$ . The  $T_2$  times of metabolite spins in biological fluids lie between a few hundreds of milliseconds and a few seconds; therefore, one can expect that a compensation technique based on the double PFG–SE sequence for diffusion times shorter than  $T_2$  will be more sensitive than the coherence transfer method.

In the Carr–Purcell–Meiboom–Gill (CPMG) method<sup>97,98</sup> the spin echo is used for  $T_2$  measurements at a spin stabilisation time of up to a few seconds under conditions of minimum phase distortions. Using this technique, it is possible to obtain a homogeneous static magnetic field (steady gradients) and compensate for artifacts that appear due to distortions of the  $180^\circ$  pulses. Based on the CPMG sequence, a pulse sequence was created for measuring diffusion coefficients in the presence of steady gradients and thermal convection (Fig. 14*a*). Bipolar pulses were used instead of the gradient pulse (Fig. 14*b*). In addition, a multiple spin-echo pulse sequence was implemented instead of a single  $180^\circ$  pulse, which permits operation with long diffusion times. The last pulse before data acquisition removes the dispersion component from the detected signal. This pulse scheme is doubled and therefore was named DMSE (Double Magnetic Spin Echo, Fig. 14*c*). To ensure bipolar gradient pulses, a  $180^\circ$  pulse is incorporated in the middle of the sequence. Theoretical description and the results of tests with human blood plasma and human seminal fluid were reported recently.<sup>123</sup> The results were compared with the data obtained using the BP–LED (Bipolarisation LED)<sup>100</sup> and MSE methods. The temperature dependence of diffusion coefficients obtained using these three pulse sequences are shown in Fig. 15.

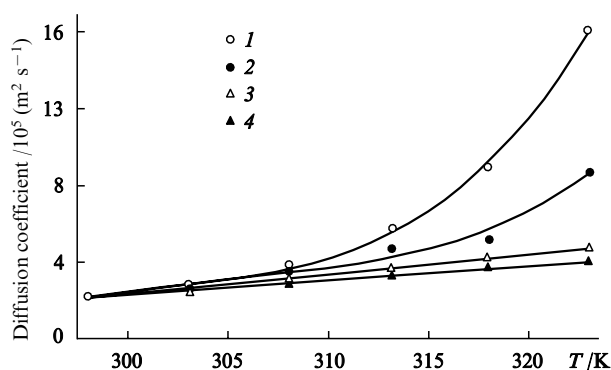


**Figure 15.** Temperature dependence of water diffusion coefficients measured using the BP–LED (1), MSE (2), DMSE (3) and other (4) methods in the range 298.2–323.2 K.

The DMSE technique permits efficient suppression of thermal convection,<sup>123</sup> being unaffected by the steady gradients. Incorporation of the CPMG sequence into the DMSE sequence allows one to operate with long diffusion times and suppress broad NMR peaks with short transverse relaxation time  $T_2$ . This possibility of spectral editing makes the DMSE technique suitable for studying the molecular mobility in complex systems. Among the other advantages of this method are good lineshapes and base line and efficient suppression of water signals.

## VI. Observation of ‘underwater’ signals. RECUR NMR technique

Efficient suppression of water signals is of crucial importance in NMR spectroscopy of complex systems.<sup>58</sup> The main efficiency criteria are as follows:

- high degree of suppression of the water peak, which is five to six orders of magnitude more intense than the peaks of the molecules under study,
- high selectivity to the signals appearing near the water peak

and

- short duration of the solvent signal suppression sequence in order to minimise the magnetisation transfer to the exchanging protons.

Among the methods designed to meet these criteria, the WET (Water Eliminated Transfer)<sup>129</sup> and WATERGATE (Water Gate)<sup>130</sup> techniques can be pointed out. The best, with respect to all criteria, is the modified WATERGATE method.<sup>131</sup> However, these schemes have a common drawback consisting of suppression of ‘underwater’ peaks.

Attempts at solving this problem in studies of macromolecules included taking into account the longitudinal relaxation time ( $T_1$ ) difference between water and the macromolecule. This means that by choosing an appropriate recovery time, which follows the inversion scheme, it is possible to observe the signals of macromolecules.<sup>132</sup>  $T_1$ -Editing was performed using the heteronuclear multiple quantum coherence (HMQC) method modified by incorporating magnetic field gradients.<sup>133</sup> The approach is efficient in natural abundance  $^{13}\text{C}$  or  $^{15}\text{N}$  studies. If the repetition time of experiments is short, the water signal can be partly suppressed owing to longer relaxation time compared to the relaxation times of the macromolecule. HMQC, HSQC (Heteronuclear Single Quantum Coherence) and magnetic field gradient experiments give satisfactory results and there is no need for further suppression of water signals. However, a long pre-delay time is required in studies of small molecules and therefore both water signals and  $^{12}\text{CH}$  signals must be additionally suppressed using the Bilinear Rotation Decoupling (BIRD) sequence. One can also use diffusion filtering for attenuation of the signals of diffusing water as in, e.g., the DRYCLEAN (Dry Clean) technique.<sup>134</sup> However, these approaches are inapplicable in studies of small metabolite molecules in biological fluids due to similar  $T_1$  values and diffusion coefficients for the molecules in question and water protons.

A number of methods based on the relaxation time  $T_2$  differences between water signals and signals of the molecules under study are also used. They are particularly efficient if the relaxation time  $T_2$  of the water signal can be reduced by, e.g., adding paramagnetic impurities.<sup>135</sup>

Some techniques were designed in order to avoid difficulties that appear when the desired signal of proton A is masked by other proton signals and thus cannot be selectively excited. The key feature of these methods is selective excitation of the second proton B coupled to the desired proton A. The magnetisation is transferred from B and A using the COSY or TOCSY sequence and the second selective pulse excites the proton A (e.g., NOE or ROE, or Rotating-frame Overhauser Effect). Using appropriate magnetic field gradient pulses, it is possible to eliminate undesired coherences in this scheme. Such methods<sup>136–140</sup> were named gs-1D CONO (COSY–NOESY), gs-1D TONO (TOCSY–NOESY) and gs-1D TORO [TOCSY–ROESY (Rotating-frame Overhauser Effect Spectroscopy)]. There are also the gs-1D ROTO and gs-1D RORO techniques which begin with the ROESY transfer. However, one should keep in mind that if a pulse sequence includes a number of selective pulses, long duration of these pulses can complicate experiments owing to long relaxation of useful signal.

A method of ‘underwater’ signal recovery using magnetisation transferred NMR spectroscopy, named RECUR NMR (Recovery of ‘Underwater’ Resonances NMR), was proposed.<sup>138</sup> The technique is based on a modified WATERGATE suppression scheme followed by magnetisation transfer. This method offers considerable advantages over other techniques.<sup>136,139</sup> Water signal suppression occurs involving a double WATERGATE sequence with a five-lobe composite pulse (W5), as shown in Fig. 16*a*.

The ‘underwater’ signals can be recovered using both the TOCSY and ROESY sequences which execute magnetisation back-transfer to the ‘underwater’ signals using scalar or dipole–dipole couplings, respectively, in 1D RECUR–TOCSY experiments (Fig. 16*b*). It should be noted that both coherence transfer

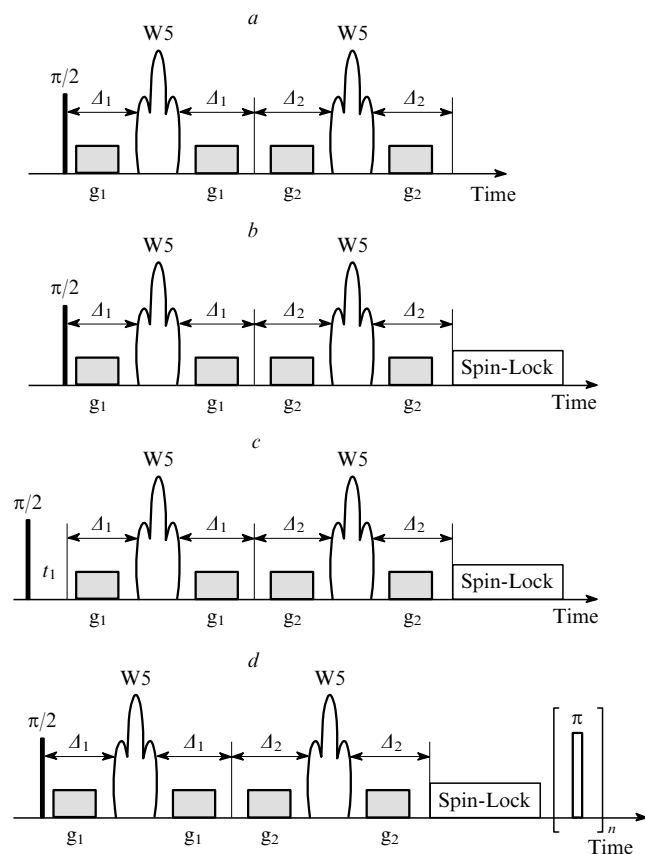


**Figure 16.** Conventional WATERGATE-W5 two-pulse sequence (a), 1D RECUR-TOCSY pulse sequence (b) and 2D RECUR-ROESY pulse sequence (c) containing the MLEV-17 spin stabilisation pulse sequence or a long pulse to create a TOCSY or ROESY type magnetisation transfer for recovery of 'underwater' signals; the RECUR-JRES and RECUR-CPMG pulse sequences (d).

schemes lead to in-phase magnetisation. This makes it possible to measure the ROE buildup rate in 1D NMR experiments using the pulse sequence shown in Fig. 16b or in 2D NMR experiments (Fig. 16c). By incorporating the CPMG sequence before the data acquisition step (see Fig. 16d, RECUR-CPMG) one can measure the transverse relaxation times of any underwater resonance. If a single spin echo technique is employed instead of this scheme, the pulse sequence can be implemented in  $^1\text{H}$ - $^1\text{H}$  homonuclear JRES NMR spectroscopy (RECUR-JRES).

The pulse sequence shown in Fig. 16c differs from the WATERGATE-TOCSY and WATERGATE-ROESY<sup>136,139</sup> sequences, in which the WATERGATE module follows the magnetisation transfer scheme. These methods involve suppression of 'underwater' signals and permit 2D NMR spectroscopy studies of macromolecules. But they cannot be implemented in 1D NMR spectroscopy experiments and prevent the ROE buildup rate or  $T_2$  of the 'underwater' signals from being measured.

The RECUR method was tested<sup>138</sup> using a 4 : 1 model mixture of D-glucose (20 mg ml<sup>-1</sup>) and D-galactose (5 mg ml<sup>-1</sup>) in 1 : 1 H<sub>2</sub>O-D<sub>2</sub>O solution. NMR spectra with and without water signal suppression, obtained using the double WATERGATE sequence, are shown in Fig. 17a,b. After TOCSY (Fig. 17c) or ROESY (Fig. 17d) magnetisation transfer with mixing times of 80 ms and 1.5 s, respectively, the 'underwater' signals are completely recovered. TOCSY magnetisation transfer occurs more efficiently. However, in the absence or in the presence of a weak spin-spin coupling the RECUR-ROESY method is optimum.

At a sufficiently high concentration of the substance under study, NMR resonances of individual CH<sub>n</sub> groups (e.g. CH<sub>3</sub>) can be recovered using the MAXY sequence.<sup>43,44</sup> The proton

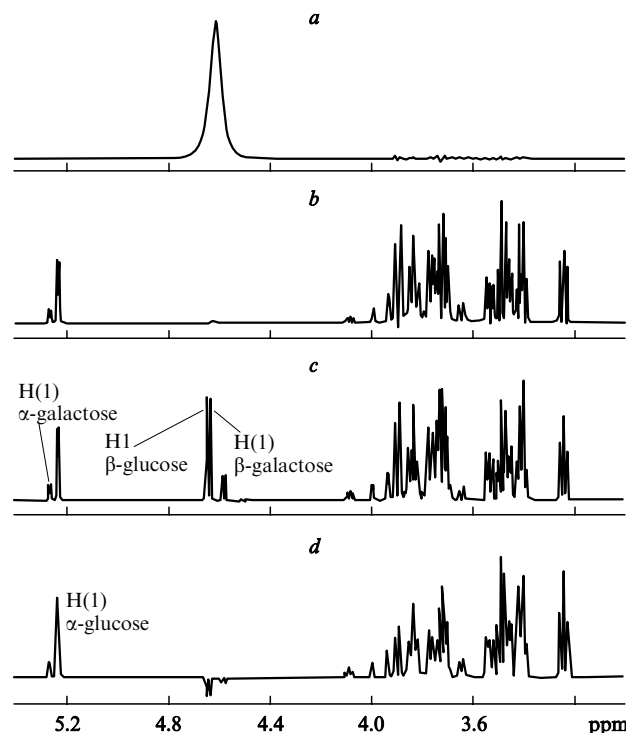


**Figure 17.** 1D NMR spectra of D-glucose and D-galactose obtained without (a) and with (b) water signal suppression using the WATERGATE double pulse sequence.

H(1) proton 'underwater' signals completely recovered using the RECUR-TOCSY (c) and RECUR-ROESY (d) methods.

spin-spin relaxation times obtained using the RECUR-CPMG sequence are as follows:<sup>138</sup>

| Compound | β-Glucose | β-Galactose | α-Glucose | α-Galactose |
|----------|-----------|-------------|-----------|-------------|
| Time/s   | 1.1       | 1.5         | 1.3       | 1.3         |

The 2D RECUR-ROESY NMR technique was used in studies of a human blood plasma sample to determine the internuclear distance in the glucose molecule.<sup>138</sup>

The RECUR-TOCSY and ROESY methods can also be used for spectral editing. For instance, at a spin stabilisation time of 70 ms it is possible to observe signals of the most flexible structural fragments of lipoproteins. Extension of this time to 700 ms causes an appreciable weakening of these signals while the signals from small metabolite molecules become less suppressed owing to comparatively longer relaxation times. When analysing 2D JRES NMR spectra, this approach allows visualisation of all peaks from small molecules, including the 'underwater' signals. The TOCSY or ROESY techniques allow the  $T_2$ , internuclear ROE and ROE buildup rate to be measured, which is important in molecular structure and dynamics studies.

## VII. Homonuclear selective methods

### 1. Selective COSY experiments

Combining selective and conventional 'hard' pulses in a single experiment permits design of a new approach, which can conveniently be exemplified by the COSY sequence.<sup>141-143</sup>

The pulse sequence shown in Fig. 18 was used in the study of brucine (Fig. 19). The coherence diagram shows that the selective 90° pulse creates coherences  $I^+$  and  $I^-$ . The antiphase magnetisation,  $2I_{H1}I_{H2z}$ , of proton 2 coupled to the first excited proton  $I_{H1}$  evolves during the d2 delay time equal to  $(1/2)J(\text{H,H})$ . Then, a 'hard' 90° pulse p2 converts it to  $2I_{H1z}I_{H2y}$ . Thus, in the data acquisition step the phase magnetisations of all the brucine protons (see Fig. 19) coupled to the selectively excited proton

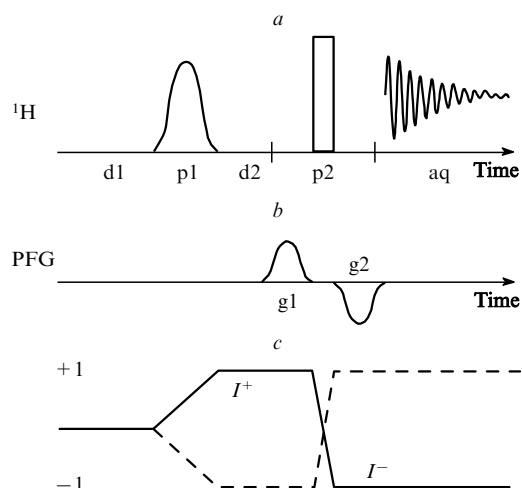


**Figure 18.** The RF pulse sequence (a), PFG sequence (b) and coherence pathway (c) in the selective gs-COSY experiment.<sup>144</sup> Transition of the spin system from a lower to a higher energy level is denoted by '+1' and the reverse transition is denoted by '-1'.

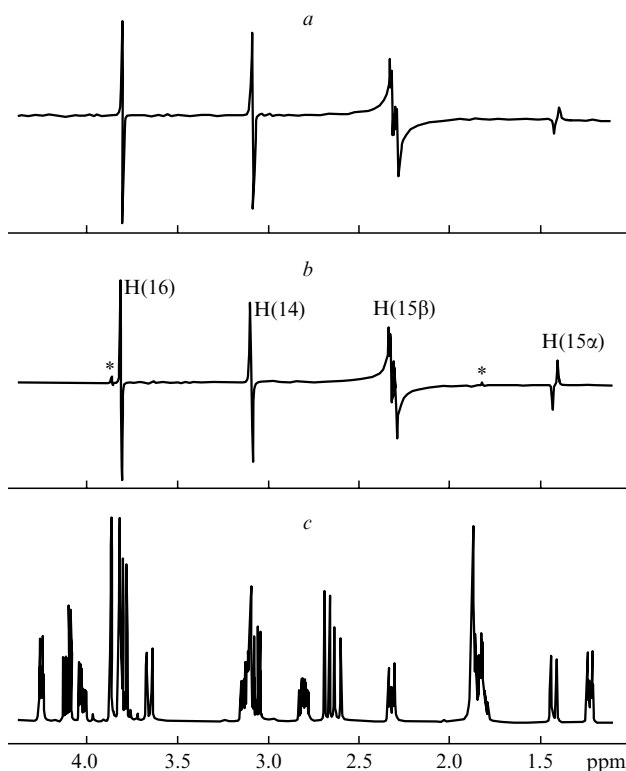


**Figure 19.** Brucine spectra obtained using the selective COSY sequence.<sup>16</sup> Selective excitation of H(14) (a), selective excitation of H(15 $\beta$ ) (b) (residual artifacts are asterisked) and conventional selective COSY spectrum (c).

evolve and can be recorded. In contrast to a conventional 2D COSY experiment, selective COSY experiments allow the NMR spectrum to be recorded rather accurately, because by applying a selective pulse only one row in the COSY matrix is measured. A 'hard'  $90^\circ$  pulse creates a transverse magnetisation of all nuclei; therefore, their signals can be suppressed using a phase cycling scheme with a minimum number of steps (two). In particular, this concerns strong signals, *e.g.*, those of methyl or methoxyl groups, which precludes analysis of multiplet signals. The problem can be solved in the PFG experiments. Application

of the gradient g1 causes dephasing of all coherences  $I^+$  and  $I^-$ . A 'hard'  $90^\circ$  pulse acts on the  $I^+$  and  $I^-$  coherences as follows:

$$I^+ \xrightarrow{90^\circ I} \frac{1}{2}(I^+ + I^-) + iI_z,$$

$$I^- \xrightarrow{90^\circ I} \frac{1}{2}(I^+ + I^-) - iI_z.$$

Here  $I^-$  is the observable coherence. It must be phase shifted by the negative gradient applied after the 'hard' pulse that can give rise to random artifacts in the 1D COSY spectrum. Signals created by the 'hard' pulse will be completely dephased by the second gradient.

It should be noted that gradients follow the upper trajectory (signals from the lower trajectory never reach the receiver). Therefore, gradient experiments with the same number of scans can be accompanied by a twofold decrease in signal intensity. When carrying out experiments on modern spectrometers, this is not an unsolvable problem because of rather high proton sensitivity in studies of conventional organic compounds. Another drawback of this pulse sequence is the use of a finite-duration gradient immediately before data acquisition, which leads to a large phase coefficient. The drawback can be overcome in two ways, (i) using a linear back-prediction proposed by Bernstein and Trimble<sup>141</sup> and (ii) by incorporating the gradient pulse into the data acquisition interval. In selective COSY experiments, an individual multiplet structure is usually of greater interest than a complete 1D NMR spectrum; therefore, it is more appropriate to adjust the phase of each multiplet individually.

## 2. Selective TOCSY method

Another selective excitation technique was proposed<sup>143</sup> for selective TOCSY experiments (Fig. 20). Initially, all protons are excited by a 'hard'  $90^\circ$  pulse and then dephased after the gradient pulse g1. Then, a selective RF  $180^\circ$  pulse changes the coherence order of the desired proton and the subsequently applied gradients g2 and g3 cause rephasing. A practical advantage of this method is that the selective  $180^\circ$  pulse can be calibrated much more easily than the selective  $90^\circ$  pulse. Moreover, it can be shown that the phase of the selective  $180^\circ$  pulses relative to the phase of the 'hard' pulses is of no significance. This allows the use of selective pulses

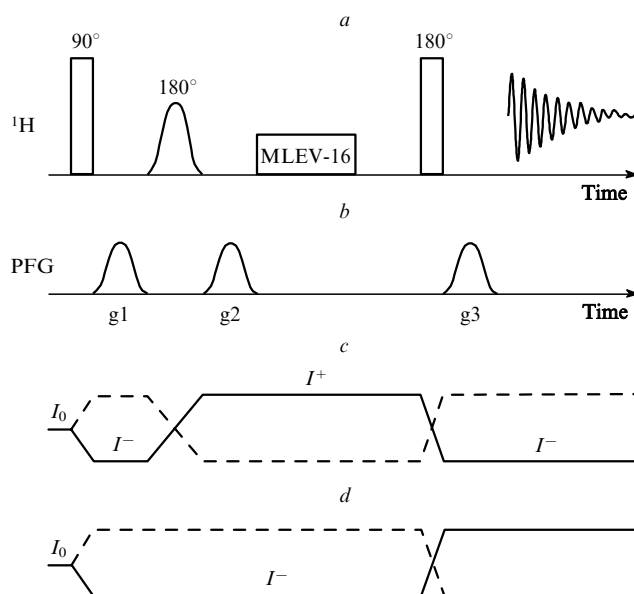


**Figure 20.** RF pulse sequence (a), PFG sequence (b) and the selective-pulse excited (c) and non-excited (d) coherence pathways in the gs-SELTOCSY (Selective TOCSY) experiments.

for which the carrier frequency is chosen to be slightly different from the basic frequency. Therefore, only one frequency can be used when changing the frequency range of the spectral window and all the protons under study. The second gradient is followed by the MLEV-16 spin stabilising scheme, which serves for retention of coherence order. The last gradient is rephased by applying a 'delay – 180° pulse – tailored gradient pulses' sequence. However, these methods are inappropriate for solving problems arising due to the mixing of the antiphase components within the same multiplet. As a consequence, a correct determination of the spin – spin coupling constants is complicated.

### 3. Double PFG echo spectroscopy

A number of methods use selective pulses and gradients for filtering unwanted magnetisations rather than excitation of particular signals. For instance, the WATERGATE technique<sup>144</sup> employs the pulse sequence shown in Fig. 21.

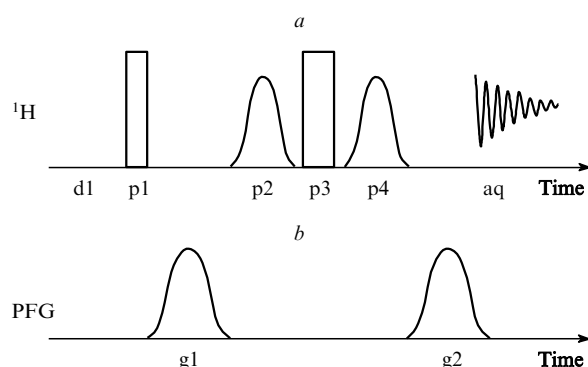


**Figure 21.** The RF pulse sequence (a) and PFG sequence (b) for the WATERGATE technique of water signal suppression.

To suppress an unwanted signal (often, water signal), two PFGs are applied along with a 'hard' 180° pulse (p3) and a selective 180° pulse. The last pulse is often composed of two 90° pulses, p2 and p4. Therefore the water resonance is affected by the effective 360° pulse, while all other signals are excited by the 180° pulse only, thus being influenced by two gradients of the same sign. A few versions of this method use a binomial sequence instead of selective pulses. The WATERGATE strategy was employed in some techniques known as PHOGSY (Pulse Heteronuclear Gradient Spectroscopy). They permit detection of bound water molecules in proteins.<sup>145–148</sup>

Hwang and Shaka<sup>16</sup> showed that the use of the double pulse sequence shown in Fig. 21 improves both suppression and the phase mode; however, the 'cost' of such improvements is a decrease in the total magnetisation relaxation during the action time of two identical sets of gradient pulses.

The pulse sequence shown in Fig. 21 can be used for improving other pulsed methods. Some of them appeared to be fruitful for organic chemistry, *e.g.*, difference NOE spectroscopy. Gradient Overhauser effect spectroscopy (GOESY)<sup>149</sup> appeared to be a major improvement over the double pulse field gradient spin echo (DPFGSE) technique.

If the inversion rate of a molecule is such that the NOE effects become insignificant or vanish, rotating-frame experiments are usually carried out, with spins blocked by a weak RF-field. There are a number of selective methods, which also employ a spin blockade, *e.g.*, Gradient Rotation Overhauser Effect Spectroscopy (GROESY).<sup>150</sup> This approach is similar to the 1D TOCSY method; however, here the spin blockade is much weaker. Such sequences are included in the selective retranslated COSY scheme.<sup>150–156</sup>

### 4. NMR studies of C – C coupling

INADEQUATE (Incredible Natural Abundance Double Quantum Transfer Experiment) type methods are used in studies of C – C spin – spin couplings, spin system connectivities and for molecular structure analysis (in the case of long-range couplings). 2D INADEQUATE experiments are a source of valuable information in studies of organic compounds.<sup>157</sup> In practice, experimenters often have very small amounts of compounds under study. To obtain correct results in 2D INADEQUATE experiments, the resulting <sup>13</sup>C NMR spectrum must exhibit a signal-to-noise ratio of at least 30 : 1 after a single 90° pulse. The selective 1D INADEQUATE method is called SELINQUATE (Selective INADEQUATE);<sup>158</sup> it can be implemented with ease because only one row in the 2D matrix is to be measured when using a carbon-selective pulse. However, the major problem in this method is suppression of false signals from the molecules having only one <sup>13</sup>C atom. The spin – spin coupling constant <sup>1</sup>J(C,C) is of the order of 40 Hz and corresponding signals can be detected with ease even if the main signal is incompletely suppressed. This is insignificant if the SELINQUATE technique is used to determine the spin system connectivity, but is of crucial importance if the method is used for measuring the <sup>2</sup>J or <sup>3</sup>J constants.

The use of magnetic field gradient pulse sequences permits improvement of the INADEQUATE technique. Willker and Leibfritz<sup>142</sup> first demonstrated the principle used in the H,H-COSY experiments with labelled <sup>13</sup>C atoms. In this case the double-quantum filter is not employed because it nearly halves the sensitivity. The method was called GRECCO (Gradient Enhanced Measurement of Carbon Coupling);<sup>159</sup> the corresponding pulse sequence is shown in Fig. 22.

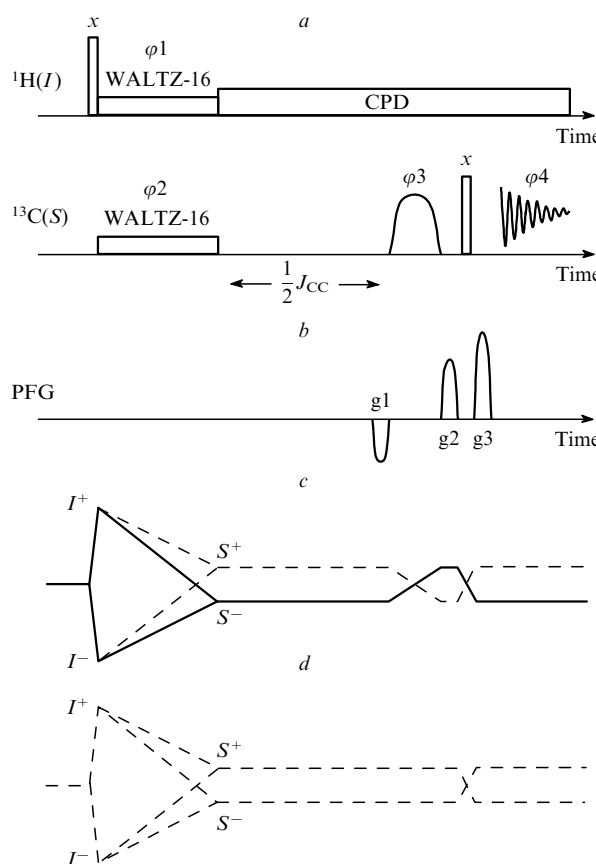


**Figure 22.** RF pulse sequence (a), PFG sequence (b) and the selective (c) and non-selective (d) coherence pathways in the GRECCO method. WALTZ-16 is the decoupling sequence and CPD stands for Cross Polarisation Decoupling.

The most important problem is to reduce the cross-polarisation (CP) to the desired carbon atoms. Selective inversion of coherence pathways is achieved using a Gaussian selective  $180^\circ$  pulse. The evolution period of duration  $(1/2)J_{CC}$  (typically, 83 ms) is followed by a Gaussian  $180^\circ$  pulse of duration lying between 10 and 50 ms. A 'hard'  $90^\circ$  ( $^{13}\text{C}$ ) pulse transfers the magnetisation between coupled spins. The gradient ratio  $g1:g2:g3$  serves to select the magnetisations inverted by the Gaussian pulse. The corresponding coherence pathway is shown in Fig. 22c. The coherence pathway given in Fig. 22d is valid for the remaining carbon coherences; it changes under the action of three gradients. The three-gradient set provides a complete suppression. This combination of semiselective CP method and the frequency selective coherence pathway selection under the action of the  $180^\circ$  pulse is used to achieve selective polarisation from proton to carbon.

Weigelt and Otting<sup>160</sup> succeeded in suppressing all unwanted signals using PFG in proton detected INADEQUATE experiments.

An ADEQUATE (Astonishingly Sensitive Double Quantum Transfer Experiment) pulse sequence for observation of  $^{13}\text{C}$ – $^{13}\text{C}$  couplings in natural compounds has been introduced recently.<sup>161</sup> It permits observation of through-bond carbon–carbon couplings for up to six bonds (Fig. 23). The method provides a greater amount of information compared to, *e.g.*, the HMBC (Heteronuclear Multiple-Bond Correlation) method. Depending on the delay time, the HMBC technique allows through-bond correlations for 4–5 bonds to be observed; however, experiments with the most typical delay times of 50–80 ms make it possible to observe through-bond correlations only for 2–3 bonds. A salient feature of the ADEQUATE method is the use of adiabatic pulses with  $\omega_1$ -defocussing (distribution of the components of the spin–spin coupling constants over the first dimension). This permits analysis of the spectra obtained in the same way as in the HMBC method. Some versions of this technique were successfully used for exact measurement of  $^{13}\text{C}$ – $^{13}\text{C}$  spin–spin coupling constants (see Ref. 162) and determination of  $^{13}\text{C}$  signal multiplicities (see Ref. 163).

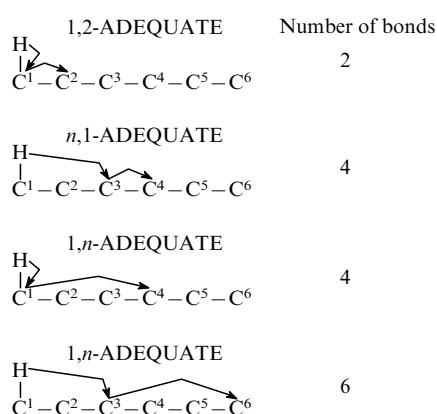


**Figure 23.** Scheme of correlations that can be obtained in different ADEQUATE experiments.

## VIII. Heteronuclear experiments

Probing carbon nuclei allows emergence of masked proton signals. Initially, a particular carbon atom is excited and then the magnetisation is transferred to a proton, which is accompanied by significant loss of the carbon magnetisation. In this case, the main problem also consists of suppression of signals of the protons coupled to  $^{13}\text{C}$ . Recently, numerous methods have been developed, which permit selective excitation of any proton through an

appropriate coupled carbon atom and subsequent transfer of the magnetisation from the proton to the  $^{13}\text{C}$  nucleus through scalar coupling.<sup>161–172</sup> The advantage of such methods is a high sensitivity.<sup>4</sup>

During excitation of a carbon atom under study the protons must be decoupled in order to ensure a single carbon signal and thus a high selectivity. To excite a chosen carbon atom, one must use a selective  $180^\circ$  pulse because it can be calibrated with ease and no phase coherence with other 'hard' carbon-selective pulses is needed.

Suppression of unwanted coherences and selective excitation of protons coupled to the chosen  $^{13}\text{C}$  atom is more efficient in the presence of PFG. To avoid relaxation losses, the pulse sequence must be as short as possible.

An HMQC-based SELINCOR (Selective Incredible Correlation) sequence<sup>161</sup> (Fig. 24) is probably the first sequence including carbon-selective excitation pulses. When using the conventional inverse-INEPT sequence, the magnetisation is back-transferred to protons and the rephasing gradient 'selects' the necessary pathway.

A conventional SELINCOR module appeared to be a universal tool in the spectroscopist's hands. More recent methods (COSY,<sup>170</sup> TOCSY,<sup>173</sup> NOESY<sup>174</sup> and ROESY) use a selectively excited proton in order to create the 1D and 2D NMR spectra of those signals that are uncoupled from other signals. Figure 25 presents a number of spectra reported by Parella *et al.*<sup>174</sup>

An interesting feature is manifestation of the NOE effect between chemically equivalent protons in, *e.g.*, symmetrical

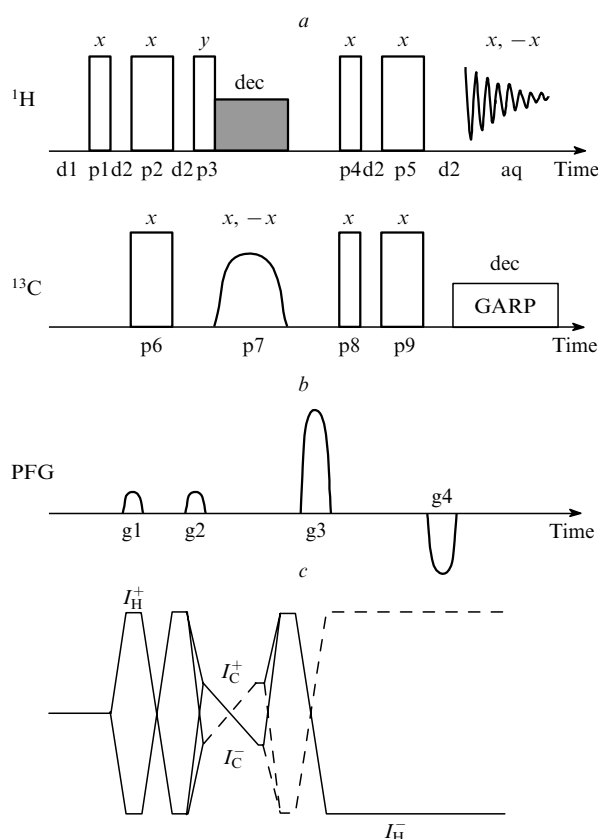


**Figure 24.** The RF pulse sequence (a), PFG sequence (b) and coherence pathway (c) in the gs-SELINCOR experiment.

The technique employs a  $180^\circ$  carbon selective pulse with a selected coherence pathway (solid line). d1 is the relaxation delay; p1, p3 and p4 are the  $90^\circ$  pulses; p2 and p5 are the  $180^\circ$  proton pulses; p6 and p9 are the  $180^\circ$  carbon pulses; p7 is the  $180^\circ$  carbon selective pulse; p8 is the  $180^\circ$  carbon pulse; g1–g4 are sinusoidal pulsed gradients; and dec is the decoupling.



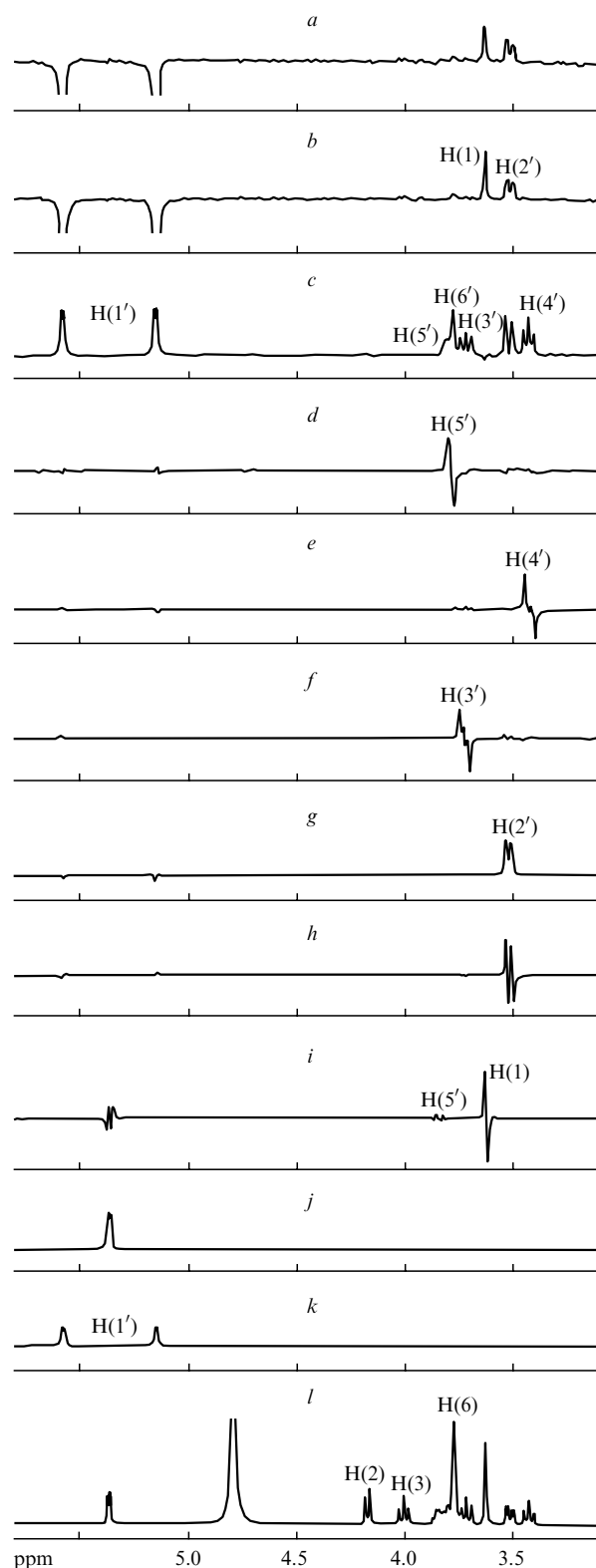


**Figure 25.**  $^1\text{H}$  NMR spectra of saccharose obtained using different versions of the gs-HSQC pulse sequence.<sup>174</sup> HSQC-ROESY (a), HSQC-NOESY (b), HSQC-TOCSY (c), HSQC+2 RELAY (d), HSQC+3 RELAY (e), HSQC+4 RELAY (f), HSQC-COSY+r+z (g) (r is refocussing, z is filtering), HSQC-COSY (h), HSQC-lr (i) (lr is long range), HSQC/D (j), HSQC/C (k), and HSQC (l). The furanose and pyranose ring hydrogens are labelled by the unprimed and primed figures, respectively.

molecules. The effect can be detected using the SELINCOR technique followed by NOE transfer. Two protons can be discriminated<sup>175</sup> by allowing one of them to couple with  $^{13}\text{C}$ . Pulsed field gradients can also be used provided that the spin-spin coupling constant is allowed. This permits measurement of proton-proton couplings when the proton signals are overlapped or masked by other signals.<sup>137</sup>

In addition to the methods shown in Fig. 25 there is yet another method of determination of the magnitude and sign of C-H coupling constants. The technique named  $\alpha/\beta$ -gs-SELINCOR-TOCSY<sup>176,177</sup> is a version of the approaches considered above.

The SELINCOR sequence can be modified with two 'soft' pulses. The first pulse excites a proton-decoupled carbon signal and the second one determines the spin state. The last ( $^1\text{H}$ ) pulse in the HSQC sequence creates multiple-quantum coherences ( $I^+S^+$ ,  $I^-S^+$ ,  $I^+S^-$  and  $I^-S^-$ ).

The method takes into account selective creation of the coherence of the protons coupled to a particular carbon atom (in the  $\alpha$ - or  $\beta$ -spin state). Then, the MLEV-16 composite pulse transfers this coherence from the protons to the carbon atom during the time interval between the second and third pulses of the TOCSY sequence. Proton coherence created using the  $\beta$ -gs-SELINCOR technique will be distributed over all protons belonging to the same coupled system. All proton signals are filtered and the separation between them is equal to the halved long-range H-C spin-spin coupling constant. Determination of this spin-spin coupling constant requires setting the time interval between corresponding signals.

Heteronuclear NOE effects can be useful in structural analysis of natural compounds. Traditionally, these effects are studied by either 2D HOESY spectroscopy or 1D NMR spectroscopy using selective irradiation of certain protons and measurement of the heteronuclear difference NOE spectrum. The use of magnetic field gradient pulses permits suppression of signals of the  $^{12}\text{C}$ -coupled protons to such a degree that weak heteronuclear NOE effects will be observed in proton detection. Besides, proton detection provides a sensitivity gain. The method based on the use of both selective RF pulses and PFG was introduced by Stott and Keeler<sup>178</sup> and named HETGOESY (Heteronuclear Gradient Overhauser Effect Spectroscopy). The main pulse sequence employed in this technique is shown in Fig. 26. The vitality of the technique was proved in studies of gibberellic acid. The

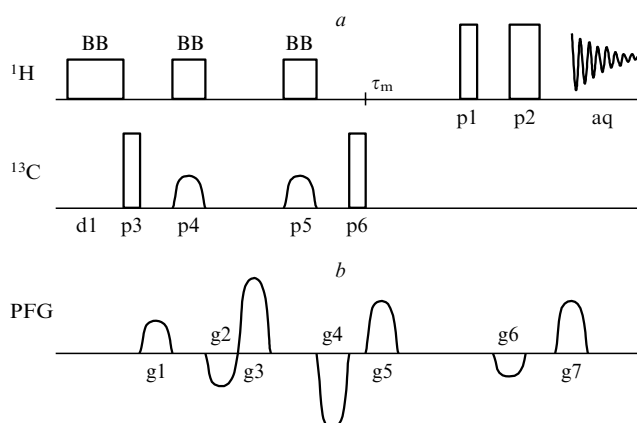


**Figure 26.** The RF pulse sequence (a) and PFG sequence (b) for NOE experiments with proton detection.<sup>171</sup>

BB is broadband decoupling; p1 and p2 are the  $90^\circ$  and  $180^\circ$  pulses, respectively; d1 is the relaxation delay; p3 and p6 are the  $90^\circ$   $^{13}\text{C}$ -pulses; p4 and p5 are the  $180^\circ$   $^{13}\text{C}$ -selective pulses; and g1-g7 are sinusoidal pulsed gradients.

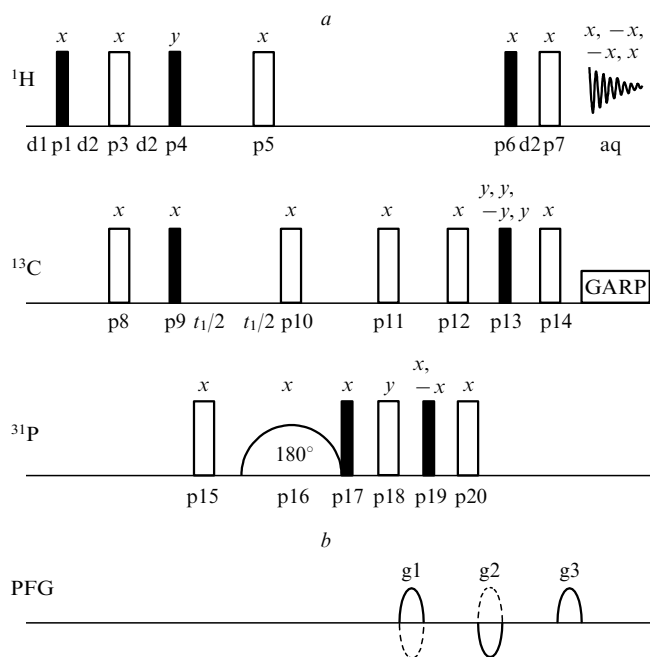


**Figure 27.** The RF pulse sequence (a) and PFG sequence (b) for gs-SELTRIP experiments.<sup>182</sup>

p16 is the 180° phosphorus selective pulse. The g1 and g2 gradients are applied in the echo–antiecho method.

approach provides a way of solving one of the most stubborn problems, namely, signal assignment of quaternary carbon atoms.

Often, the subjects of biochemical studies and investigations of organometallic compounds are molecules containing more than one atom (nucleus Y) in the heterocycle. Such molecules can be studied by 3D NMR spectroscopy using 3D <sup>1</sup>H NMR spectra and the <sup>13</sup>C and <sup>31</sup>P frequencies (see Refs 178–181). However, this technique is very time-consuming and offers a limited resolution. A selective triple resonance (SELTRIP) experiment<sup>181</sup> combines a 2D HSQC NMR technique and a selective 90° (Y) pulse in order to reduce the dimension of the problem to 2D. A modified version (gs-SELTRIP) of SELTRIP experiments is illustrated in Fig. 27.<sup>182</sup>

## IX. Two-dimensional correlation experiments based on heteronuclear *J*-cross-polarisation

Modern versions of the HSQC method<sup>183</sup> can be used in multi-dimensional NMR experiments based on the same principles. A widely used, improved HSQC–PEP (Pulse Enhancement Polarisation) scheme<sup>184</sup> offers the following advantages: (i) coherence selection by PFG; (ii) a maximum sensitivity and optimisable resolution obtained by combining the echo–antiecho and PEP techniques; (iii) efficient suppression of solvent signals, achieved either using PFG (solely) or water flip-back; (iv) wide use of various pairs of NMR active nuclei; (v) applicability to both natural abundance studies of natural compounds and investigations of labelled biomolecules; and (vi) flexibility in incorporating new modules into the pulse sequence.

Design of modified HSQC techniques for selective manipulation of the spin state  $\alpha$  and/or  $\beta$  has become a fruitful approach in multidimensional NMR spectroscopy. For instance, the well-known Exclusive Correlation Spectroscopy (E.COSY)<sup>185</sup> is widely used in the determination of homonuclear and heteronuclear spin–spin coupling constants in labelled biomolecules. To determine the sign and magnitude of very small spin–spin coupling constants, one has to measure the relative offset between cross-peaks corresponding to the spin states  $\alpha$  and/or  $\beta$  in the E.COSY spectra. Recently, numerous versions of the HSQC

method have been reported, which allow selection of only  $\alpha$  or only  $\beta$  spin state in individual 2D NMR spectra. A simple example is provided by HSQC- $\alpha/\beta$  experiments,<sup>186</sup> in which the second part of the retro-INEPT pulse sequence of a conventional HSQC–PEP experiment<sup>187</sup> is shortened to a single 90° pulse. This shortened module selects two different coherences, one in the form of an in-phase multiplet and the second in the form of an antiphase multiplet. Simultaneous addition or subtraction of this coherence before the data acquisition stage permits selection of the  $\alpha$ - or  $\beta$ -component, respectively, with retention of maximum sensitivity. This experiment allows one to obtain edited 2D correlation NMR spectra containing only one of the two multiplet signals. The spin state can be selected during the indirect evolution time; this is a coupled edited <sup>1</sup>H–X correlation NMR experiment named  $\alpha/\beta$ -HSQC (or IPAP experiment).<sup>188</sup> The major advantage of this method is that transverse relaxation during indirect X-measurement is not as critical as in the case of <sup>1</sup>H-measurement in studies of large biomolecules. Both approaches can be combined in a single  $\alpha/\beta$ -HSQC- $\alpha/\beta$  experiment, with the best example provided by the popular TROSY technique.<sup>189</sup> NMR experiments with editing are widely used for measuring scalar and residual dipolar coupling constants and specifying basic principles of modern NMR methods of structural and dynamics studies of large biomolecules in high-strength magnetic fields.

Correlation NMR experiments provide an attractive alternative to conventional HSQC experiments.<sup>190</sup> A feature of the pulse sequences proposed in that study is the use of heteronuclear cross-polarisation (HCP) for the magnetisation transfer from nucleus X to <sup>1</sup>H and/or from <sup>1</sup>H to X instead of a conventional INEPT sequence. The idea of using HCP in studies of isotropic fluids is not new. Relevant theoretical aspects have been documented (see, e.g., Refs 191 and 192), including applications to protein<sup>193</sup> and nucleic acid studies.<sup>194</sup> During the last decade, analogous NMR experiments (HMQC and HSQC) have been routine tools in studies of both small molecules and large labelled and unlabelled biomolecules.

Unlike free precession <sup>1</sup>H–X-correlation experiments, HCP-experiments are based on synchronous application of two magnetic fields to both nuclei, <sup>1</sup>H (spin *I*) and X (spin *S*), and on achievement of maximum heteronuclear coherence transfer provided that the so-called Hartmann–Hahn condition is met.<sup>195</sup>

According to theoretical predictions, the HCP-based experiments<sup>190</sup> must exhibit a maximum sensitivity due to selection and combination of two different magnetisations. The anisotropy of heteronuclear coherence transfer involving HCP mixing processes is demonstrated by strong dependence of the transfer mechanism on the relative phase between the input magnetisation and the HCP mixing sequence. A number of similar pulse schemes have been designed for simple and selective manipulation of various coherences available before and after the HCP mixing. Such schemes are characterised by high sensitivity, good stability to RF field inhomogeneities, better (compared to HSQC experiments) behaviour of the spin system in the relaxation and chemical exchange processes, versatility and possibility of being slightly modified.

The use of novel, optimised, ultrabroadband heteronuclear cross-polarisation sequences including improved multiple-pulse sequences or adiabatic pulses and HCP-based strategies presents an alternative to the most popular HSQC pulse schemes. In addition, various HCP modules can be incorporated into multi-dimensional NMR experiments as efficient preparation and mixing modules.

## X. Combined use of selective and non-selective excitation in NMR experiments

A method of studying molecular dynamics processes was proposed.<sup>196</sup> The technique involves excitation of a single nucleus in a coupled spin system using the Multiplet-Selective Excitation (MUSEX) pulse sequence.<sup>197</sup> The usefulness of the method

**Table 5.** Versions of the MUSEX COSY technique.<sup>196</sup>

| Version                   | Pulse sequence                                                                                                                                                         | 2D spectral pattern |
|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| NSP–SP(A)<br>MUSEX COSY   | $90_x^\circ - t_1 - 90_x^\circ(A) - t_2$                                                                                                                               |                     |
| SP(A)–NSP<br>MUSEX COSY   | $90_x^\circ(A) - t_1 - 90_x^\circ - t_2$<br>$\sigma_4^{\text{expl}} = I_{Ay} S_A^1 C_J^1 S_A^2 C_J^2 +$<br>$+ I_{By} S_A^1 S_J^1 S_B^2 S_J^2 - I_{By} C_B^2 C_J^2$     |                     |
| SP(A)–SP(A)<br>MUSEX COSY | $90_x^\circ(A) - t_1 - 90_x^\circ(A) - t_2$<br>$\sigma_4^{\text{expl}} = I_{Ay} C_A^1 S_J^1 C_A^2 S_J^2 +$<br>$+ I_{Ay} S_A^1 C_J^1 S_B^2 C_J^2$                       |                     |
| SP(A)–SP(B)<br>MUSEX COSY | $90_x^\circ(A) - t_1 - 90_x^\circ(B) - t_2$<br>$\sigma_4^{\text{expl}} = -I_{Ay} C_A^1 C_J^1 C_A^2 C_J^2 +$<br>$+ I_{Ay} S_A^1 C_J^1 S_B^2 C_J^2 - I_{By} C_B^2 C_J^2$ |                     |

**Note.** Here and in Table 6 we use the following notations: NSP is the non-selective pulse; SP(A(B)) is the selective pulse exciting the A or B nuclei, respectively;  $C_{A(B)}^{1(2),\tau} = \cos \Omega_{A(B)} t_{1(2)}$ ;  $C_J^{1(2),\tau} = \cos \pi J_{AB} t_{1(2)}$ ;  $S_{A(B)}^{1(2),\tau} = \sin \Omega_{A(B)} t_{1(2)}$ ;  $S_J^{1(2),\tau} = \sin \pi J_{AB} t_{1(2)}$ ; filled circles in the 2D spectral patterns denote positive intensity;  $t_1$  and  $t_2$  are variable time intervals, and  $\tau$  is a constant time interval.

consists of minimisation of information loss on the spin–spin coupling, which favours simplification of detection technique and signal assignment in spin systems. This requires experiments with combined selective and non-selective excitation.

Consider the behaviour of a weakly coupled AB spin system under the action of a two-pulse MUSEX COSY sequence.<sup>196</sup> The case of two non-selective pulses presents a well-known conventional COSY experiment.<sup>4,197</sup> It is of interest to consider all possible combinations of selective and non-selective pulses. Table 5 schematically depicts 2D NMR spectra with explicitly observable components.

NSP–SP(A) MUSEX COSY experiments allow the NMR spectral pattern to be simplified without loss of information on the spin–spin coupling (here,  $J$ -cross-peaks are absent because of selective excitation).

The SP(A)–SP(A) MUSEX COSY technique can be implemented in EXSY experiments used in chemical exchange studies.

The SP(A)–SP(B) MUSEX COSY method can be useful for obtaining information on the spin–spin coupling between any two spins in a multiple-spin system.

Non-selective NMR spectra often include a number of regions with overlapped multiplet signals, which leads to ambiguity in the interpretation of such spectra. A particular value of the approach<sup>196</sup> is the possibility of avoiding this ambiguity. MUSEX experiments allow the size of the data array to be reduced and the duration of experiments to be shortened. The techniques mentioned above are applicable to all types of 2D experiments. Table 6 lists all observable components for spin A and provides their schematic representation in the form of a 2D NMR spectrum for the three-pulse sequences containing a complete set of possible combinations of non-selective and multiplet-selective pulses. Excitation of spin B gives rise to an axial doublet in the NMR spectrum. A distinctive feature of the experiments consists of the use of alternating spin excitation (ALEX) using the MUSEX

**Table 6.** 2D subspectral patterns.<sup>196, 198</sup>

| Number | Pulse sequence                                                     | 2D spectral pattern |
|--------|--------------------------------------------------------------------|---------------------|
| 1      | $90_x^\circ(B) - t_1 - 90_x^\circ(A) - \tau - 90_x^\circ(A) - t_2$ |                     |
| 2      | $90_x^\circ(A) - t_1 - 90_x^\circ(A) - \tau - 90_x^\circ(B) - t_2$ |                     |
| 3      | $90_x^\circ(B) - t_1 - 90_x^\circ(B) - \tau - 90_x^\circ(A) - t_2$ |                     |

**Note.** Open circles in the 2D spectral patterns denote negative intensity.

sequence. All calculations were carried out using the operator product formalism, as in the MUSEX COSY method.

The pulse sequences 1 and 2 allow visualisation of each coupling in a multiplet system. The pulse sequence 1 can be used in a stepwise manner for identification of all coupled partners in a complex spin system, because the MUSEX COSY experiments allow all couplings to be followed simultaneously. The pulse sequence 2 is convenient for studying relaxation mechanisms. The resulting NMR spectrum (pulse sequence 3) exhibits a spin-A diagonal peak appearing as a result of interference of eight components, of which four components are single-quantum coherences and the remaining components were transferred from double-quantum and zero-quantum coherences. In this case the first two pulses represent the ALEX COSY technique and the last B-nucleus pulse is used as the detection pulse. With an appropriately adjusted phase, two resonance lines for the diagonal peaks can disappear, thus leaving only diagonal lines.

\* \* \*

At present, NMR spectroscopy offers a variety of methods which permit identification and investigation of the structure and dynamics of complex biomolecules and biosystems. Advantages in these studies are to a great extent due to both design of new hardware and the use of various selective methods. Combining radiofrequency pulses and magnetic field gradient pulses allowed a number of problems arising in the experiments with selective pulses (in particular, the problem of selection of desired coherences) to be solved. One can expect that some of these methods will become routine techniques in NMR spectroscopy of organic compounds, because often they give a fast and detailed answer to those questions that were unanswerable a few years ago.

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# 1,2,3-Triazole and its derivatives. Development of methods for the formation of the triazole ring

V P Krivopalov, O P Shkurko

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**Abstract.** Data on the synthetic routes to substituted 1,2,3-triazoles, including those containing functional groups, based on cyclisation of various nitrogen compounds published during the last 15 years are described. Examples of using new triazole derivatives in agrochemistry, medicine and engineering are given. The bibliography includes 583 references.

## I. Introduction

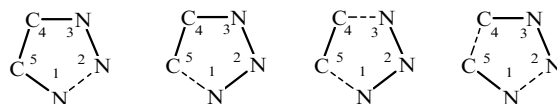
The 1,2,3-triazole (*v*-triazole) heterocyclic system has been known for more than one hundred years. The synthesis of the first representatives of these compounds was reported in the late 19th century by Pechmann;<sup>1</sup> during the subsequent decades, several routes to various substituted triazoles, including polyfunctional ones, have been developed. The results of synthetic studies have been reported in a number of publications, the most recent of which are reviews;<sup>2–19</sup> the structures, properties and chemical transformations of 1,2,3-triazole and its derivatives are considered in some sections of monographs.<sup>14, 20, 21</sup> In the last two decades, the chemistry of 1,2,3-triazoles has gained a new impetus to the development due to the discovery of diverse biological activities of many triazole derivatives. The number of patents dealing with the use of these derivatives as drugs and agrochemicals has grown. This has attracted the attention of researchers to the development of new and perfection of the known methods for the synthesis of triazole derivatives.

The triazole ring itself is relatively stable, which allows one to carry out various chemical modifications of substituents and functional groups. These modifications are usually carried out by standard synthetic methods, which are fully reflected in the monographs cited above. However, on treatment with strong bases or highly nucleophilic reagents (as well as on thermolysis and photolysis), the triazole ring can open to give reactive intermediates, which undergo diverse chemical transformations to yield new carbo- and heterocyclic structures.<sup>22</sup> These problems

are considered in a large number of publications from the last decade, for example, the works.<sup>23–37</sup>

This review covers the data dealing with the formation of the 1,2,3-triazole ring published mainly from 1986 to 2002.

The methods of formation of a heterocyclic system are usually considered in terms of the closure of particular bonds in pre-arranged structural blocks. Within the framework of this approach, the information on triazole synthesis can be classified into four sections dealing with the methods of formation of particular bonds of the triazole ring, namely, the N(1)–N(2), C(5)–N(1) [or C(4)–N(3)], C(5)–N(1) and C(4)–N(3) bonds; and the C(4)–C(5) and N(1)–N(2) bonds.



In some cases, researchers propose original methods for the synthesis of triazole systems. However, by considering the step-wise mechanisms of relevant reactions, one can often assign them formally to one of the above groups.

## II. Methods of formation of the N(1)–N(2) bond

### 1. Condensation of amines with $\alpha$ -diazocarbonyl compounds

A possible way of formation of a triazole ring is the reaction of amines with  $\alpha$ -diazodicarbonyl compounds, which proceeds through intermediate  $\alpha$ -diazoidimines. Since  $\alpha$ -diazoidimines are highly reactive, they readily cyclise into isomeric 1*H*-1,2,3-triazoles even during their synthesis. The diazo derivatives of 1,3-dicarbonyl or other compounds with an active methylene group can act as triazole precursors.<sup>38</sup>

The simplest derivative of  $\alpha$ -diazo- $\beta$ -oxoaldehydes, namely, the diazo derivative of malonodialdehyde, condenses with aniline hydrochloride to give 1-phenyltriazole-4-carbaldehyde in a high yield.<sup>39</sup> However, other  $\alpha$ -diazo- $\beta$ -oxoaldehydes have long been poorly accessible. It has been found recently<sup>40</sup> that 2-azido-1-ethylpyridinium tetrafluoroborate transfers the diazo group onto various  $\beta$ -oxoaldehydes **1** in the presence of bases with retention of the aldehyde function. These reactions underlay a general method for the synthesis of  $\alpha$ -diazo- $\beta$ -oxoaldehydes **2**, which were used to prepare 1-substituted 4-acyltriazoles **3**.<sup>41–45</sup> The diazomethyl ketone  $R^1C(O)CH=N_2$  impurity formed at the diazotisation stage did not influence the subsequent synthesis of acyltriazoles. Ammonia, aliphatic and aromatic amines, hydroxylamine and semicarbazide were involved in the condensation with  $\alpha$ -diazo- $\beta$ -

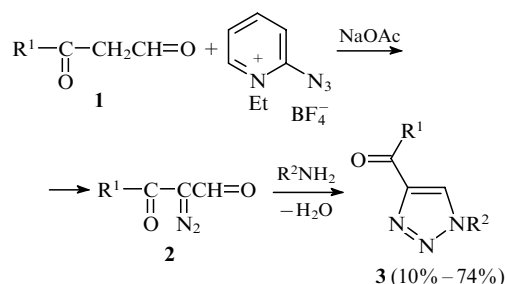
V P Krivopalov, O P Shkurko N N Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, prosp. Akad. Lavrent'eva 9, 630090 Novosibirsk, Russian Federation. Fax (7-3832) 30 97 52, tel. (7-3832) 30 96 64, e-mail: krivic@nioch.nsc.ru (V P Krivopalov), oshk@nioch.nsc.ru (O P Shkurko)

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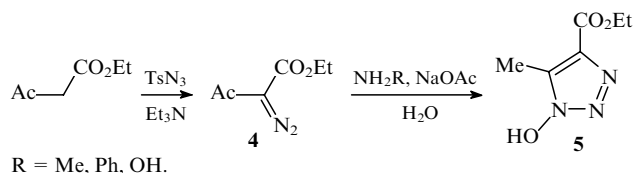


oxoaldehydes.<sup>41</sup> An advantage of this method is the formation of only one regioisomer, because condensation is directed at the more electrophilic formyl group rather than the acyl group. With hydroxylamine or semicarbazide, triazole oximes or semicarbazones **3** are formed in some cases



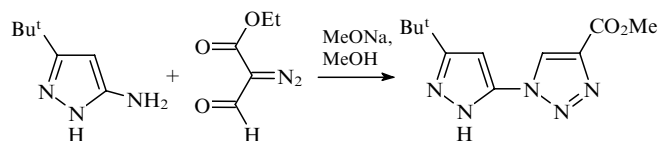
$R^1 = \text{Me, EtO, 2,4-Cl}_2\text{C}_6\text{H}_3, 2,4\text{-Br}_2\text{C}_6\text{H}_3$ ;  $R^2 = \text{H, Pr}^i, \text{Bu}^i, \text{Ph, 1-naphthyl (Naph), 4-ClC}_6\text{H}_4, 2,4\text{-Cl}_2\text{C}_6\text{H}_3, 3,4\text{-Cl}_2\text{C}_6\text{H}_3, 2,4\text{-Br}_2\text{C}_6\text{H}_3, 2,4,6\text{-Me}_3\text{C}_6\text{H}_2, \text{HO, EtO, NH}_2\text{CONH}$ .

When diazo  $\beta$ -oxoesters **4** react with hydroxylamine<sup>46</sup> or with aniline and methylamine,<sup>47</sup> the ester group is retained in the triazole **5** molecule.

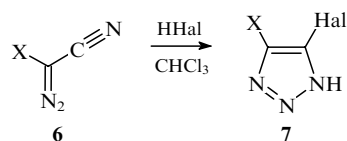


$R = \text{Me, Ph, OH}$ .

This method has also been used to prepare hetaryltriazoles, for example, methyl 1-(5-pyrazolyl)triazole-4-carboxylate.<sup>48</sup>



Carbonyl derivatives of  $\alpha$ -diazooacetonitrile **6** [ $X = \text{RC(O)}$ ] readily cyclise under the action of hydrogen halides to give 4-acyl-5-halotriazoles **7**,<sup>49</sup> the yields of which (45%–94%) depend on the nature of the halogen and the substituent. This method was used to prepare 5-chlorotriazole derivatives with amide, urethane,<sup>50</sup> and phosphoryl groups.<sup>51</sup>

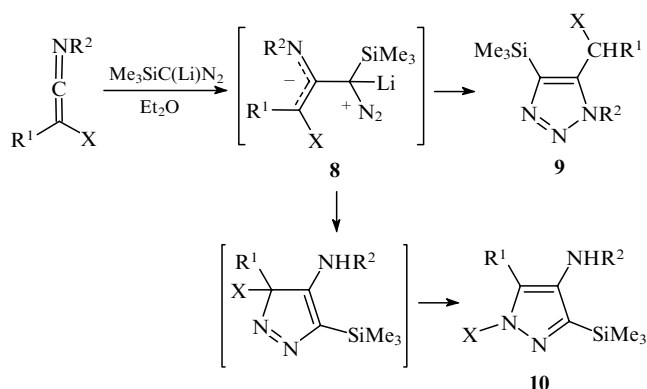


$X = \text{RC(O)}$ :  $\text{Hal} = \text{Cl, Br, I}$ ;  $R = \text{EtO, NH}_2, \text{MeNH, Ph}$ ;  
 $X = (\text{RO})_2\text{P(O)}$ :  $\text{Hal} = \text{Cl}$ ;  $R = \text{Me}$  (62%),  $\text{Et}$  (86%).

Detailed study of the reaction has shown that the scope of its application is limited to diazo compounds that have only  $\alpha$ -carbonyl or  $\alpha$ -phosphoryl groups.<sup>52</sup> The reaction mechanism formally includes two steps, in particular, the addition of hydrogen halide to  $\alpha$ -carbonyldiazonitrile to give intermediate  $\alpha$ -diazohalimine, which then undergoes a heteroelectrocyclic process yielding 5-halotriazole. In essence, cyclisation of  $\alpha$ -carbonyldiazonitriles can be considered as a series of tandem pseudopericyclic processes.<sup>52</sup>

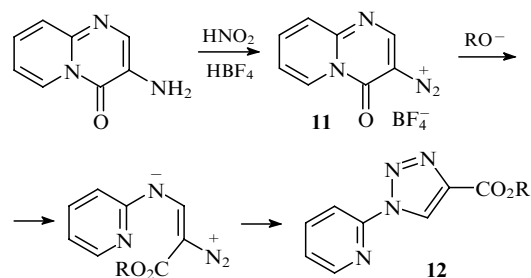
Triazoles can be obtained from  $\alpha$ -aminodiazocompounds if the molecule does not contain any other nucleophilic centres. For example, the cyclisation route of diazo(lithio)trimethylsilylmethane **8** depends on the nature of the substituent  $X$ : for  $X = \text{Alk}$  or  $\text{Ar}$ , the reaction gives 4-trimethylsilyltriazoles **9**, while in the

presence of electron-withdrawing substituents, 3-trimethylsilyltriazoles **10** are formed most often.<sup>53, 54</sup>



$R^1 = \text{Me, Ph}$ ;  $R^2 = \text{Et, Ph}$ ;  $X = \text{Alk, Ar, Ac, EtO}_2\text{C, NC, PhSO}_2, (\text{EtO})_2\text{PO}$ .

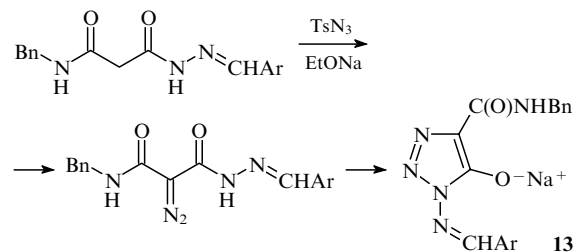
Recyclisation of 4-oxypyrido[*a*]pyrimidinyldiazonium **11** in the presence of alcoholates resulting in alkyl 1-(2-pyridyl)triazole-4-carboxylates **12** can be assigned to the same type of reaction.<sup>55</sup>



$R = \text{Me, Et, Pr}^n, \text{Bu}^n, n\text{-C}_5\text{H}_{11}$ .

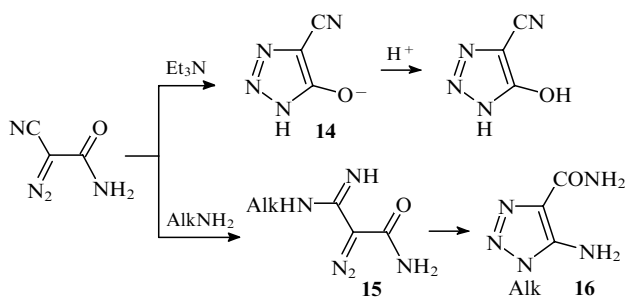
Similarly, 3-amino-4*H*-pyrimido[1,2-*b*]pyridazin-4-ones are converted into the corresponding 1-(pyridazin-2-yl)triazole-4-carboxylates.<sup>56</sup> Diazotisation of 7 $\beta$ -aminocephalosporin sulfones also gives a 1,2,3-triazole derivative. The opening of the  $\beta$ -lactam ring and the attack by the diazonium cation on the nitrogen atom are the key steps in this process.<sup>57</sup>

Cyclisation of diazo compounds of this type containing amide, amidine or imidate groups is a convenient method for the preparation of polyfunctional derivatives of triazole. An example is the synthesis of 4-substituted 1-(arylideneamino)triazol-5-olates **13**.<sup>58</sup>

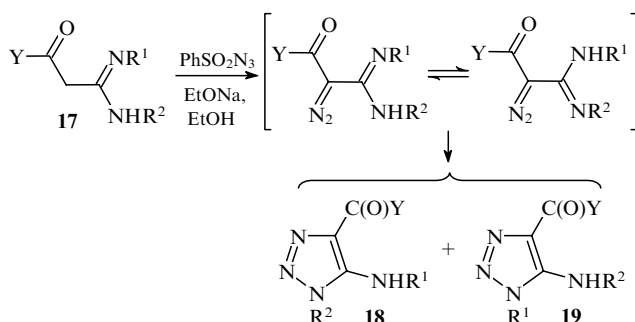


$\text{Ar} = 4\text{-FC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4$ .

If the molecule of the diazo compound contains a cyano group, apart from the above-listed groups, base-induced cyclisation occurs through attack by the terminal nitrogen atom of the diazo group on the nucleophilic nitrogen atom of the amide to give 4-cyanotriazol-5-olates **14**. When primary amines are used, amine addition to the cyano group takes place giving rise to  $\alpha$ -diazo-*N*-alkylamidines **15**, whose cyclisation involves the amidine nitrogen atom and results in 1-alkyl-5-amino-4-carbamoyltriazoles **16**.<sup>59</sup>



Cyclisation of amidine **17** containing different substituents at nitrogen atoms affords either one of isomers **18**, **19** or their mixture, depending on the nature of the radicals  $R^1$  and  $R^2$  (see Ref. 60).



$R^1 = \text{H, Me; } R^2 = \text{Me, Bn, 2-Py, 4-MeC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4$ ;  
 $Y = \text{NH}_2, \text{MeNH, EtO}$ .

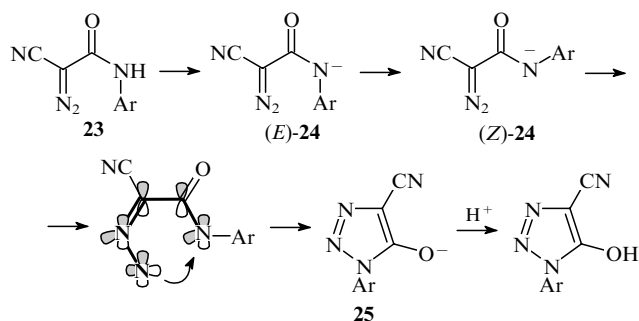
For example, in the case of  $R^1 = \text{H}$ ,  $R^2 = \text{Bn}$ , and  $Y = \text{NH}_2$  regioisomer **18** is formed in 74% yield, while with  $R^2 = 2\text{-pyridyl}$ , the reaction route changes, triazole **19** becoming the predominant product (yield 83%). In the case of  $R^1 = \text{Me}$ ,  $R^2 = \text{Bn}$ ,  $Y = \text{NHMe}$ , the reaction mixture contains both isomers (yield 56%).<sup>60</sup>

Triazoles **20a** and **21a** have been prepared through the  $\alpha$ -diazomalonamide derivative of cyanoacetic acid *N*-benzylidenetriazide<sup>61</sup> using the transformation sequence shown in Scheme 1 (pathway *a*).

Similar 2-(*N*-methylcarbamoyl)- (**22b**) and 2-ethoxycarbonyl derivatives (**22c**) react with tosyl azide and sodium ethoxide immediately to give sodium salts of hydroxytriazoles **21** (pathway *b*) rather than intermediate diazo compounds.<sup>61</sup> The use of diazo transfer to these hydrazides is impossible due to a side reaction involving the hydrazide group. However, arylmethylidene-protected acetohydrazides react with tosyl azide (pathway *c*) to be smoothly converted into the sodium salts of 1-(arylmethylidene-amino)hydroxytriazoles **20b,c**.<sup>62</sup> It has been noted that in the case of carbamoyl derivatives, no isomeric triazoles resulting from

cyclisation at the nitrogen atom of the amide group are formed. Acidification of aqueous solutions of sodium salts yields 5-hydroxytriazoles, which occur in equilibrium with the open forms of diazo compounds.<sup>63–65</sup> After removal of the benzylidene protection and upon acidification, 1-aminotriazoles **21a–c** also mainly exist as the open form of diazo compounds.<sup>59</sup>

The mechanism of heterocyclisation of 2-cyanoacetamides into 5-hydroxytriazoles has been studied in detail.<sup>66,67</sup> It was shown that 2-diazo-2-cyanoacetamides undergo partial cyclisation on refluxing in ethanol in which the equilibrium between the cyclic and open forms is rapidly established, whereas in the case of diazomalonodiamide, the equilibrium is established very slowly. In polar solvents, the equilibrium shifts towards cyclic forms. The position of the equilibrium depends only slightly on the electronic and steric properties of the substituent at the carboxamide nitrogen atom, although electron-withdrawing substituents have been noted to destabilise to some extent the cyclic structure.<sup>67</sup> On the basis of experimental values of the activation energy of the cyclisation, the  $\rho$  reaction parameters and the kinetic isotope effects, together with the results of theoretical calculations, it has been concluded that the cyclisation mechanisms of *N*-aryl and *N*-alkyl derivatives of diazocynoacetamides are different. In the former case, the reaction starts with proton elimination from the amide nitrogen atom of *N*-aryl derivatives **23** to give imidolate anion **24**, which then isomerises and cyclises into triazolate anion **25** by an electrocyclic mechanism. The process ends in the protonation of the triazolate anion to give 5-hydroxytriazole.<sup>67</sup> These transformations have been considered in a review.<sup>68</sup>

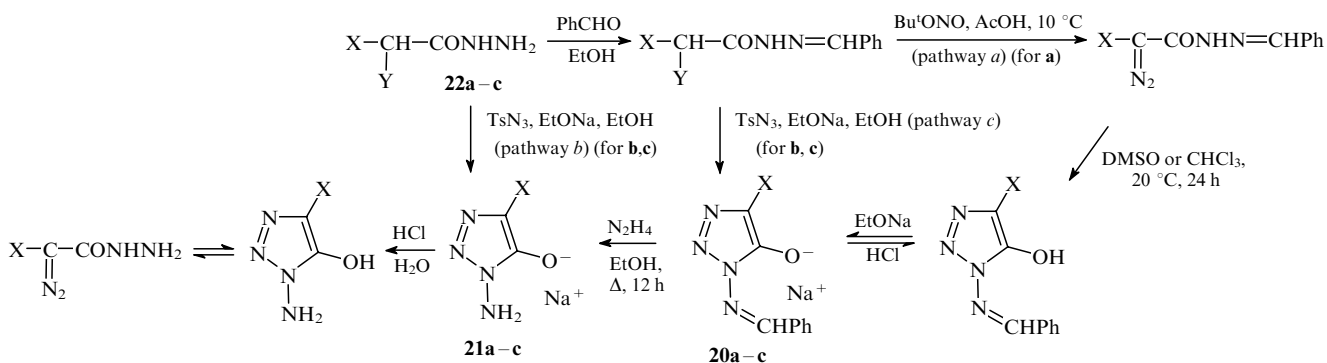


$\text{Ar} = \text{Ph, 4-MeC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4, 4\text{-EtO}_2\text{CC}_6\text{H}_4$ .

Apparently, cyclisation of *N*-sulfonyldiazomalonamides [ $\text{ArSO}_2\text{NHCOC}(=\text{N}_2)\text{CONHSO}_2\text{Ar}$ ] to 1-sulfonyltriazoles occurs in a similar way.<sup>69</sup>

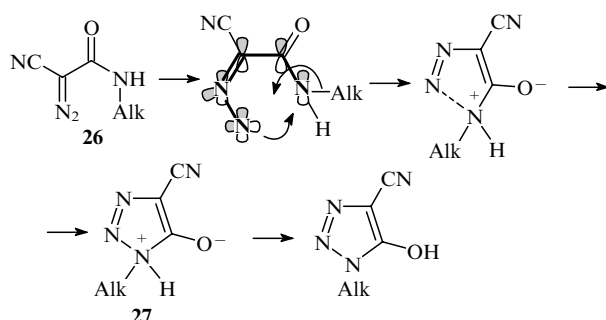
Meanwhile, in the case of *N*-alkyl derivatives **26**, which have a lower NH-acidity, the substituents rotate around the C–N bond to give cyclic zwitterionic structure **27** (monorotatory mechanism).<sup>67</sup>

Scheme 1



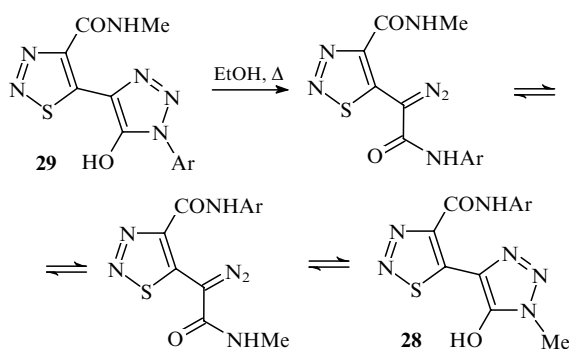
$X = \text{CN, Y} = \text{NH}_2$  (**a**);  $Y = \text{H; } X = \text{MeNHC}$  (**b**),  $\text{CO}_2\text{Et}$  (**c**).



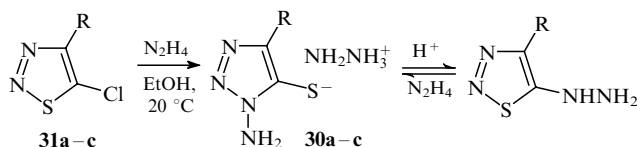


Alk = H, Me, n-C<sub>6</sub>H<sub>13</sub>, Bn.

Proceeding from the ability of triazoles to undergo easy cleavage of the heterocycle to be converted into linear diazo compounds, researchers<sup>64,69</sup> have developed a method for the synthesis of 4-substituted 1-alkyl-5-hydroxytriazoles **28** from more readily available 1-aryl derivatives **29**.<sup>65,70</sup> The rearrangement proceeds on refluxing the starting triazole in ethanol and includes the following steps: triazole ring opening, isomerisation of diazoacetamide and triazole ring closure.

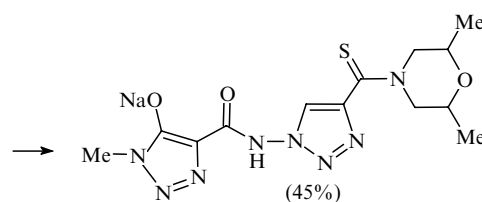
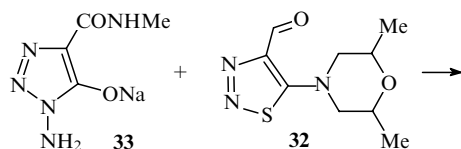


The ability of 5-amino-1,2,3-thiadiazoles to isomerise into 5-mercaptotriazoles has been used in the synthesis of 1-amino-4-R-5-thiolates **30** from the corresponding 5-chlorothiadiiazoles **31** on treatment with excess hydrazine.<sup>71–73</sup> In the case of the ethoxycarbonyl derivative **31c**, the reaction proceeds at room temperature, whereas for derivatives **31a,b**, replacement of the chlorine atoms in thiadiazole requires heating. When the resulting thiolate **30** is treated with an acid, triazole ring transformation takes place to give hydrazinothiadiazole.<sup>71</sup>

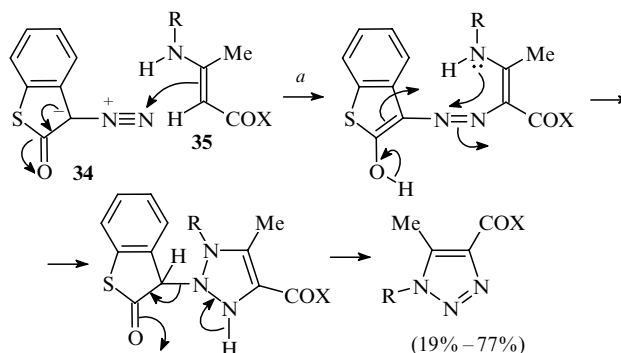


R = H (a), Ph (b), CO<sub>2</sub>Et (c).

On treatment of 5-morpholino-1,2,3-thiadiazole-4-carbaldehyde with primary amines, the imine readily undergoes the Conforth rearrangement, being converted into 1-R-4-morpholinothiocabonyl-1,2,3-triazole.<sup>74</sup> The tandem Conforth rearrangement was carried out in the reaction of thiadiazole-4-carbaldehyde **32** with 1-amino-4-carbamoyltriazol-5-olate **33**.<sup>75</sup>



Recently, a new method for triazole synthesis has been reported in which the heterocycle is formed *via* diazo transfer.<sup>76</sup> Using the reaction of 3-diazo-2-one (**34**) with N-substituted enaminocarbonyl compounds **35** as an example, a process mechanism has been proposed.

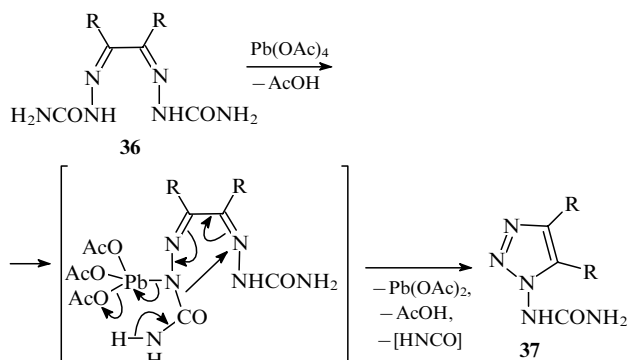


R = Me, Bu<sup>t</sup>; X = Me, EtO; a is PhH or PhMe,  $\Delta$ .

This reaction has been carried out for not only various enaminones,<sup>76</sup> but also for 3-diazo derivatives of 5-nitrooxyindole, 1-methyl-5-nitro-oxyindole and 5,7-dinitro-oxyindole as substrates.<sup>76,77</sup>

## 2. Cyclisation of nitrogen derivatives of 1,2-dicarbonyl compounds

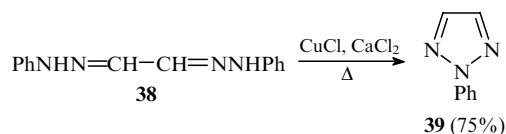
This pathway to 1,2,3-triazoles was first proposed by Pechmann<sup>78</sup> and later developed by many researchers. It was shown that heating bishydrazones or bissemicarbazones of  $\alpha$ -dicarbonyl compounds in the presence of oxidants such as MnO<sub>2</sub>, HgO, Hg(OAc)<sub>2</sub>, FeCl<sub>3</sub>, NiO<sub>2</sub>, CuCl, CuSO<sub>4</sub>, and Pb(OAc)<sub>4</sub> gives rise to substituted triazoles. The process includes the complexation stage and subsequent cyclisation in which a metal compound in a reduced state is eliminated. The transformations of  $\alpha$ -diketone bissemicarbazones **36** into 1-ureidotriazoles **37** on treatment with lead tetraacetate has been studied:<sup>79</sup>



R = H, Me, Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>.

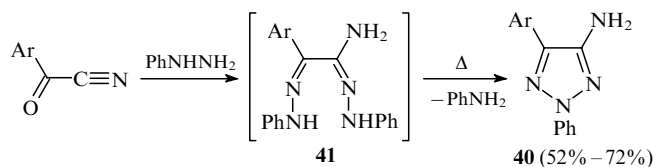
The product yields in this cyclisation are usually relatively low. Despite a number of modifications, this method has not received wide use.<sup>2</sup> Nevertheless, substituted 2H-triazoles can be synthesised in this way.<sup>14,15</sup> Thus the oxidation of glyoxal phenylosazone **38** yields bis(phenylazo)ethylene, which is then converted into 2-phenyltriazole **39** on treatment with FeCl<sub>3</sub>, CuCl or CuSO<sub>4</sub>, but the yields do not exceed 50%. The optimal conditions for this

reaction were chosen, namely, heating of a mixture of osazone, CuCl and anhydrous CaCl<sub>2</sub> with continuous evaporation of the product *in vacuo*; the yield of 2-phenyltriazole **39** was thus increased to 75%.<sup>80</sup>



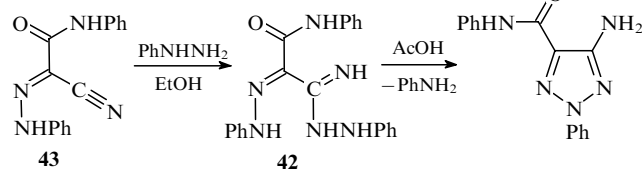
An example of the preparation of bis(triazol-2-yl)-substituted arylenes using  $\alpha$ -diketones and arylenebis(hydrazines) has been reported.<sup>81</sup> Proceeding from D-arabinose osazone, 2-(3-nitrophenyl)-4-( $\beta$ -D-erythrofuranosyl)triazole has been synthesised.<sup>82</sup> The potential of using osazones of low-molecular-weight carbohydrates for the preparation of heterocyclic compounds, including 1,2,3-triazole derivatives, is described in a review.<sup>83</sup>

Heating of aroyl cyanides with phenylhydrazine (ratio 1 : 2) results in 4-amino-5-aryl-2-phenyltriazoles **40**.<sup>84</sup> The researchers assume that the reaction proceeds through the formation of intermediate  $\alpha$ -amino- $\alpha'$ -arylglyoxal bis(phenylhydrazones) **41**, which cyclise with the loss of an aniline molecule.



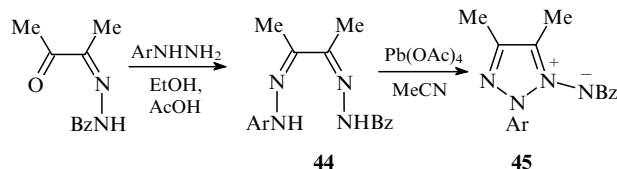
Ar = Ph, 3-MeC<sub>6</sub>H<sub>4</sub>, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>.

The intermediate product of phenylhydrazine addition at the C $\equiv$ N bond (compound **42**) has been isolated in a similar transformation of 2-oxocycanoacetanilide phenylhydrazones **43**.<sup>85</sup>



The oxidative cyclisation of analogous arylhydrazones of 2-oxocycanoacetamides has resulted in the synthesis of a series of 4-amino-2-aryl-5-cyanotriazoles,<sup>86</sup> and the reaction of acyl cyanides with methylhydrazine gave 4-amino-5-aryl-2-methyltriazoles.<sup>87</sup>

In the case of dimethylglyoxal bishydrazones with *N*-aryl and *N'*-benzoyl groups (compound **44**), oxidation with lead tetraacetate results in rather stable triazole derivatives of the ylide type **45**.<sup>28</sup> These compounds are additionally stabilised due to negative charge delocalisation involving the carbonyl group.

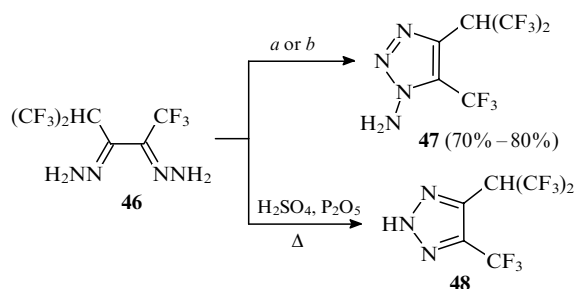


Ar = Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>.

Note that cyclisation of *N*-unsubstituted phenylglyoxal bishydrazones furnishes 1-amino-4-phenyltriazole.<sup>14</sup>

The oxidation of asymmetric dimethylglyoxal aroylhydrazones yielding isomeric *N*-(4,5-dimethyltriazol-1-yl)arylcarboximido acids has been considered.<sup>88</sup> The oxidative cyclisation of bis(acetylhydrazones) of 1,2-dicarbonyl compounds results in the formation of 1-(*N*-acetyl)- and *N,N*-bis(acetylamino)triazoles.<sup>89</sup>

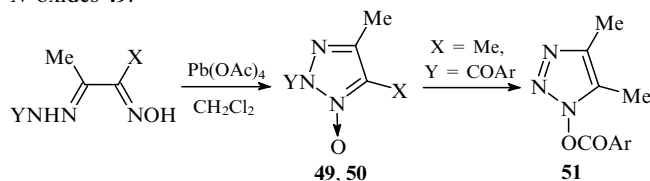
It is noteworthy that cyclisation of the bishydrazones of polyfluorinated diketone **46** induced by bromine or sulfuryl chloride at room temperature gives only 1-amino-4-hexafluoroisopropyl-5-trifluoromethyltriazole **47**.<sup>90, 91</sup>



(a) Br<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>; (b) SO<sub>2</sub>Cl<sub>2</sub>, CaCl<sub>2</sub>.

Cyclisation giving triazole with a more electron-withdrawing group at the 5-position also takes place during the oxidation of (5-hydroperfluoropentyl)glyoxal bishydrazones on treatment with SeO<sub>2</sub>.<sup>92</sup> Under more rigorous conditions, compound **46** was converted into a deamination product, namely, 4,5-disubstituted 2*H*-triazole **48**.<sup>93</sup> The formation of only one regioisomer of 1-phenylsulfonyltetrahydrobenzotriazole is observed in the reaction of methyl derivatives of cyclohexane-1,2-diones with phenylsulfonylhydrazine.<sup>94</sup>

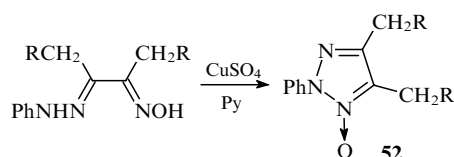
The oxidative cyclisation of  $\alpha$ -arylhyaazono ketone anils affords 1,2-diaryltriazolium derivatives,<sup>95</sup> while that of  $\alpha$ -hydroxyimino ketones results in the corresponding triazole *N*-oxides.<sup>96</sup> This method was used to prepare a series of 5-acyltriazole *N*-oxides **49**.<sup>97</sup>



Y = Ar: X = COMe, C<sub>6</sub>H<sub>5</sub> (**49**); X = Me, Y = ArCO (**50**);  
Ar = Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>.

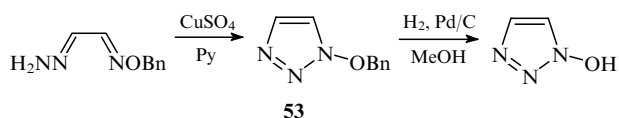
When *N*-arylhyaazonos of  $\alpha$ -hydroxyimino ketones are used in this reaction, migration of the aroyl group to the oxygen atom takes place in the intermediate *N*-oxides **50** to give triazoles **51**.<sup>98</sup>

The oxidative cyclisation of (*N*-phenylhydrazono)oximes of ethyl acetoacetate on treatment with MnO<sub>2</sub> affords different isomers of 4(5)-methyl-2-phenyl-5(4)-ethoxycarbonyltriazole *N*-oxide depending on the position of the oximino and hydrazono groups in the initial compound.<sup>99</sup> This method has been used to prepare symmetric 4,5-disubstituted 2-phenyltriazole 1-oxides **52**. Cyclisation induced by other oxidants, *i.e.*, *N*-iodosuccinimide or copper sulfate, shows a higher efficiency of the latter compound (the yield exceeds 90% almost in all cases).<sup>100</sup>

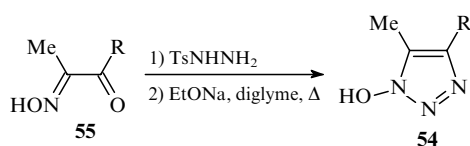


R = Ph, 2-MeC<sub>6</sub>H<sub>4</sub>, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>, 1-Naph, cyclo-C<sub>6</sub>H<sub>11</sub> (Cy).

The same reagent was used to prepare 1-(benzyloxy)triazole **53** from *O*-benzyloxime glyoxal monohydrazones.<sup>101</sup> The possibility of debenzoylation of triazole **53** to give unsubstituted 1-hydroxytriazole was demonstrated.



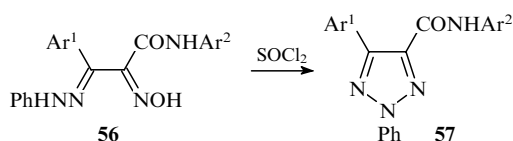
It is worth noting that 1-hydroxy-1*H*-triazoles and their O-derivatives have attracted the attention of researchers as new condensing reagents in the peptide synthesis, which are able to suppress racemisation and other side reactions. To study the properties of compounds of this class, a series of new 1-hydroxytriazole derivatives have been prepared<sup>46, 102</sup> by different synthetic routes. Alkyl- and aryl-substituted 1-hydroxytriazoles **54** were synthesised by treatment of 1,2-diketone *N*-tosylhydrazone oxime **55** with sodium ethoxide with subsequent short-term refluxing in diglyme.<sup>46</sup>



R = Me, Ph, 4-MeOC<sub>6</sub>H<sub>4</sub>.

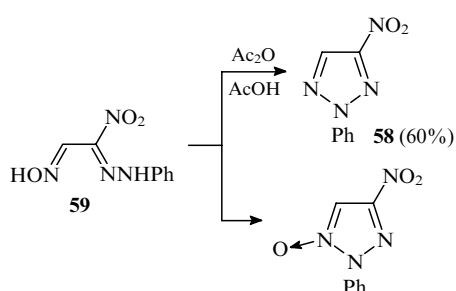
This method proved to be inapplicable for the synthesis of 1-hydroxy-1*H*-triazole with an ester group (R = CO<sub>2</sub>Me); this compound was prepared by cyclisation of the oxime of ethyl diazoacetoacetate.<sup>46</sup>

The cyclisation of phenylhydrazone oximes **56** induced by dehydrating agents (Ac<sub>2</sub>O, SOCl<sub>2</sub>) affords 2-phenyltriazoles **57** with an unsubstituted 1-position.<sup>103</sup>



Ar<sup>1</sup> = Ph, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>; Ar<sup>2</sup> = Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 2-MeOC<sub>6</sub>H<sub>4</sub>, 2-ClC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 2,4-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>.

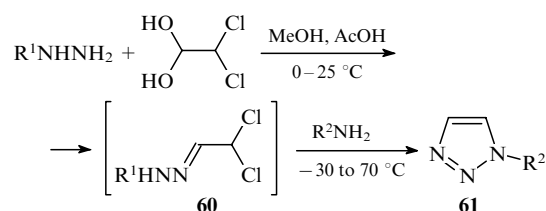
Similarly, aroyl glyoxal 1,2-bis(phenylhydrazones) [ArCOC(=NNHPh)CH(=NNHPh), where Ar = Ph, 2-furyl] are converted into 4-aryl-2-phenyltriazoles.<sup>104</sup> This route was used to synthesise 4-nitro-2-phenyltriazole **58** from 2-nitro-2-phenylhydrazonoacetoxime **59**.<sup>105</sup> It is noteworthy<sup>106</sup> that in the oxidative cyclisation {K<sub>3</sub>[Fe(CN)<sub>6</sub>], KOH, dioxane}, this oxime results in triazole with an *N*-oxide group at the 1-position.



However, 2-nitro-2-phenylhydrazonoacetamidoxime forms 4-amino-5-nitro-2-phenyltriazole only on heating with urea.<sup>105</sup> On coupling of 2-nitroacetaldehyde oxime with 1,2,4-triazole-3-diazonium salts followed by the cyclisation of the corresponding hydrazonoacetaldehyde oximes, 4-nitro-2-(1,2,4-triazol-3-yl)-1,2,3-triazoles were prepared.<sup>107, 108</sup>

Several approaches have been proposed to obtain unsubstituted triazole. Harada *et al.*<sup>109</sup> carried out cyclisation of glyoxal monoxime monohydrazone on treatment with acetic anhydride, and the resulting 2-acetyltriazole was subjected to alcoholysis.

Unsubstituted triazole is formed in the reaction of tosylhydrazine with a mixture of ammonia and glyoxal on heating in aqueous methanol<sup>110</sup> or on bubbling ammonia into water or into an organic solvent.<sup>111</sup> A two-step method based on the reaction of dichloroacetaldehyde with sulfonylhydrazines with the subsequent cyclisation of the resulting hydrazone **60** under the action of ammonia has been developed.<sup>112</sup> A drawback of this approach is related to the use of toxic dichloroacetaldehyde and its proneness to polymerisation. The procedure modified by other researchers<sup>113</sup> does not imply the isolation of the intermediate hydrazone and provides triazole **61** (R<sup>2</sup> = H) in 55% yield. By introducing aliphatic, aromatic or heteroaromatic amines into this reaction instead of ammonia, a series of 1-substituted triazoles **61** have been obtained. The solvents used were water, alcohols, acetonitrile, dioxane, DMSO, or DMF.<sup>113, 114</sup>

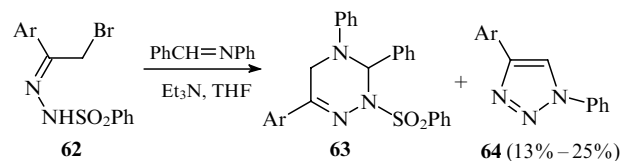


R<sup>1</sup> = R<sup>3</sup>CO, R<sup>3</sup>SO<sub>2</sub>; R<sup>3</sup> = Me, Et, Pr<sup>n</sup>, Pr<sup>i</sup>, Bu<sup>n</sup>, Ph, XC<sub>6</sub>H<sub>4</sub> (X = Alk, AlkO, Cl, Br, NO<sub>2</sub>); R<sup>2</sup> = H, Alk, Ar, Het.

This method was utilised to prepare 1,1'-bitriazole.<sup>115</sup> 1-Aminotriazole served as the amino component; it was prepared by treatment of arylsulfonylhydrazone of dichloroacetaldehyde with hydrazine hydrate in the presence of Et<sub>3</sub>N (PrOH, 40 °C, yield 65%)<sup>116, 117</sup> or by cyclisation of glyoxal bishydrazone in aqueous hydrogen peroxide in the presence of catalytic amounts of transition metal oxides.<sup>118</sup>

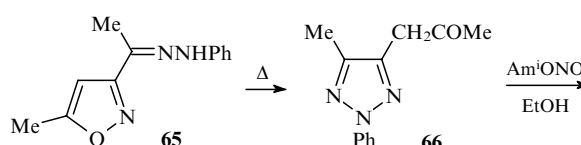
Similarly, reactions of methyl- and benzylamine with 1,1-dichloroacetone tosylhydrazone afford 1-methyl(or benzyl)-4-methyltriazoles in high yields, while the reactions with chloral tosylhydrazone give the corresponding 5-amino-substituted triazoles.<sup>119</sup> The reaction of ω,ω-dichloroacetophenone with tosylhydrazine resulted in 1-tosylamino-4-phenyltriazole (yield 20%).<sup>119</sup>

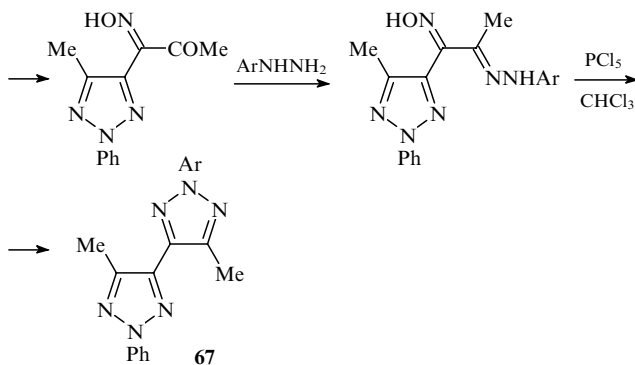
By the reactions of hydrazones of substituted ω-bromoacetophenones **62** with benzylideneaniline in the presence of Et<sub>3</sub>N, mixtures of aryl-substituted tetrahydrotriazines **63** and 4-aryl-1-phenyltriazoles **64** have been obtained.<sup>120</sup>



Ar = Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>.

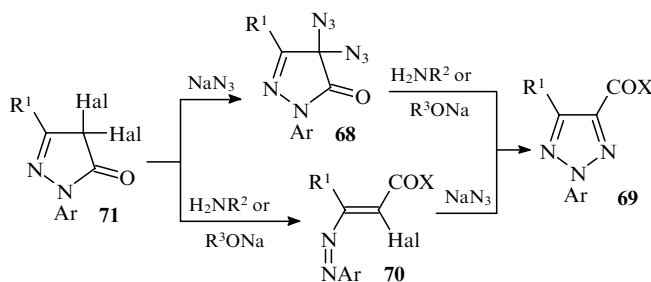
The thermally induced ring transformation in phenylhydrazones of 3-acetylisoaxazoles **65** to give 4-acetonyl-2-phenyltriazoles **66** can be assigned to the same Section. The subsequent nitrosation, transition of oximino derivatives into arylhydrazones and treatment of these products with PCl<sub>5</sub> yield 2,2'-diaryl-4,4'-bistriazoles **67**.<sup>121</sup> Substituted phenylhydrazones of acetylisoaxazoles undergo the same transformations.





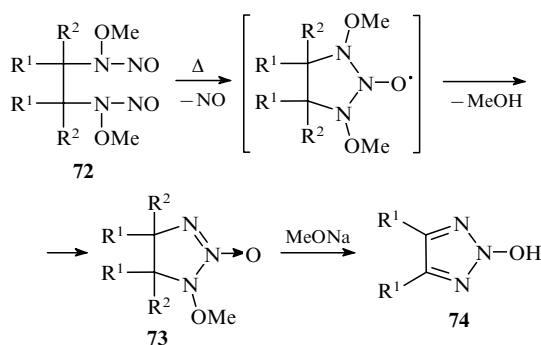
Ar = Ph, 2-ClC<sub>6</sub>H<sub>4</sub>, 3-ClC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 2-BrC<sub>6</sub>H<sub>4</sub>, 3-BrC<sub>6</sub>H<sub>4</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>; Am<sup>i</sup> is isoamyl.

1-Aryl-4,4-diazidopyrazolin-5-ones **68** open the pyrazoline ring at room temperature in the presence of alkali to give the intermediate hydrazidiazide, which cyclises into 2-aryl-4-carboxy-1,2,3-triazole-5-carboxylic acids with nitrogen extrusion.<sup>122</sup> Subsequently, other researchers have shown that if amines or alkoxides are introduced into the reaction instead of alkali, the reaction gives the corresponding derivatives of acid **69**.<sup>123</sup> The same products can be prepared by the reaction of NaN<sub>3</sub> with arylazovinyl halide **70**, which is formed upon ring opening in dihalopyrazolinone **71** on treatment with bases.



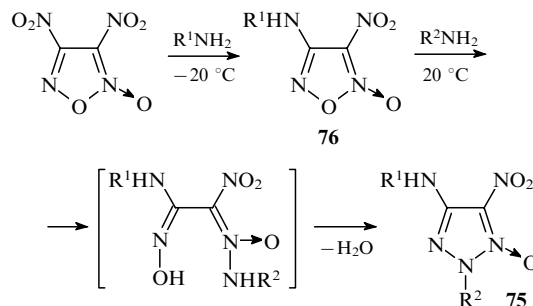
R<sup>1</sup> = Me, Ph; Ar = Ph, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>; X = NH<sub>2</sub>, EtNH, EtO;  
R<sup>2</sup>, R<sup>3</sup> = Alk.

The formation of the triazole ring on heating 1,2-bis(*N*-methoxy-*N*-nitrosoamino)ethane **72** (R<sup>1</sup> = R<sup>2</sup> = H) has been described.<sup>124</sup> On treatment with sodium methoxide, *N*-oxide **73** is converted into 2-hydroxytriazole **74**.<sup>124</sup>



If 1,2-dialkyl-substituted 1,2-bis(*N*-alkoxy-*N*-nitrosoamino)ethanes **72** (R<sup>1</sup> = Alk, R<sup>2</sup> = H) are introduced in this reaction, 4,5-dialkyl-2-hydroxytriazoles **74** (R<sup>1</sup> = Alk) are produced. In the case of tetrasubstituted *N*-alkoxy derivatives **72** (R<sup>1</sup> = R<sup>2</sup> = Alk), the reaction stops after the formation of 1-alkoxy-4,5-dihydrotriazole 2-oxide **73**.<sup>125</sup>

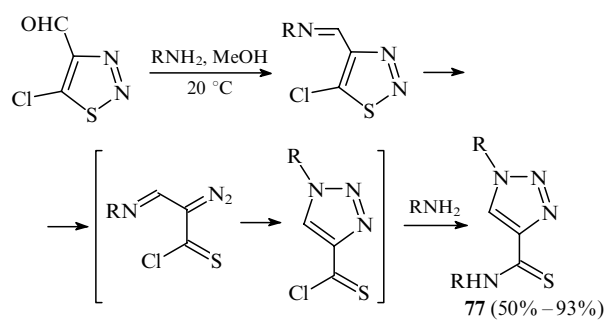
Proceeding from readily available 3,4-dinitrofuroxan, a new method for the synthesis of 4-amino-substituted 5-nitro-2*R*-triazole 1-oxides **75** via *N*-alkylamino derivatives **76** has been developed.<sup>126–128</sup>



R<sup>1</sup> = H, Me, Et, HO(CH<sub>2</sub>)<sub>2</sub>, NC(CH<sub>2</sub>)<sub>2</sub>; R<sup>2</sup> = Me, Et, CH<sub>2</sub> = CHCH<sub>2</sub>.

These transformations occur similarly to the recyclisation of benzofuroxans into 1,2,3-triazole oxides under the action of acylanilide anions.<sup>129, 130</sup>

5-Chloro-1,2,3-thiadiazole-4-carbaldehyde reacts with a number of amines to give 1-substituted triazole-4-thiocarboxamides **77**. The mechanism proposed for ring transformation includes the formation of imino derivatives, thiadiazole ring opening at the N–S bond, and triazole ring closure.<sup>131</sup>

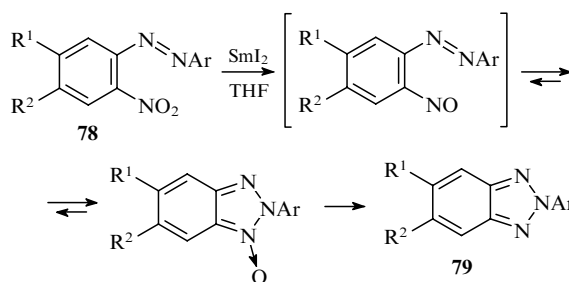


R = Me, Et, Bn, Ph, 4-MeOC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, NH<sub>2</sub>, O(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>N.

The mechanism of recyclisation of 3-benzoyl-5-phenyl-1,2,4-oxadiazole arylhydrazones into 2-aryl-4-benzoylamino-5-phenyl-1,2,3-triazoles depends on the nature of substituents in arylhydrazone.<sup>132, 133</sup>

### 3. Cyclisation of *ortho*-disubstituted nitrogen derivatives of aromatic compounds

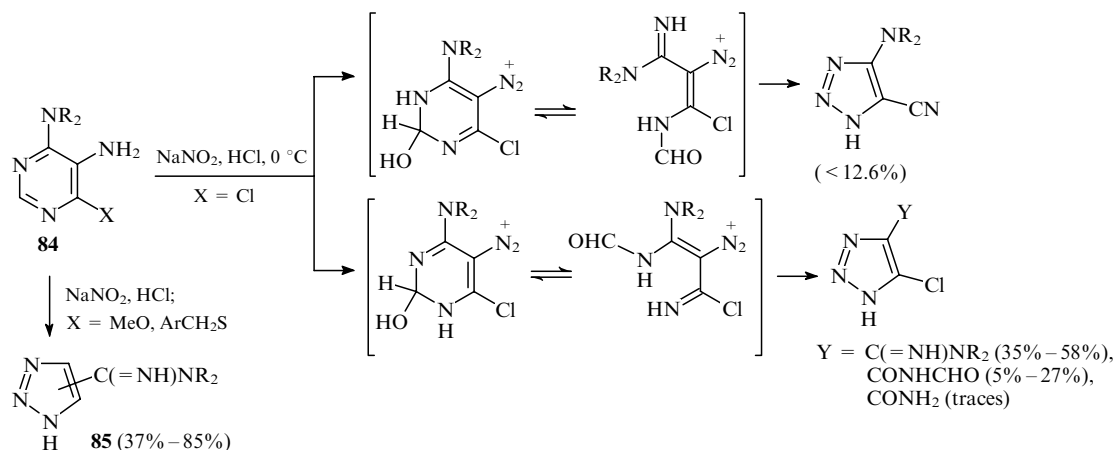
The presence of two nitrogen-containing functional groups in the *ortho*-position of the benzene ring allows the use of these compounds for construction of the benzotriazole system. Depending on the nature of the groups and the reagents used, the intramolecular cyclisation can yield different substituted benzotriazoles, in particular, *N*-oxides and *N*-hydroxy derivatives.<sup>14</sup> Data on the reductive cyclisation of *o*-nitrophenylazobenzenes **78** into 2-arylbenzotriazoles **79** on treatment with SmI<sub>2</sub> have been published recently.<sup>134</sup> The putative reaction mechanism includes the reduction of the nitro group to the nitroso group, intramolecular cyclisation to give 2-arylbenzotriazole 1-oxide and its subsequent deoxygenation.



R<sup>1</sup>, R<sup>2</sup> = H, Cl; Ar = 2-HO-5-MeC<sub>6</sub>H<sub>3</sub>, 2-HO-3,5-Bu<sub>2</sub>C<sub>6</sub>H<sub>2</sub>.

The electrochemical reduction of 2-hydroxy-5-methyl-2'-nitroazobenzene during the preparation of 2-(2*H*-benzotriazol-2-

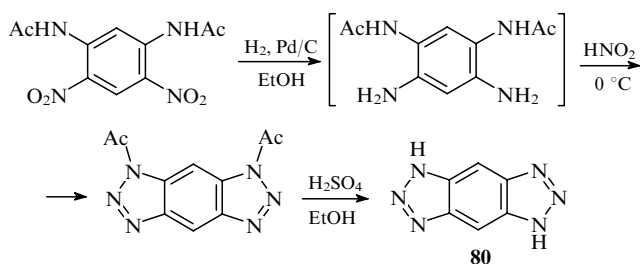
Scheme 2



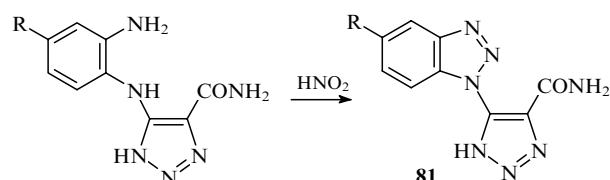
R–R = Me<sub>2</sub>, (CH<sub>2</sub>)<sub>5</sub>, (CH<sub>2</sub>)<sub>2</sub>O(CH<sub>2</sub>)<sub>2</sub>; Ar = Ph, 3,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>.

yl)-4-methylphenol (known as the light stabiliser Benazol-P) proceeds in a similar way.<sup>135</sup>

The synthesis of 1*H*,5*H*-benzo[1,2-*d*:4,5-*d'*]bistriazole **80**, which is converted into 1,5- and 1,7-diamino derivatives upon amination, has been accomplished using diazotisation of the diacetyl derivative of tetraaminobenzene.<sup>136</sup>

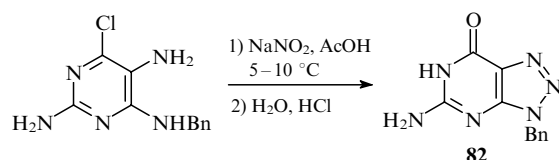


This method underlies the synthesis of a series of 1-(4-carboxamidotriazol-5-yl)benzotriazoles **81**.<sup>137</sup>

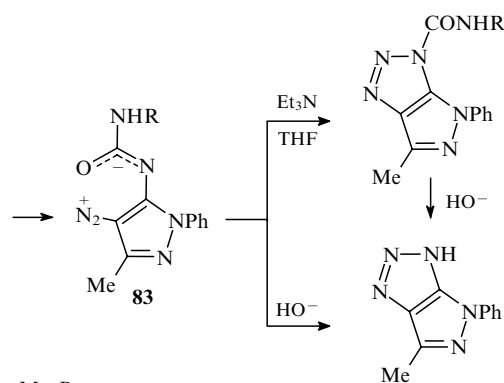
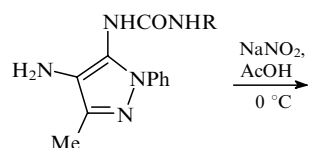


R = H, Me, MeO, F, Cl, CF<sub>3</sub>.

and the regioselective synthesis of 9-substituted 8-azaguanines **82**.<sup>138, 139</sup>



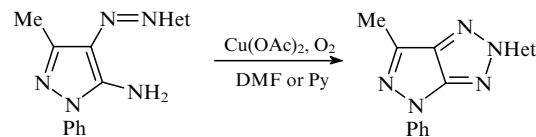
4-Diazopyrazoles **83**, which are prepared by diazotisation of *N*-alkyl-*N'*-(4-aminopyrazol-5-yl)ureas proved to be convenient synthons for the construction of various heterocyclic systems, for example, pyrazolo[4,5-*d*]triazole.<sup>140</sup>



R = Me, Bn.

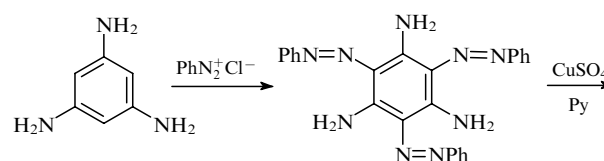
Diazotisation of 4-dialkylamino-5-aminopyrimidines **84** in an acidic aqueous medium results in opening of the pyrimidine ring followed by attack by the diazo group on a nitrogen atom. This affords triazoles of different structures, depending on the substituent at the 6-position of pyrimidine.<sup>141</sup> For example, in the presence of 6-MeO or 6-ArCH<sub>2</sub>S groups in the pyrimidine ring, only 4(5)-carboxamidotriazoles **85** are formed, whereas in the case of the 6-Cl substituent, cyano- and carboxamidotriazoles have also been isolated as minor products (Scheme 2).

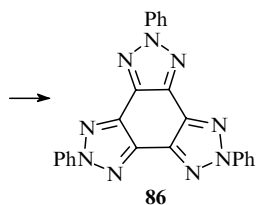
The anodic oxidation of 2-arylazo-3-aminocrotonitrile to 2-aryl-4-cyanotriazole<sup>142</sup> and oxidative cyclisation of pyrazole azo compounds containing an amino group can be assigned to the same type of triazole ring construction.<sup>143</sup>



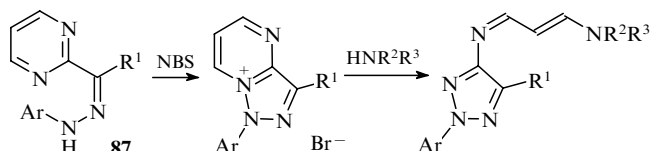
Het = 2-Py, thiazol-2-yl, pyrazol-5-yl.

A similar method has been used to synthesise derivatives of benzotriazole and more complex fused systems,<sup>144, 145</sup> including those containing several triazole rings, for example, heterocyclic compound **86**.<sup>146</sup>



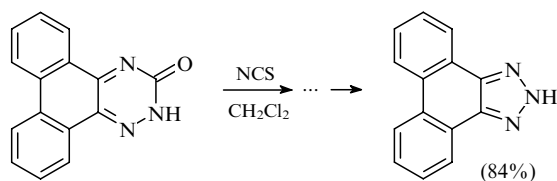


A review<sup>147</sup> has been devoted to the closure of the triazole ring in 2-acylazine hydrazones. The triazoloazinium cations thus formed tend to undergo cleavage of the six-membered ring on treatment with nucleophilic agents. For pyrimidine **87**, this sequence can be represented as follows:

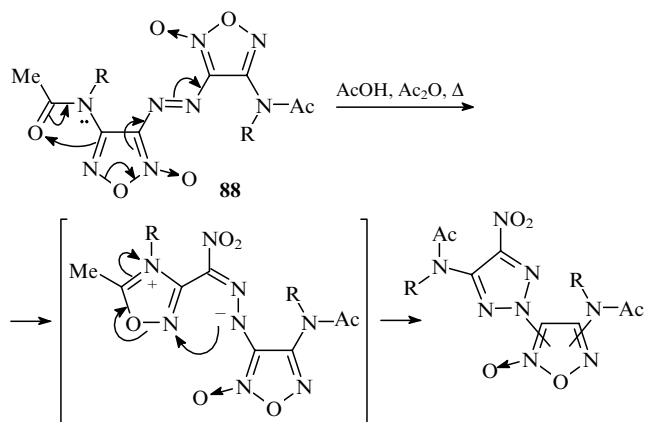


NBS is *N*-bromosuccinimide.

The transformation of annelated 1,2,4-triazin-3-one into the corresponding 1,2,3-triazole induced by *N*-chlorosuccinimide (NCS) has been described;<sup>148</sup> by analogy with the ring transformations known previously,<sup>149</sup> this process includes *N*-chlorination, azine ring opening and triazole ring closure followed by the removal of chlorine.



A thermal rearrangement of 4,4'-diacetamido-3,3'-azodifuroxans **88** has been detected.<sup>150</sup> The presence of acetamide groups in the starting azodifuroxan was shown to be a necessary condition for this process. According to the reaction mechanism proposed by the researchers, two successive rearrangements take place. The first one is the transformation of one furoxan ring into a 1,2,4-oxadiazole ring with O(1)–N(5) bond cleavage and formation of the nitromethylene fragment, while the second ring transformation gives rise to a new bond of the triazole ring. Isomerisation of the furoxan fragment is possible at the final stage, resulting in the formation of two isomeric products.

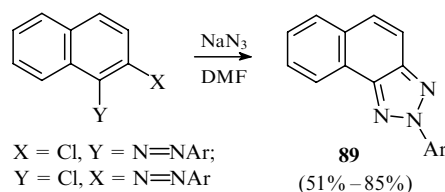


R = H, Me.

4-Acetylamino-3-arylazofuroxans undergo the same cascade rearrangement in an alkaline medium to give 2-aryl-4-acetylamino-5-nitro-2*H*-triazoles (Ar = 4-MeOC<sub>6</sub>H<sub>4</sub>, 4-EtOC<sub>6</sub>H<sub>4</sub>, 2,4-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>),<sup>151</sup> while 4-acetyl(or benzoyl)-3-methylfuroxan phenylhydrazones are transformed on heating into

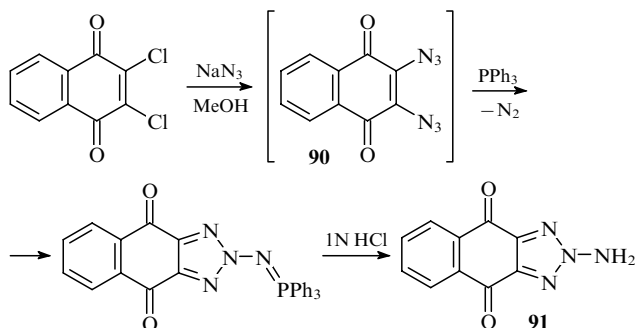
5-acetyl-4-methyl(or phenyl)-2-phenyl-2*H*-triazole 1-oxide oximes.<sup>152</sup>

The reaction of *vic*-chlorinated 1- or 2-arylaazonaphthalenes with sodium azide can also be ascribed to this type of reaction. In both cases, 2-aryl-2*H*-naphtho[1,2-*c*]triazoles **89** are formed.<sup>153</sup>



Ar = Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>, 2-ClC<sub>6</sub>H<sub>4</sub>, 3-ClC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>, 2-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 3-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>.

Triphenylphosphine-induced cyclisation of 2,3-diazo-1,4-naphthoquinone **90** prepared *in situ* has been reported.<sup>154,155</sup> The reaction proceeds smoothly, the yield of 2-aminobenzotriazole **91** being nearly quantitative.

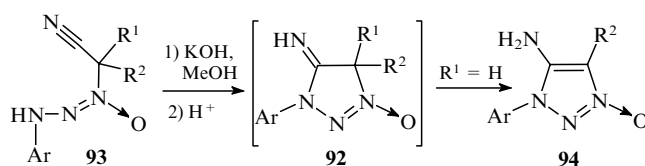


Although the reaction mechanism has not been studied in detail, it is assumed that PPh<sub>3</sub> adds to the terminal nitrogen of the azide group according to the Staudinger reaction type, while the second nitrogen atom of the same group attacks the neighbouring azide group. This is accompanied by elimination of a nitrogen molecule, which is really observed in experiments. Thus, this reaction is similar to thermal and photochemical intramolecular cyclisations of aryl azides which involve neighbouring unsaturated substituents.<sup>154</sup>

### III. Methods of formation of the C(5)–N(1) or C(4)–N(3) bond

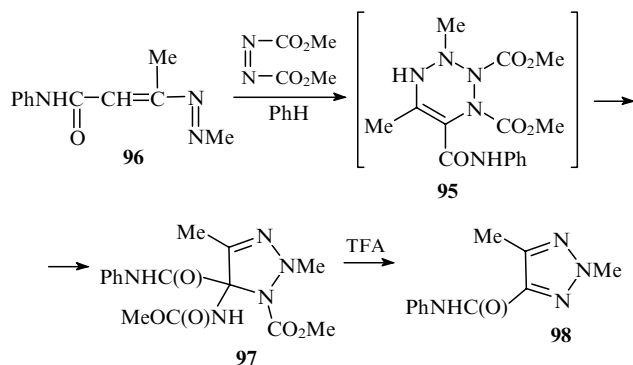
This group of reactions includes examples of intramolecular cyclisation of cyano-containing triazenes.

Recently, a new approach to the synthesis of iminodihydrotriazole 1-oxides **92**, namely, KOH-induced cyclisation of cyano-containing aromatic and heterocyclic triazene 1-oxides **93**, has been proposed.<sup>156,157</sup> A possible sequence of transformations includes base-induced formation of an anionic centre on N(3) of the triazene oxide fragment and nucleophilic attack by this centre on the electron-deficient carbon atom of the nitrile group. In the case of 3-(het)aryltriazene 1-oxides containing an active hydrogen atom in the α-position to the cyano and triazene oxide groups, the iminodihydrotriazole 1-oxides **92** (R<sup>1</sup> = H) formed are isomerised into the *N*-oxides of aminotriazoles **94**.



Ar = Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>, 1,2,4-triazol-3-yl; R<sup>1</sup> = R<sup>2</sup> = Me; R<sup>1</sup>–R<sup>2</sup> = (CH<sub>2</sub>)<sub>5</sub>.

Formally, the rearrangement of unstable 1,2,3,4-tetrahydro-1,2,3,4-tetrazine **95**, which is formed upon the reaction of azoalkene **96** with dimethyl azodicarboxylate and is converted into 1,5-dihydro-2*H*-triazole **97** already during the reaction, can also be classified as the method in question for 1,2,3-triazole ring formation. The product **97** eliminates methyl carbamate on treatment with trifluoroacetic acid (TFA) to give 2,4,5-trisubstituted 2*H*-triazole **98** in 80% yield.<sup>158</sup>

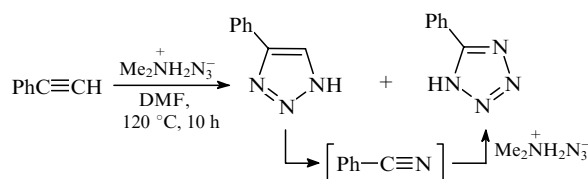


#### IV. Methods of formation of two C–N bonds

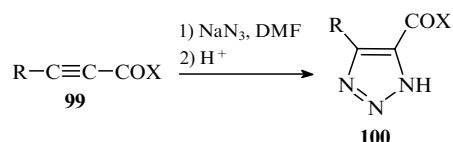
This group of reactions is used most often to prepare the triazole system and can be exemplified by the largest number of cases. This approach is based on 1,3-dipolar cycloaddition of organic azides to unsaturated compounds.

##### 1. Reactions of azides with substituted acetylenes

The published examples of reactions of azides with alkynes, resulting in triazole derivatives, are rather numerous. It is expedient to start this Section by considering reactions of inorganic azides, which were the first to be used in this method for triazole synthesis. Unsubstituted 1,2,3-triazole was first prepared in a relatively low yield by the addition of HN<sub>3</sub> to acetylene at 100 °C in a sealed tube under an elevated pressure;<sup>159</sup> subsequently, conditions were chosen to bring the product yield up to 86%.<sup>160</sup> Recently, it has been shown<sup>161</sup> that phenylacetylene reacts with dimethylammonium azide to give a mixture of 4-phenyltriazole and 5-phenyltetrazole.



The presence of an amide or an acyl group in phenylacetylene **99** (R = Ph) allows the reaction with sodium azide to be carried out with heating in DMF; the reaction gives 5-amido- or 5-acyl-triazoles **100** (R = Ph), respectively, in high yields.<sup>162–165</sup>



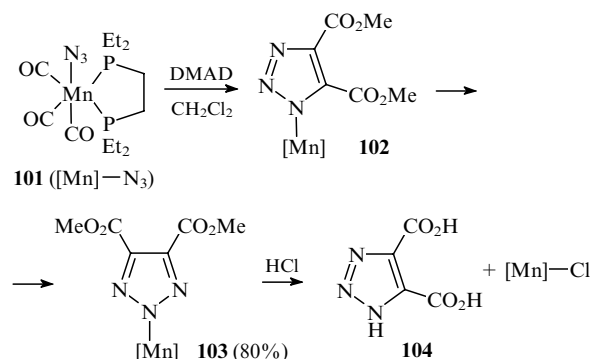
R = Ph; X = NH<sub>2</sub>, CH<sub>2</sub>COAr; Ar = Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>;  
R = CH<sub>2</sub>NAIk<sub>2</sub>, X = NH<sub>2</sub>.

In the case of 3-(*N,N*-dialkylaminomethyl)propiolamides **99** (R = CH<sub>2</sub>NAIk<sub>2</sub>, X = NH<sub>2</sub>), carboxamidotriazoles **100** (R = CH<sub>2</sub>NAIk<sub>2</sub>) are also formed. This was used for the design of complex biologically active compounds containing a triazole ring with secondary aminomethyl substituents.<sup>166, 167</sup>

Triazole derivatives have also been synthesised under the same conditions by the reaction of NaN<sub>3</sub> with acetylenic aldehydes,<sup>168</sup>

1-alkylthio-2-chloroacetylenes<sup>169</sup> and esters of long-chain oxoacetylenic fatty acids.<sup>170</sup> The use of hydrogen azide or metal azides in the cycloaddition results in 1,2,3-triazoles unsubstituted at the ring nitrogen atom. However, conduction of these reactions, especially on a preparative scale, is associated with a risk of explosion. The safety aspects for the work with sodium azide on an industrial scale, in particular, in the production of 1,2,3-triazoles, have been discussed in a brief review.<sup>171</sup> The use of trimethylsilyl azide as the reagent reduces the risk and allows one to synthesise 1-trimethylsilyltriazoles, from which the silyl group can subsequently be removed.<sup>172</sup>

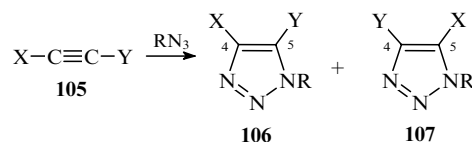
The azide group bound in the complex with Mn(I) **101** proved to undergo cycloaddition to dimethyl acetylenedicarboxylate (DMAD) at room temperature. This yields (under kinetic control) 1-triazolate complex **102**, which is converted into thermodynamically more stable 2-triazolate complex **103**.<sup>173</sup> Treatment of this product with HCl results in triazole-4,5-dicarboxylic acid **104**.



The phenylpalladium(II) azide complex shows a similar behaviour in the reaction with DMAD.<sup>174</sup> A series of 2-allyltriazoles have been obtained in a three-component condensation of allyl methyl carbonate, trimethylsilyl azide and a substituted acetylene catalysed by a Pd(0) complex. Presumably, a  $\pi$ -allylpalladium azide complex is formed first; then it undergoes 1,3-dipolar cycloaddition at the triple bond to give 1-( $\eta^3$ -allylpalladium)triazoles; these rearrange to 2-( $\eta^3$ -allylpalladium)triazoles, which are converted into 2-substituted triazoles, formed in moderate yields, through reductive elimination of Pd(0).<sup>175</sup>

The cycloaddition to a triple bond proceeds more easily with organic azides than with inorganic ones, especially when the alkyne molecule contains substituents.<sup>2</sup> This reaction underlies the development of synthetic routes to numerous N-substituted 1,2,3-triazoles. For instance, substituted 1-trityltriazoles have been prepared by the reaction of acetylene with sterically hindered trityl azides carried out by heating in various organic solvents under a pressure of up to 20 kg cm<sup>–2</sup>.<sup>176</sup>

The cycloaddition of aryl azides and benzyl azides to substituted acetylenes containing electron-withdrawing groups proceeds most easily.<sup>18</sup> In the case of symmetric alkynes **105** (X = Y), one product is formed, while the reactions with asymmetric alkynes **105** (X ≠ Y) may yield both regioisomers **106** and **107**.<sup>177</sup>



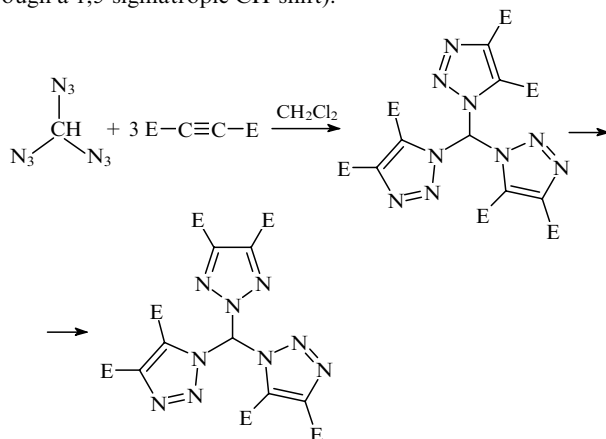
R = Ph, Bn; X = H, CO<sub>2</sub>Me; Y = Ph, CO<sub>2</sub>Me, CO<sub>2</sub>Et;  
R = 4-C<sub>5</sub>F<sub>4</sub>N; X = H, Y = Ph; R = Ph(CH<sub>2</sub>)<sub>n</sub>; X = H,  
Y = CONHBn; n = 1, 3.

The formation of both regioisomers has also been noted for the reactions of pentafluorophenyl azide and 4-azidotetrafluoropyridine with phenylacetylene<sup>178</sup> and benzyl azide and 3-phenylpropyl azide with acetylenic amides **105** (X = H, Y = CONHBn).<sup>179</sup> In the last-mentioned case, the 1,4-regioiso-



mers **107** were formed in substantially predominant amounts, which was attributed to lower steric strain in these compounds compared to the 1,5-isomers **106**.

Dimethyl acetylenedicarboxylate is often used as the starting alkyne, and then the chemical modification of both ester groups is carried out for the preparation of various 4,5-bifunctional 1-aryl-triazoles.<sup>180–183</sup> Diazido- and triazidomethanes readily react with DMAD to afford bis- and tris(triazol-1-yl)methanes; however, in the latter compound, one triazole ring isomerises (apparently, through a 1,5-sigmatropic CH-shift).<sup>184</sup>



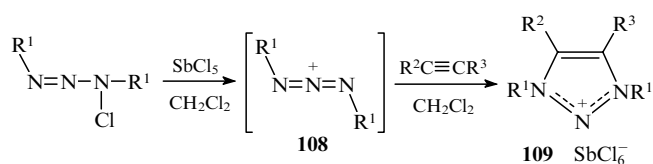
E = CO<sub>2</sub>Me.

Acetylene dicarboxylic acid diamide is much less reactive than DMAD and requires more rigorous conditions to be involved in reactions with organic azides.<sup>18, 179, 185</sup>

The hydroxymethyl and chloromethyl acetylene derivatives **105** (X = Y = CH<sub>2</sub>OH, CH<sub>2</sub>Cl) have been made to react with aryl azides containing various substituents in the ring (Cl, Br, MeO, NO<sub>2</sub>).<sup>180, 186</sup> The functional groups were utilised for further modifications of the triazoles.

The influence of the electronic nature of the substituents in the acetylene molecule on the regiochemistry of the cycloaddition of aromatic azides can be illustrated in relation to the use of phenoxyacetylene and methylpropiolate as dipolarophiles; this results in 1-aryl-substituted 5-phenoxytriazoles<sup>187</sup> and 4-methoxycarbonyltriazoles.<sup>188, 189</sup>

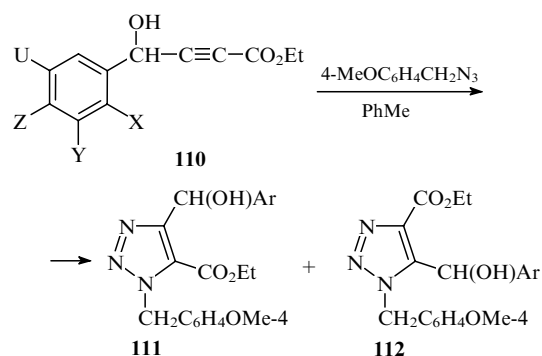
The nitrogen heteroallene cations **108** (1,3-diaza-2-azoniaallene salts) can also enter into cycloaddition with substituted acetylenes, giving rise to 1,2,3-triazolium salts **109**.<sup>190, 191</sup>



R<sup>1</sup> = 4-MeC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 2,4,6-Cl<sub>3</sub>C<sub>6</sub>H<sub>2</sub>; R<sup>2</sup> = R<sup>3</sup> = H, Me, Et, Bu<sup>n</sup>, Bu<sup>t</sup>, HOCH<sub>2</sub>, ClCH<sub>2</sub>, Ph, CO<sub>2</sub>Me.

A large series of 4,5-disubstituted and 4(5)-monosubstituted 1-benzyltriazoles have been prepared on the basis of substituted benzyl azides RC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>N<sub>3</sub>, where R = H, 2-Me, 3-Me, 4-Me, 3-MeO, 4-MeO, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br, 2-NO<sub>2</sub>, 3-NO<sub>2</sub>, and 4-NO<sub>2</sub>, which were made to react with DMAD, phenylacetylene and ethyl propiolate.<sup>177</sup> It was shown that the reaction of benzyl azides with unsubstituted ethyl propiolate, unlike the reaction with phenylacetylene, is strictly regioselective, giving rise to 1-benzyl-4-ethoxycarbonyltriazoles. However, when a terminal group is introduced into the ethyl propiolate, both regioisomers are formed. Thus the cyclocondensation of ethyl 4-aryl-4-hydroxybut-2-ynoates **110** with 4-methoxybenzyl azide gives, most often, mixtures of ethyl 1-(4-methoxybenzyl)triazole-4(5)-carbox-

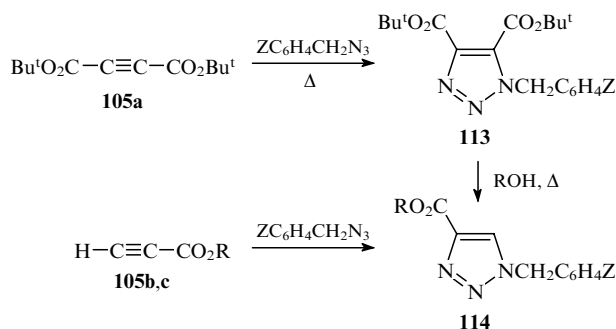
ylates **111** and **112** in ~1 : 1 ratio. Only in two cases was the ratio different (3 : 1 for X = NO<sub>2</sub>, Y = U = H, Z = NHAc and 1 : 1.5 for X = NHCOOCH<sub>2</sub>Ph, Y = U = H, Z = CF<sub>3</sub>).<sup>192</sup>



X = NO<sub>2</sub>, NHCO<sub>2</sub>CH<sub>2</sub>Ph; Y = H, Me, MeO; Z = H, Me, CF<sub>3</sub>, MeO, Pr<sup>i</sup>O, NHAc, NHCO<sub>2</sub>Bu<sup>t</sup>; U = H, Me, MeO, Pr<sup>i</sup>O, MeOCH<sub>2</sub>O.

The cyclisation of substituted 2-fluorobenzyl azides with acetylenic acid derivatives **105** (X = H, Y = CO<sub>2</sub>H, CONH<sub>2</sub>; X = Y = CO<sub>2</sub>Me; X = Y = CONH<sub>2</sub>) has been carried out on heating in toluene, dioxane or DMSO.<sup>193, 194</sup>

The influence of solvents on the course of 1,3-dipolar cycloaddition of di-*tert*-butylacetylenedicarboxylate **105a** to substituted benzyl azides and the concomitant transformations of ester groups in the triazole ring has been studied.<sup>195</sup>

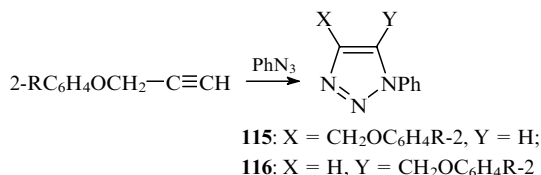


Z = H, 2-Me, 3-Me, 4-Me, 3-MeO, 4-MeO, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br, 2-NO<sub>2</sub>, 3-NO<sub>2</sub>, 4-NO<sub>2</sub>; R = Me (**b**), Et (**c**).

It was found that the reaction proceeds much more slowly in boiling benzene or THF than in methanol or ethanol and results in the expected 4,5-bis-*tert*-butyl esters **113** (yields 73%–94%). However, long-term refluxing of functionally substituted benzyl azides (Z ≠ H, Me) in alcohols results in trans-esterification with partial decarboxylation. This affords 4-alkoxycarbonyltriazoles **114**, whose formation has been confirmed by alternative synthesis from alkynes **105b,c** (yields 88%–95%).

Protected acetylenedicarboxaldehydes can be involved in reactions with azides. During the reactions, the acetal protection is removed. For example, bis[(4,5-diformyltriazol-1-yl)methyl]benzene acetal has been obtained from bis(azidomethyl)benzene and acetylenedicarboxaldehyde bis(diethyl acetal).<sup>196</sup>

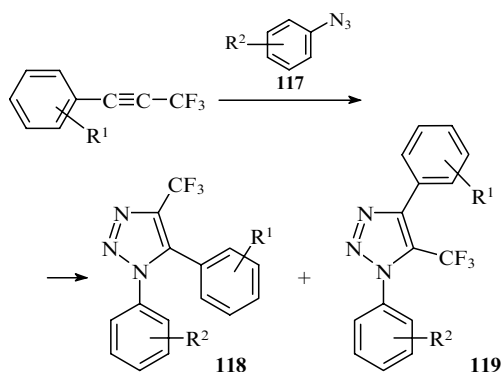
Using the same azide, bis(triazolylmethyl)benzene has been prepared with dibenzoylacetylene as the dipolarophile.<sup>197</sup> 4,5-Diaroyloxymethyl-1-phenyltriazoles are produced from phenyl azide and symmetric bis(aroxyloxymethyl) derivatives of acetylene **105** (X = Y = CH<sub>2</sub>OCOAr).<sup>198</sup> In the case of monosubstituted acetylenes **105** (X = H; Y = CH<sub>2</sub>OCOAr, CH<sub>2</sub>OAr, CH<sub>2</sub>OH), the reaction gives mixtures of 4- and 5-substituted 1-aryltriazole isomers, for example, compounds **115** and **116** (see the studies<sup>199–201</sup>) with predominance of the former compound.



R = H, Me, F, Cl, Br, I, NO<sub>2</sub>.

Propargylthio derivatives also react with organic azides. 1-Pyrazolyl-2-propargylthiobenzoimidazole was converted into the corresponding triazolylmethylthiobenzoimidazole derivative.<sup>202</sup> The synthesis of 1-[(triazol-1-yl)methyl]-1,5-benzodiazepine by the reaction of 1-propargyl-4-phenyl-1,5-benzodiazepin-2-one with benzyl azide has been reported.<sup>203</sup>

The cycloaddition reaction of substituted trifluoromethylphenylacetylenes with aryl azides **117** showed a high regioselectivity; as expected,<sup>204</sup> the 4-CF<sub>3</sub> regioisomer **118** predominated in all cases. This was confirmed by quantum-chemical calculations for the frontier orbitals of the reacting species.<sup>205, 206</sup>



| R <sup>1</sup>    | R <sup>2</sup>      | The ratio <b>118</b> : <b>119</b> |
|-------------------|---------------------|-----------------------------------|
| 2-Cl              | H                   | 93 : 7                            |
| 4-Cl              | H                   | 82 : 18                           |
| 4-NO <sub>2</sub> | H                   | 72 : 28                           |
| 4-MeO             | H                   | 80 : 20                           |
| 4-NH <sub>2</sub> | H                   | 88 : 12                           |
| 4-NO <sub>2</sub> | 2,6-Cl <sub>2</sub> | 71 : 29                           |
| 4-MeO             | 2,6-Cl <sub>2</sub> | 79 : 21                           |
| 4-Cl              | 4-NO <sub>2</sub>   | 80 : 20                           |

The calculations showed that on introduction of an electron-withdrawing CF<sub>3</sub> group, the reaction obeys orbital control and the transition state leading to regioisomer **118** becomes preferred. It is noteworthy that the theory of frontier orbitals is not always able to predict quantitatively the isomer ratio. For this purpose, it is proposed to calculate the local electron density indices in terms of electron density functional theory, which are sensitive to changes in the chemical potential upon the introduction of substituents.<sup>207</sup>

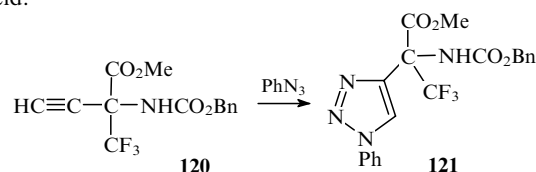
Although the nature of the substituents in both phenyl groups has little influence on the cycloaddition regioselectivity, it does influence the reaction rate (the presence of electron-withdrawing NO<sub>2</sub> group in the azide molecule retards the process).<sup>204</sup>

The reaction of pentafluorophenylacetylene with aryl azides affords only the 1,4-regioisomer, which corresponds to the electron density distribution in the reacting molecules;<sup>208</sup> the reaction of conjugated trifluoromethyldiacetylenes with phenyl azide involves only one triple bond, which carries the CF<sub>3</sub> group, and also results in one 1,4-isomer.<sup>208</sup>

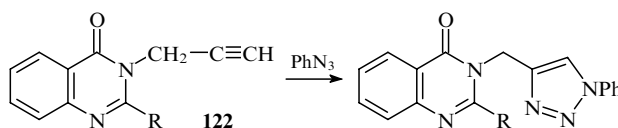
The similar effect of an electron-withdrawing substituent (CO<sub>2</sub>Alk) at the triple bond of the alkyne on the regioselectivity of cycloaddition with phenyl azide is also observed for methyl 3-phenylpropiolate and methylbut-2-ynoate, which were converted into 4- and 5-methoxycarbonyl-substituted triazoles in 66 : 34 and 70 : 30 ratios, respectively.<sup>209</sup> A similar result has been

obtained in reactions of a chiral azide, 1-[(*R*)-3-azido-3-cyclohexylpropanoyl]pyrrolidin-2-ol, with methyl propiolate and ethyl but-2-ynoate<sup>210</sup> and a number of aryl azides with methyl 4-oxo(or hydroxy)but-2-ynoates.<sup>211, 212</sup> However, in the case of 1-phenylseleno-2-(*p*-tolylsulfonyl)acetylene, triazole with the tosyl group at the 5-position is formed predominantly.<sup>213</sup>

The bulky Me<sub>3</sub>Si group in the acetylene molecule is favourable for the formation of 1-(het)aryl-4-trimethylsilyltriazoles in the reaction of trimethylsilylacetylene **105** (X = H, Y = SiMe<sub>3</sub>) with aryl azides and azido derivatives of seleno(thio)phene.<sup>214, 215</sup> These examples were used to establish the logarithmic dependence of the reaction rate on the pressure and to select the optimal conditions for the preparation of 1,4-disubstituted triazoles (20 °C, ~1 GPa).<sup>216</sup> The presence of the bulky tertiary substituent in the propargylamine **120** molecule is also favourable for the formation of only 4-substituted 1-phenyltriazole **121** in a high yield.<sup>217</sup>



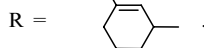
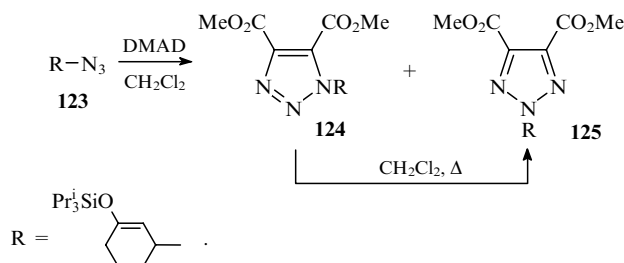
Steric factors may be responsible for the predominant formation of 4-substituted 1-phenyltriazoles upon the reaction of phenyl azide with *tert*-butyl 2-(*tert*-butyloxycarbonylamino)-4-oxohex-5-ynoate<sup>218, 219</sup> and trimethylstannylacetylene.<sup>220</sup> A similar result has been obtained in the reaction of phenyl azide with 3-propargylquinazolones **122**.<sup>221</sup>



R = H, Me, Ph.

Thus, 1,3-dipolar cycloaddition of aliphatic and aromatic azides to terminal alkynes under kinetic control conditions results in the corresponding 1,4-disubstituted triazoles.

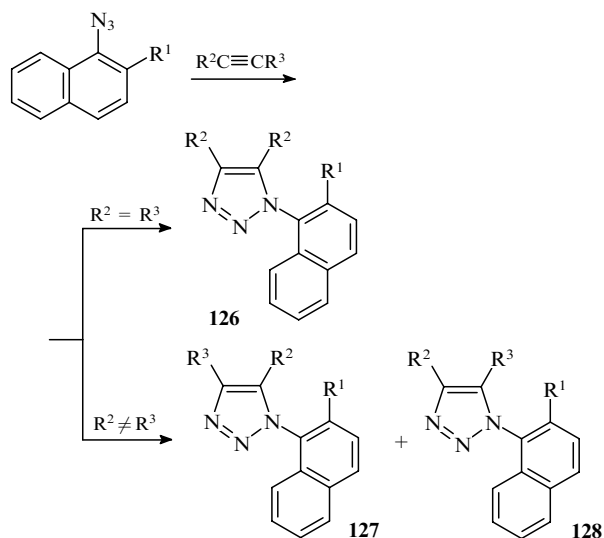
The formation of an unusual isomer was detected in the reaction with a symmetrical alkyne. Monitoring of the reaction of the triisopropylsilyl ether of the enol of 3-azido cyclohexanone **123** with DMAD in boiling CH<sub>2</sub>Cl<sub>2</sub> has shown that 1-cyclohexenol triazole derivative **124** is formed initially; after 17 h, the presence of substantial amounts of the 2-isomer **125** can be detected (the yields are 27% and 45%, respectively); after 72 h, only triazole **125** remains in the reaction mixture.<sup>222</sup>



This fact suggests that 1-substituted triazole **124** is ionised under the given conditions followed by recombination of ions into thermodynamically more stable 2-isomer **125**. The suggestion is based on new theoretical and experimental data on triazole<sup>223, 224</sup> and benzotriazole<sup>225, 226</sup> tautomerism.

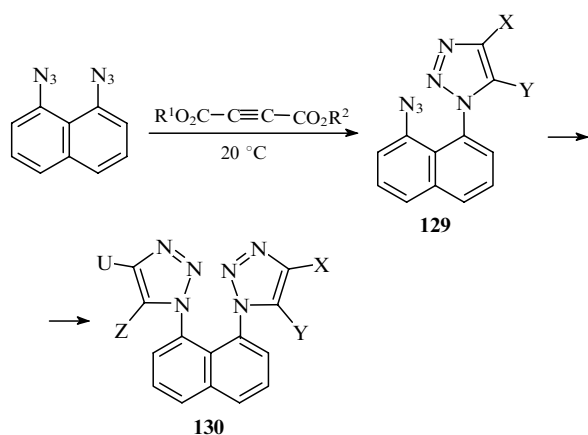
Cycloaddition of 1-naphthyl azides to symmetrical disubstituted alkynes also proceeds under relatively mild conditions to give 4,5-disubstituted 1-naphthyltriazole **126**,<sup>182</sup> whereas the reaction with asymmetric alkynes yields predominantly 4-substituted 1-naphthyltriazole **127**.<sup>24, 227</sup> Thus in the reaction of 1-naphthyl azide with ethyl propiolate, the yield of the 4-ethoxycarbonyl

derivative **127** ( $R^1 = R^2 = \text{H}$ ,  $R^3 = \text{CO}_2\text{Et}$ ) amounts to 71%, and the yield of 5-regioisomer **128** ( $R^1 = R^2 = \text{H}$ ,  $R^3 = \text{CO}_2\text{Et}$ ) is only 18%.<sup>227</sup>



$R^1 = \text{H}$ , Me;  $R^2 = R^3 = \text{CO}_2\text{Et}$ ;  $R^2 = \text{H}$ ,  $R^3 = \text{CO}_2\text{Et}$ ;  
 $R^2 = \text{Me}$ ,  $R^3 = \text{CO}_2\text{Me}$ .

In the presence of two azido groups located in the *peri*-positions, the reaction with diethyl acetylenedicarboxylate proceeds in several stages: first, two isomeric monotriazolynaphthalenes **129** are formed, the 4-ethoxycarbonyl derivative ( $Y = \text{H}$ ,  $X = \text{CO}_2\text{Et}$ ) being the predominant isomer; on long-term keeping of the reaction mixture, a mixture of 1,8-ditriazolynaphthalenes **130** is formed.<sup>227</sup>



| X                  | Y                  | Z                  | U                  | Yield of <b>130</b> (%) <sup>a</sup> |
|--------------------|--------------------|--------------------|--------------------|--------------------------------------|
| CO <sub>2</sub> Et | H                  | H                  | CO <sub>2</sub> Et | 52                                   |
| CO <sub>2</sub> Et | H                  | CO <sub>2</sub> Et | H                  | 24                                   |
| H                  | CO <sub>2</sub> Et | CO <sub>2</sub> Et | H                  | 2                                    |

<sup>a</sup> For  $R^1 = R^2 = \text{Et}$ .

Various dialkyl acetylenedicarboxylates ( $R^1 \neq R^2$ ) have been employed in the cyclocondensation with 1,8-diazidonaphthalene. The subsequent chemical transformations of the azide and ester groups gave rise to diverse functional derivatives **130**.<sup>227–229</sup>

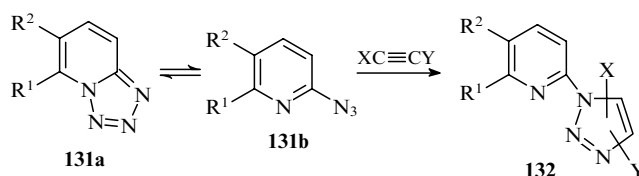
Recently, it has been found that Cu(I)-catalysed cycloaddition of azides to terminal acetylenes is regiospecific and gives 1,4-disubstituted triazoles.<sup>230–236</sup> The use of encapsulation techniques in the reaction of phenyl azide with phenylacetylene made it possible not only to increase appreciably the reaction rate but also to obtain the only isomer, 1,4-diphenyltriazole.<sup>237</sup>

A new, in principle, method for regiocontrol of the dipolar cycloaddition, based on the chemical recognition principle, has

been proposed.<sup>238</sup> The method implies selective spatial fixation of the reacting molecules of a dipolar compound and a dipolarophile. A crown ether fragment (in the azide molecule) and a terminal ammonium group (in the substituted acetylene molecule) are used as the structural blocks than ensure the chemical recognition. Due to the formation of a bound complex between these blocks, the cycloaddition becomes pseudo-intramolecular, which facilitates the reaction and markedly increases the regioselectivity (only 3% of the second regioisomer) compared to the model reaction carried out without complex formation (in this case, up to 43% of the second isomer is formed).<sup>238</sup>

Heterocyclic azides have also been used in reactions with acetylene derivatives, for example, 6-azido-2,3-diphenylindole,<sup>239</sup> tetrathiafulvalene azido derivatives,<sup>240</sup> fluoroquinolonecarboxylic acid azido derivatives<sup>241</sup> and azidobenzo[*b*]thiophenes.<sup>214, 242</sup> 9-Azidoacridine reacts with alkynes to give regioisomers of 9-(4,5-disubstituted 1*H*-1,2,3-triazol-1-yl)acridines; only in the case of trimethylsilylacetylene, does the reaction proceed regioselectively.<sup>243</sup> The attempts to introduce acetylene and its homologues into the reaction with 5- and 6-azido-2-methylbenzothiazoles did not lead to the desired outcome, whereas the use of more reactive organomagnesium derivatives  $\text{RC}\equiv\text{CMgBr}$  ( $R = \text{Me}$ ,  $\text{Ph}$ ) (Iotsich complexes) made it possible to obtain the corresponding 1,5-disubstituted triazoles.<sup>244</sup>

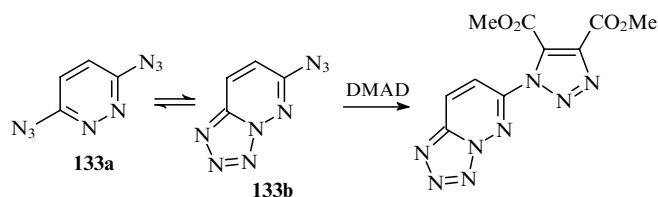
For azido derivatives of azines, the influence of additional factors on the cycloaddition reaction has been noted. On the one hand, the electron-withdrawing properties of the heterocycle favour polarisation of the azide fragment. On the other hand, in the case of  $\alpha$ -isomers, there exists a tautomeric equilibrium between the azidoazine and the cyclic form, tetrazoloazine, the stability of which is determined by the nature and the positions of substituents in the azine ring. The influence of these factors accounts for the different reactivities of substituted 2-azidopyridines **131** upon reaction with DMAD. Previously, it has been shown<sup>245</sup> that 2-azido-6-chloropyridine **131** ( $R^1 = \text{Cl}$ ,  $R^2 = \text{H}$ ) forms the corresponding 1-pyridyltriazole **132** ( $R^1 = \text{Cl}$ ,  $R^2 = \text{H}$ ) in boiling chloroform, whereas unsubstituted 2-azidopyridine and its 5-derivatives ( $R^1 = \text{H}$ ;  $R^2 = \text{H}$ ,  $\text{Br}$ ,  $\text{NO}_2$ ) react with DMAD only on strong heating in the absence of a solvent. The reaction of 2-azidopyridine with methyl propiolate ( $X = \text{H}$ ,  $Y = \text{CO}_2\text{Me}$ ) and diphenylacetylene ( $X = Y = \text{Ph}$ ) proceeds in a similar way.<sup>246</sup> The 6- $\text{CF}_3$  derivative reacts with phenylacetylene to give a mixture of 4- and 5-regioisomers in  $\sim 1:1$  ratio.<sup>247</sup>



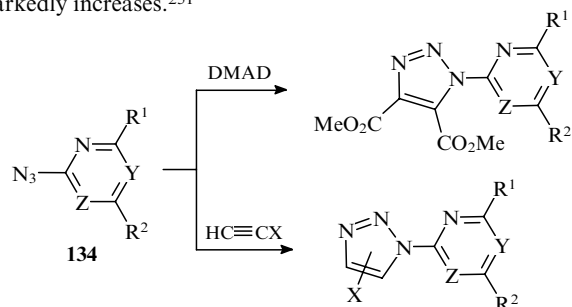
$R^1 = \text{H}$ ,  $\text{Cl}$ ,  $\text{CF}_3$ ;  $R^2 = \text{H}$ ,  $\text{Br}$ ,  $\text{NO}_2$ ;  $X = Y = \text{CO}_2\text{Me}$ ;  $X = Y = \text{Ph}$ ;  
 $X = \text{H}$ ;  $Y = \text{CO}_2\text{Me}$ ,  $\text{Ph}$ .

According to a publication,<sup>248</sup> 4- and 6-substituted (by  $\text{Cl}$ ,  $\text{Br}$ ,  $\text{CF}_3$ ) 2-azidopyridines form 1-pyridyl-4-methoxycarbonyltriazoles in high yields on refluxing with methyl propiolate in  $\text{CHCl}_3$ . 4-Azidotetrafluoropyridine reacts with diphenylacetylene on heating in  $\text{CCl}_4$ ; however, the yield of the cycloadduct is very low under these conditions.<sup>249</sup>

The reaction of azido derivatives of pyrimidine and pyrazine with DMAD and methyl propiolate takes place under milder conditions than the reaction with azidopyridines due to the stronger electron-withdrawing properties of the heterocycle.<sup>246, 250</sup> 3,6-Diazidopyridazine **133a** reacts with transformation of only one azido group even under drastic conditions, because the second azido group exists predominantly in the cyclic tetrazole form (tautomer **133b**).<sup>250</sup>



2- and 4-Azidopyrimidines **134**, containing a phenyl and/or *o*-hydroxyphenyl group in the heterocycle react with DMAD, phenylacetylene and propargyl alcohol to give substituted 1-pyrimidyltriazoles in 70%–90% yields. It was found that conducting the reaction at 140 °C in the presence of excess alkyne is optimal, whereas on heating in solvents, the reaction time markedly increases.<sup>251</sup>

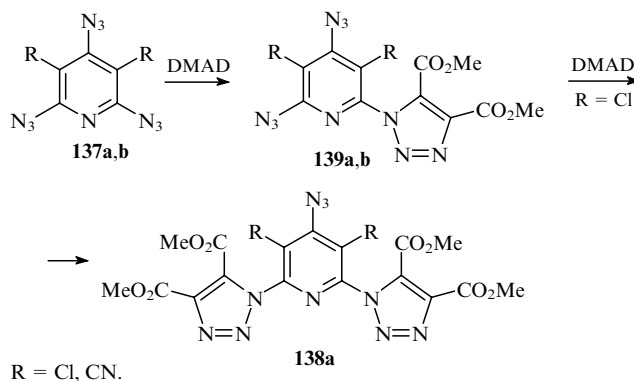


Y = CH, Z = N; Y = N, Z = CH; R<sup>1</sup>, R<sup>2</sup> = H, Ph, 2-HOC<sub>6</sub>H<sub>4</sub>;  
X = Ph, CH<sub>2</sub>OH.

On the basis of cycloaddition of 6-azidouracils to DMAD and phenylacetylene, a method for the synthesis of new potentially biologically active triazolyluracils has been developed.<sup>252</sup> This reaction readily proceeds on refluxing in toluene and the product yields are high. Recently, it has been shown that a broad range of mono- and bis(triazolyl)pyrimidines can be synthesised on the basis of diazidopyrimidines and acetylenic dipolarophiles. The presence of an active azido group in the pyrimidine ring of the monosubstituted derivatives permits the nucleophilic substitution of this group by various functional groups. Moreover, azidation of triazolylpyrimidines demonstrated nucleofugacity of the 1*H*-1,2,3-triazolyl fragment,<sup>253</sup> whose mobility is governed by the nature of substituents in the pyrimidine and triazole rings (Scheme 3). The researchers cited found an unusual reaction of

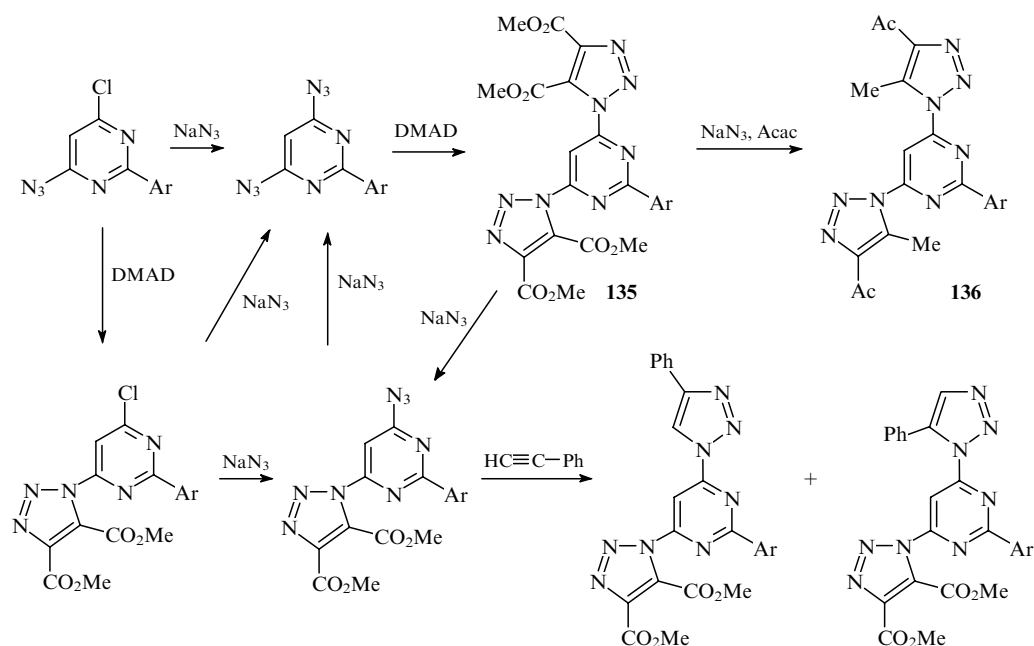
bis(triazolyl)pyrimidine **135** with acetylacetone, which can be formally considered as replacement of two carbon fragments of DMAD by the corresponding fragments of 'dehydrated' acetylacetone ('Ac–C≡C–Me') to give compound **136** (see Section IV.3).

When the pyridine ring contains three azide groups at the 2-, 4- and 6-positions, the route and level of the cycloaddition depend to a large extent on the nature of the dipolarophile. Using triazido-pyridine **137** as an example, it was found that two DMAD molecules easily add to 2- and 6-azido groups yielding bis(triazolyl)pyridine **138a** in a high yield.<sup>254–256</sup>



On the basis of quantum-chemical calculations (PM3), it has been shown that the electron densities on the frontier orbitals are different for the  $\alpha$ - and  $\gamma$ -azide groups in molecule **137a**. For example, the HOMO has a high orbital density on the  $\alpha$ -azide group and a low density on the  $\gamma$ -analogue, which results in reactions with electron-deficient dipolarophiles (for example, DMAD) at the azide group in the 2-position. Conversely, the higher orbital density on the  $\gamma$ -azide group in the LUMO of molecule **137a** is favourable for reactions with electron-enriched dipolarophiles (for example, with norbornene) to give aziridine. It also follows from the calculations that the presence of the triazolyl group in molecule **139a** does not change the situation significantly, and therefore, the reaction with DMAD further involves the second  $\alpha$ -azido group.<sup>255</sup> A similar reaction of a more electron-deficient dicyano-substituted pyridine **137b** with DMAD stops after the formation of the monoadduct 2,4-diazido-6-triazolyl-3,5-dicyanopyridine **139b** (yield 34%).<sup>257</sup> The thermal reaction of

Scheme 3

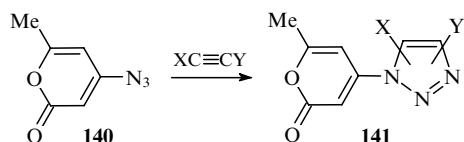


Acac is acetylacetone.

4-azido-2,6-bis-(2-pyridyl)pyridine with DMAD gives the 2*H*-azirine derivative rather than triazole.<sup>258</sup>

7-*R*-8-Azidoquinolines (*R* = H, Me) readily react with DMAD and dehydrobenzene to give esters of 1-(8-quinolyl)triazole-4,5-dicarboxylic acids and benzotriazole, respectively, in high yields.<sup>259</sup>

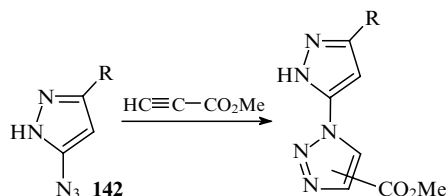
On heating with symmetric alkynes (*X* = *Y*), 4-azido-6-methyl-2*H*-pyran-2-one **140** gives disubstituted triazolypyrones **141** in high yields.<sup>260</sup> In the case of phenylacetylene (*X* = H, *Y* = Ph), the reaction products contain both regioisomers, 5-phenyl-substituted triazole **141** (*Y* = 5-Ph) somewhat predominating over the 4-regioisomer **141** (*Y* = 4-Ph), whereas ethoxyacetylene (*X* = H, *Y* = OEt) furnishes only 5-ethoxytriazole **141** (*Y* = 5-OEt).<sup>260</sup>



*X* = *Y* = Ph; *X* = *Y* = CH<sub>2</sub>OH; *X* = H, *Y* = Ph; *X* = H, *Y* = OEt.

A series of 4-(triazol-1-yl)-2*H*-benzopyran-2-ones have been prepared by cyclocondensation of 7-diethylamino-4-azidobenzopyranone with mono- and disubstituted acetylenes (H, Ph, CH<sub>2</sub>Cl and CH<sub>2</sub>OH as substituents).<sup>261</sup>

Examples of the synthesis of azolytriazoles have been reported. 5-Azidopyrazoles **142** were used for the synthesis of pyrazolyltriazoles. It was found that the reaction with methyl propiolate takes place on refluxing the reactants in acetonitrile or toluene; 4-regioisomers predominated in the reaction products.<sup>48, 262</sup> The cyclocondensation with DMAD occurs in the usual way; dipolarophiles such as phenylacetylene, ethyl phenylpropiolate and ethyltrimethylsilyl propiolate proved insufficiently reactive and did not enter into this reaction.<sup>262</sup>



*R* = Ph (45%); H, Bu<sup>t</sup> (79%–86%).

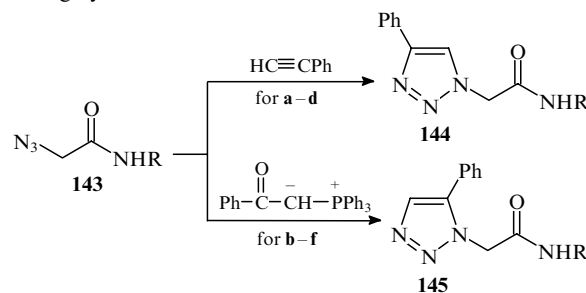
2-Azidoimidazole has not been involved into the reaction with methyl propiolate even in boiling toluene,<sup>262</sup> whereas 5-azido-2-aryl-4-trifluoromethylthiazoles (Ar = 2-thienyl, 2-furyl, 4-MeC<sub>6</sub>H<sub>4</sub>) form mixtures of the corresponding substituted (triazol-1-yl)thiazoles.<sup>263, 264</sup>

The synthesis of some (triazol-1-yl)oxazolines<sup>265</sup> and furazans<sup>266, 267</sup> have been described. In relation to the reaction of 3-azido-4-aminofurazan with ethoxycarbonylacetylenes, it was shown that the use of an ionic liquid as the reaction medium shortens the time of synthesis several-fold.<sup>268</sup>

Despite the fact that examples of the use of various alkynes and azides in 1,3-dipolar cycloadditions are quite diverse and have been considered previously in many publications, the range of reagents used to prepare new triazole derivatives has been markedly extended in recent years. For example, dehydrobenzenes and 2,3-dehydronaphthalene generated in the reaction mixture *in situ* have been used in this reaction as dipolarophiles. This resulted in the synthesis of a series of substituted 1-naphthylbenzotriazoles and 1-(2-methyl-1-naphthyl)naphtho[2,3-*c*]triazole.<sup>259</sup>

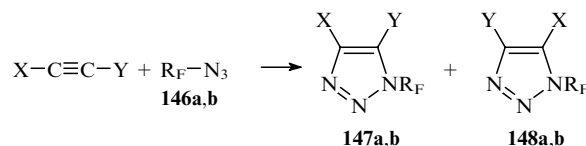
Various alkyl azides<sup>269–272</sup> and amidoalkyl azides **143**<sup>273</sup> have been made to react with asymmetric acetylene derivatives. This was found to give predominantly 1,4-disubstituted triazoles **144**. An exception is acetophenone triphenylphosphorus ylide

(formally, the latent form of phenylacetylene), which reacts with amidoalkyl azides **143** to give the corresponding 5-phenyl isomers **145** in high yields.<sup>273</sup>



*R* = Ph (**a**), 2-MeC<sub>6</sub>H<sub>4</sub> (**b**), 4-MeC<sub>6</sub>H<sub>4</sub> (**c**), 2-ClC<sub>6</sub>H<sub>4</sub> (**d**), 4-ClC<sub>6</sub>H<sub>4</sub> (**e**), Bn (**f**).

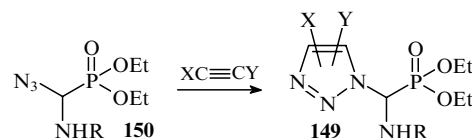
The earlier attempts to involve fluorinated alkyl azides into cycloaddition with diphenylacetylene have failed.<sup>274</sup> However, recently, reactions of 2*H*-perfluoropropyl azide **146a** and methyl 3-azidoperfluoropropionate with various acetylene derivatives have been carried out.<sup>275</sup> The reaction with monosubstituted acetylenes is carried out in an autoclave with heating to 90–130 °C, while that with disubstituted acetylenes is carried out at 170 °C. The regioselectivity of cycloaddition (ratio of **147**:**148** isomers) depends on the type of substituents in the reactants.



*X* = Bu<sup>n</sup>, Ph, CO<sub>2</sub>Me, SiMe<sub>3</sub>; *Y* = H, Ph, CO<sub>2</sub>Me;  
*R*<sub>F</sub> = CF<sub>3</sub>CHFCF<sub>2</sub> (**a**), MeO<sub>2</sub>C(CF<sub>2</sub>)<sub>2</sub> (**b**).

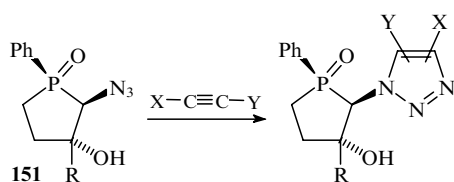
| <i>X</i>           | <i>Y</i>           | Yields (%)  |             |
|--------------------|--------------------|-------------|-------------|
|                    |                    | <b>147a</b> | <b>148a</b> |
| Ph                 | H                  | 32          | 62          |
| Bu <sup>n</sup>    | H                  | 37          | 58          |
| CO <sub>2</sub> Me | H                  | 70          | 18          |
| SiMe <sub>3</sub>  | H                  | 50          | —           |
| CO <sub>2</sub> Me | CO <sub>2</sub> Me | 96          | —           |
| Ph                 | Ph                 | 88          | —           |
| SiMe <sub>3</sub>  | Ph                 | 35          | 5           |

Derivatives of α-azido-α-amino acids have also been used as substrates in reactions with dipolarophiles.<sup>276, 277</sup> Esters of α-amino-α-(triazol-1-yl)phosphonic acid **149** are readily formed upon condensation of diethyl α-azido-α-aminophosphonic acid **150** with alkynes.<sup>278, 279</sup> In the case of monosubstituted acetylenes (*X* = H; *Y* = Bu, CH<sub>2</sub>Cl, CH<sub>2</sub>Br), the 1,4-disubstituted triazole to 1,5-isomer ratio in the reaction products varies from 2:1 to 5:1; in other cases, the 5-regioisomer is detected in only minor amounts.



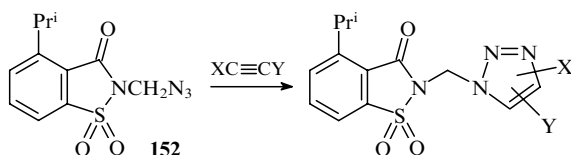
*R* = PhCO, CO<sub>2</sub>CH<sub>2</sub>CCl<sub>3</sub>; *X* = H, Ph, CO<sub>2</sub>Me; *Y* = Bu<sup>n</sup>, CH<sub>2</sub>Cl, CH<sub>2</sub>Br, PrCH(OH), Ph, CO<sub>2</sub>Me, CO<sub>2</sub>Et.

Several publications are devoted to cycloaddition to alkynes of other phosphorus-containing azides: ω-azidoalkyltriphenylphosphonium bromides<sup>280</sup> and azidomethylphosphonates.<sup>281–284</sup> From 2-azido-3-hydroxy-1-phenylphospholane 1-oxides **151**, a number of optically active triazole derivatives have been prepared.<sup>285–290</sup>



R = H, Alk; X, Y = H, Alk, CO<sub>2</sub>Alk.

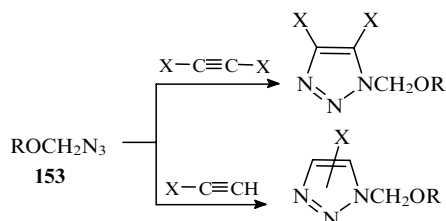
The influence of spatial factors on the regioselectivity of the cycloaddition to asymmetrical alkynes has been studied in relation to the reaction of the azidomethyl derivative of sulfone **152**.<sup>291</sup> The regioselectivity was found to be controlled by the steric effects of the substituents X and Y. As the substituent bulk increases in the series H < Ph < Bu<sup>t</sup> < Me<sub>3</sub>Si, the ratio of the regioisomers in the reaction products varies in parallel, except for the Me<sub>3</sub>Si group. The steric effect of the last-mentioned group acts in the same direction as the electronic effect, whose role is to stabilise the induced positive charge on the acetylene β-carbon atom in the transition state. Both effects promote the formation of 4-trimethylsilyl isomers as the only products in high yields. An increase in the pressure to 10 kbar increases substantially the reaction rate.<sup>291</sup>



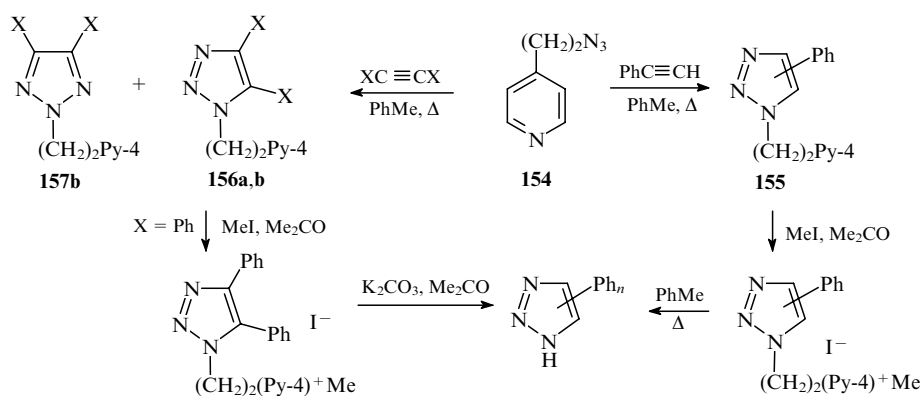
X = H: Y = CO<sub>2</sub>Me, SiMe<sub>3</sub>, SO<sub>2</sub>Ph; X = Ph, Y = CO<sub>2</sub>Et;

X = Bu<sup>t</sup>, Y = SO<sub>2</sub>Ph; X = SiMe<sub>3</sub>: Y = CO<sub>2</sub>Me, SO<sub>2</sub>Ph, SO<sub>2</sub>NMe<sub>2</sub>.

The 1,3-dipolar cycloaddition of the substituted alkoxyethyl azides **153** to symmetrical and asymmetrical alkynes has been used to prepare an extensive series of 1-alkoxyethyltriazole derivatives.<sup>292</sup> The yields of the isolated compounds varied from 11% to 95%; the low yields can be attributed to the low thermal stability of the starting alkyl azides.



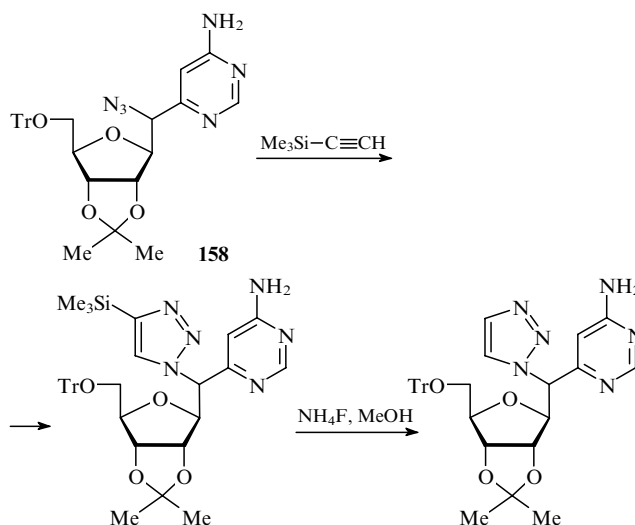
R = HO(CH<sub>2</sub>)<sub>2</sub>, MeO<sub>2</sub>C(CH<sub>2</sub>)<sub>2</sub>, BnO(CH<sub>2</sub>)<sub>2</sub>, (BnOCH<sub>2</sub>)<sub>2</sub>CH,  
BnO(BnOCH<sub>2</sub>)CHCH<sub>2</sub>; X = CO<sub>2</sub>Me, Ph, 4-ClC<sub>6</sub>H<sub>4</sub>, 2-Py.



X = Ph (**a**), C<sup>o</sup>Ph (**b**); n = 1, 2.

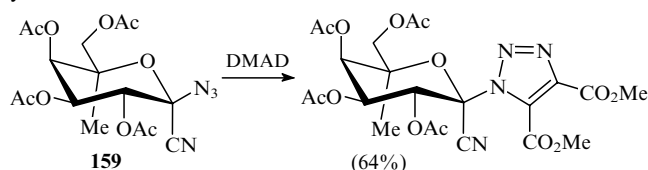
Interesting results have been obtained<sup>293</sup> by refluxing 2-(4-pyridyl)ethyl azide **154** with substituted alkynes in toluene. In the case of phenylacetylene, a mixture of 4- and 5-phenyl-2-(4-pyridyl)ethyltriazole **155** was synthesised (regioisomer ratio 1 : 2, quantitative yield). If the reaction is carried out with diphenylacetylene, 4,5-diphenyltriazole **156a** is formed in a relatively low yield. In the case of dibenzoylacetylene, in addition to 4,5-dibenzoyl derivative **156b**, the rearrangement product **157b** was obtained (yield 8%, **156b** : **157b** = 4 : 1). The compounds **155**, **156a**, which are quaternised at the pyridine nitrogen atom, undergo the retro-Michael rearrangement to give 1-unsubstituted triazoles (Scheme 4).<sup>293</sup>

The synthesis of a number of β-lactams containing a triazolyl group from the corresponding azides has been described.<sup>294</sup> New-type homo-C-nucleosides have been obtained by the 1,3-dipolar cycloaddition of trimethylsilylacetylene to the azide groups of 4-amino-6-(ribofuranosyl)azidomethylpyrimidine **158** epimers.<sup>295, 296</sup>



Tr is triphenylmethyl (trityl).

Quite a few examples of using this strategy for the preparation of glycosylated triazoles from azido derivatives are documented. Thus on refluxing in toluene with DMAD, acetylated 1-azidoglycopyranosyl cyanide **159** gives the cycloaddition product in a good yield.<sup>297–299</sup>



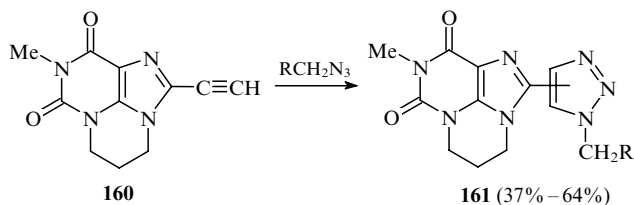
Scheme 4

Under the same conditions, DMAD reacts with 3-azido-3-deoxy- $\alpha$ -D-glucufuranose derivatives<sup>298,300</sup> and with 6-azido-6-deoxycyclodextrins.<sup>301,302</sup> The reactions of acetylated cellobiosyl, lactosyl, maltosyl and melibiosyl azides with various esters of acetylenedicarboxylic acid affords the corresponding 1-glycobiosyltriazaolones, which were used in the synthesis of oligosaccharides and anthracycline antibiotics.<sup>303</sup>

The reactions of 5-azido-5-deoxy- $\alpha$ -D-xylofuranose derivatives, methyl 5-azido-5-deoxy- $\beta$ -D-ribofuranoside and other azido sugars with various acetylene derivatives were carried out to prepare nucleoside analogues containing triazole as the nitrogenous base.<sup>19, 231, 232, 304–315</sup> The other compounds used as substrates in the reaction with alkynes include 3'-azido-2',3'-dideoxythymidine and 3'-azido-2',3'-dideoxyuridine,<sup>185,316</sup> 3'-azido-3'-deoxythymidine and 5'-azido-5'-deoxythymidine,<sup>317,318</sup> as well as azido derivatives of acyclonucleosides<sup>319</sup> and the carbocyclic analogue of furanose.<sup>320</sup>

The cycloaddition using a soluble polymer (based on polyethylene glycol succinate) with one of the reactants attached to it, either azide (for example, 5-azido-5-deoxy-1,2-*O*-isopropylidene- $\alpha$ -D-xylofuranose) or acetylene (for example, propargyl alcohol), has been proposed.<sup>306</sup> Except for the reaction of polymer-supported azide with diphenylacetylene, both versions of this process give products in quantitative yields. The product is removed from the polymer support by treatment of the methanol solution with excess ammonia followed by ether precipitation of the polymer.

The reaction of organic azides with alkynes allows the use of broad ranges of both reactants. For example, various acetylene derivatives containing heterocyclic fragments were used as dipolarophiles. Pyrimido[1,2,3-*cd*]purine-8,10-dione **160** as the acetylene derivative and a number of organic azides were made to react to give 2-(4- and 5-triazolyl) derivatives (~1:1) of heterocyclic system **161**.<sup>321</sup>



R = HOCH<sub>2</sub>, HOCH<sub>2</sub>CH(OH), HOCH<sub>2</sub>(CHOH)<sub>2</sub>CH(OH), CO<sub>2</sub>Me, Ph.

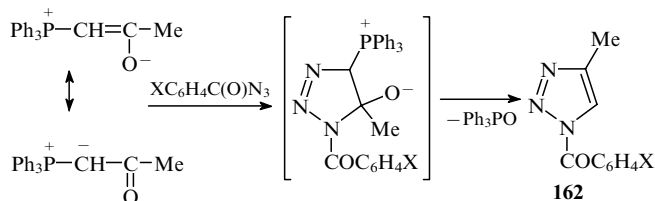
The reaction of 9-propargylguanidine with AcOCH<sub>2</sub>.CH<sub>2</sub>OCH<sub>2</sub>N<sub>3</sub> affords the 1,4- and 1,5-regioisomers in a 7:3 ratio (overall yield 71%).<sup>322</sup> The use of a ZnCl<sub>2</sub>-doped natural phosphate as the catalyst allows one to shorten the reaction time by an order of magnitude without changing the yield and the isomer composition.

The dipolar 1,3-cycloaddition has been used successfully to synthesise triazole derivatives of various classes of large molecules and some polymers, in particular, crown ethers,<sup>323,324</sup> rotaxanes,<sup>325–327</sup> pseudorotaxanes,<sup>328</sup> dendrimers<sup>329</sup> and polystyrenes.<sup>236</sup>

N-substituted histidine analogues have been obtained by the reaction of azides with C-propargylglycine, while reactions with terminal alkynes containing peptide residues gave peptidotriazoles.<sup>230</sup> This strategy has found application as a tool for studying proteins, for example, the protein shell of the plant mosaic virus<sup>330</sup> and a number of enzymes.<sup>331</sup> The reaction between N-protected propargylamine and the azide obtained from D-leucine is a route to cyclic peptides with triazole fragments capable of self-organisation and formation of peptide nanotubes.<sup>234</sup>

Numerous examples of the use of phosphorus-containing alkynes in reactions with azides have been described. 4,5-Disubstituted triazoles have been prepared on the basis of symmetric disubstituted acetylenes with diphenyl and thiophosphinoyl

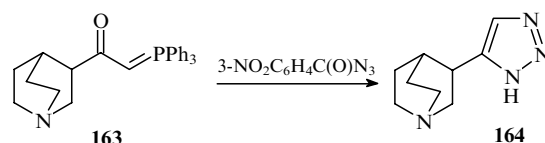
groups.<sup>332,333</sup> Phosphorus ylides containing an  $\alpha$ -oxo group in the chain (Wittig reagents, see above) behave similarly to electron-enriched acetylenes; they react with organic azides to give the corresponding triazoles.<sup>2,8,273</sup> This method has been used to obtain two benzoyl triazole isomers based on acetone triphenylphosphorus ylide (acetylmethyltriphenylphosphorane).<sup>334</sup> In a similar reaction with *o*- and *m*-phthalimidobenzoyl azides, 4-methyltriazaolones **162** are formed in high yields. Presumably, the azide adds to the enol form of the ylide and this is followed by elimination of a triphenylphosphine oxide molecule.



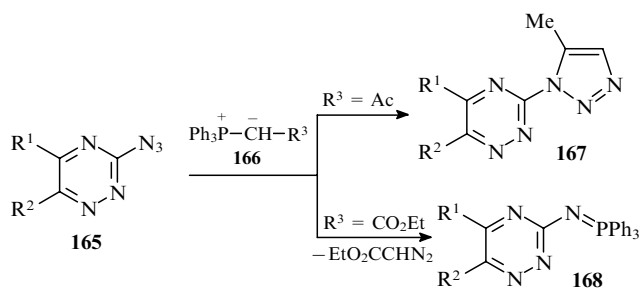
X = 2- and 3-phthalimido.

It was shown that the preparation of 1-aryl-5-substituted triazoles from aryl azides and phosphonium ylides is sharply accelerated when the reactions are initiated by microwave irradiation of the reactant mixture supported on SiO<sub>2</sub>.<sup>335</sup>

The reaction of the 3-quinuclidine analogue of the Wittig reagent **163** with 3-nitrobenzoyl azide has yielded a product that was debenzoylated during chromatography on Al<sub>2</sub>O<sub>3</sub>, being converted into N-unsubstituted (3-quinuclidinyl) triazole **164**.<sup>336</sup>



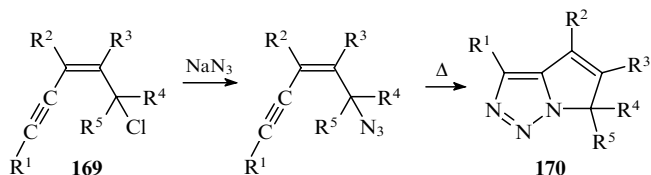
The use of glycosyl azides as substrates in the cycloaddition of 2-oxoalkylenetriphenylphosphoranes has been reported.<sup>337</sup> Azido derivatives of 5,6-diphenyl-*as*-triazine **165** and its phenanthrene analogue react with acetylmethylenetriphenylphosphorane **166** (R<sup>3</sup> = Ac) being converted into 1-azinyl-5-methyltriazaolones **167** in high yields.<sup>338</sup> However, the replacement of the acetyl substituent in the phosphorane by the ethoxycarbonyl group results in the formation of only iminophosphoranes **168**. In the latter case, ethyl diazoacetate is also formed in 70% yield.<sup>338</sup>



R<sup>1</sup> = R<sup>2</sup> = Ph, R<sup>1</sup>–R<sup>2</sup> = *o,o'*-biphenylene, R<sup>3</sup> = Ac, CO<sub>2</sub>Et.

5-Substituted 1-[1-(diethoxyphosphonyl)alkyl]triazaolones are formed in good yields in the reaction of diethyl 1-azidoalkylphosphonates with 2-oxoalkylenetriphenylphosphoranes.<sup>339</sup> Acetyl- and benzoylphosphoranes were transformed into 4 $\beta$ -(triazol-1-yl)podophyllotoxin derivatives to study their cytotoxic properties.<sup>340</sup>

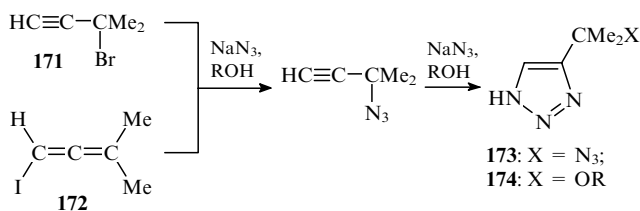
Worth mentioning are numerous examples of the combination of two functions, an azide group and a triple bond linked by an at least three-carbon bridge in one molecule. The cyclisation of the azide obtained from enyne **169** allows the synthesis of annelated triazole systems, for example, pyrrolotriazole **170**.<sup>341</sup>



$R^1, R^2, R^3, R^4, R^5 = H, Me; R^2-R^3 = (CH_2)_4$ .

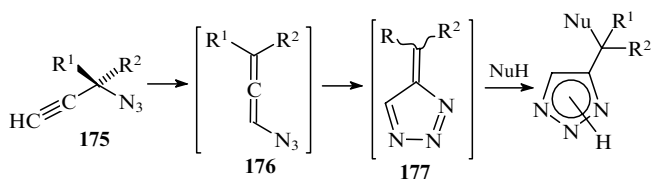
A similar result has been attained in the case of a saturated chain of three carbon atoms.<sup>210</sup>

If the azide group and the triple bond are separated in the molecule by only a methylene group, the presence of nucleophilic agents is needed for cyclisation. Thus treatment of bromobutyne **171** or iodoallene **172** with sodium azide in alcohol at room temperature affords a mixture of 4-(1-azido-1-methylethyl)-1*H*-triazole **173** and 4-(1-alkoxy-1-methylethyl)-1*H*-triazole **174**.<sup>342</sup>



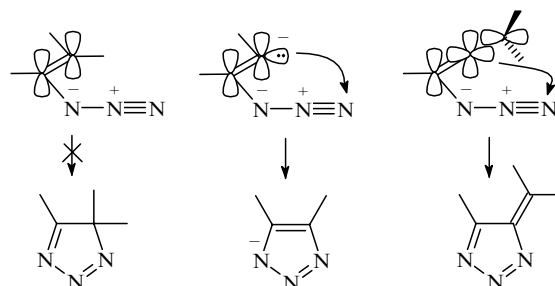
$R = Me, Et$ .

The mechanism of the reaction that includes the rearrangement of propargyl azide **175** to short-lived allenyl azide **176**, which rapidly forms triazafulvene **177**, has been studied.<sup>342</sup> The last-mentioned product adds a nucleophilic molecule at the exocyclic double bond, being converted into the final product.



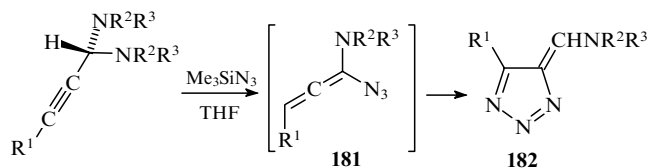
This route was supported by an experiment with optically active 3-azido-3-methylbut-1-yne **175** ( $R^1 = H, R^2 = Me$ ), where complete product racemisation was observed. These transformations cannot be accomplished in an aprotic solvent such as chloroform. It was shown that in the absence of nucleophiles, propargyl azides polymerise as a result of intermolecular 1,3-dipolar cycloaddition. The ring closure in vinyl azides takes place only for  $\alpha$ -azidoenamines;<sup>343</sup> simple vinyl azides are not converted into triazoles<sup>344</sup> due to the low nucleophilicity of the C(5) atoms

and, in some cases, also an unfavourable geometry. The probability of cyclisation becomes higher for not only the vinyl azide carbanion but also for the allenyl azide anion owing to the presence of a p orbital at the central carbon atom of the allene system.<sup>342, 345</sup>



The transformation of various propargyl derivatives, first into propargyl azides **178** and then into triazoles is carried out with isolation of intermediate compounds, which makes this method of synthesis safe and convenient. However, it was shown that, depending on the structure of the starting compounds and on the conditions, the reaction may give isomeric allenenes and triazafulvenes, which react with nucleophiles to give isomeric N-unsubstituted triazoles,<sup>346</sup> for example, **179** and **180** (Scheme 5). This approach has been used to synthesise various biologically active compounds containing a triazole ring with secondary amino-methyl substituents.<sup>166, 347–349</sup>

Azidoaminoallenes **181**, which are formed as intermediate products in the reaction of phenylpropiolaldehyde aminals with trimethylsilyl azide, undergo intramolecular cyclisation to give 4-alkylidene-4*H*-triazoles **182**.<sup>350</sup>

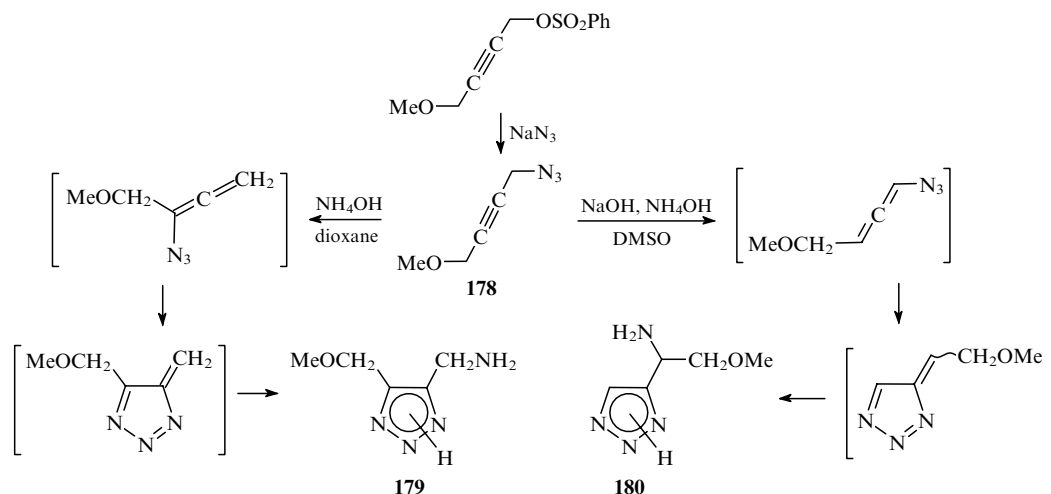


$R^1 = EtOCH_2, Me_2NCH_2, Ph; R^2-R^3 = Me_2, (CH_2)_5, (CH_2)_2O(CH_2)_2, (CH_2)_2NMe(CH_2)_2$ .

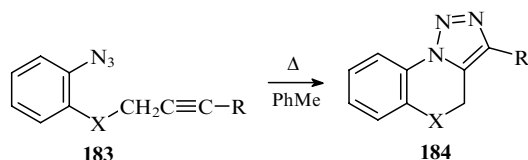
Subsequently, several modifications of this method as applied to various allene systems, including those containing heterocyclic rings, have been developed.<sup>351</sup>

The intramolecular cyclisation of *ortho*-propargyloxy(or thio)-substituted phenyl azides **183**, which takes place on heating in toluene, affords annelated triazoles **184**.<sup>352</sup>

Scheme 5

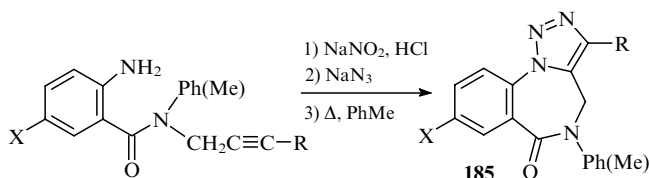






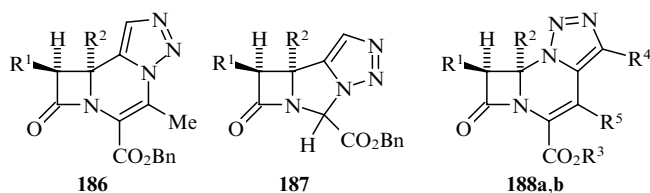
X = O, S; R = H, HOCH<sub>2</sub>, MeOCH<sub>2</sub>, Ph.

The same approach was used to prepare a series of triazolo[1,5-*a*]benzodiazepinones **185**.<sup>353,354</sup> The key stages of the preparation of triazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-one derivatives on a polymer support have been optimised.<sup>355</sup>



X = H, Cl, F, NO<sub>2</sub>, NH<sub>2</sub>; R = H, Me, Ph.

Other examples of intramolecular cyclisation involving an azide group and a triple bond present in various structures have been reported in original studies<sup>356–358</sup> and in a review.<sup>359</sup> Thus numerous annelated triazoles with a β-lactam fragment (for example, compounds **186–188**) have been obtained from azide derivatives of β-lactam antibiotics; these products can be used for subsequent structural modifications and as antibacterial agents.<sup>359</sup>



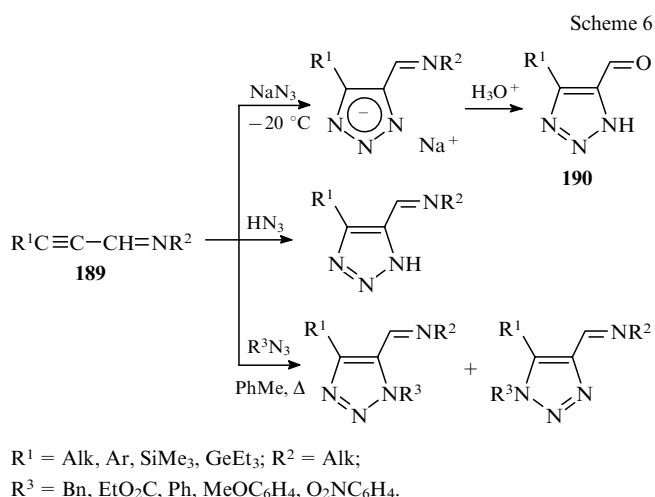
R<sup>1</sup>, R<sup>2</sup> = Alk; R<sup>3</sup>, R<sup>4</sup> = H, R<sup>5</sup> = Me (**188a**); R<sup>3</sup> = Bu<sup>t</sup>, R<sup>4</sup> = Alk, R<sup>5</sup> = H (**188b**).

The azide molecule entering into intramolecular 1,3-cycloaddition to give triazole can contain not only a triple bond but also a double bond, either C=C or C=N. Examples of such reactions are documented.<sup>360–365</sup>

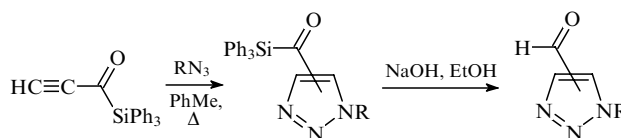
Of particular interest as the initial components for the synthesis of the triazole ring are acetylene aldehydes and aldimines (1-aza-1,3-enynes).<sup>366</sup> Both inorganic (HN<sub>3</sub>, NaN<sub>3</sub>) and organic (R<sup>3</sup>N<sub>3</sub>) azides were found to add to acetylene aldimines **189** at the triple bond to give substituted triazoles containing a formyl or iminomethyl group at the 5-position.<sup>367–373</sup> The structure of the product depends on the nature of the azide.

Sodium azide adds to the triple bond of azaenynes in DMF even at –20 °C to give salts that are hydrolysed to formyltriazoles **190**. If the azaenynone contains a trimethylsilyl group (**189**, R<sup>1</sup> = Me<sub>3</sub>Si), this reaction is accompanied by desilylation to yield 5-formyltriazole **190** (R<sup>1</sup> = H), whereas the germanium analogue (**189**, R<sup>1</sup> = Et<sub>3</sub>Ge) retains the substituent. Hydrazoic acid adds chemospecifically to the aldimine triple bond. The reaction of acetylenic aldimines with organic azides occurs under much more drastic conditions and goes to completion only after long-term heating of the reactants in toluene. The addition is also chemospecific and involves the triple bond, the process regioselectivity increasing with an increase in the bulk of the substituent at the triple bond (from Ph to Bu<sup>t</sup>, Me<sub>3</sub>Si, and Et<sub>3</sub>Ge) and on passing from alkyl azides to aryl azides (Scheme 6).

Acetylenic silyl ketones react with various azides in boiling toluene as effective dipolarophiles to give mixtures of isomeric triazoles in which the 1,4-regioisomer markedly predominates.<sup>271</sup>

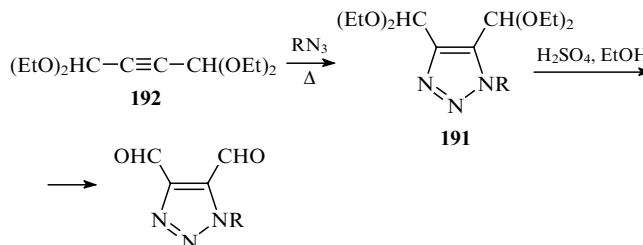


Desilylation of the resulting triazolylacysilanes induced by alkali furnishes the corresponding triazolecarboxaldehydes.



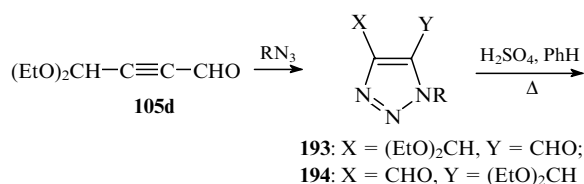
R = Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>, PhSCH<sub>2</sub>, Me<sub>3</sub>SiCO(CH<sub>2</sub>)<sub>2</sub>, Ad (1-adamantyl), benzo[*b*]thiophen-3-yl.

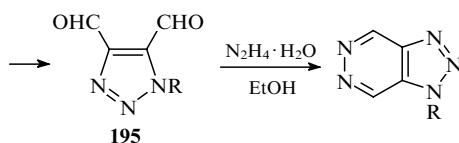
Dialdehydes of the triazole series can easily be obtained from diacetals **191**. These are formed on long-term heating of acetylenedicarbaldehyde bis(diethyl acetal) **192** with phenyl and alkyl azides in a sealed tube.<sup>374</sup>



R = n-C<sub>6</sub>H<sub>13</sub>, n-C<sub>10</sub>H<sub>21</sub>, Br, Ph.

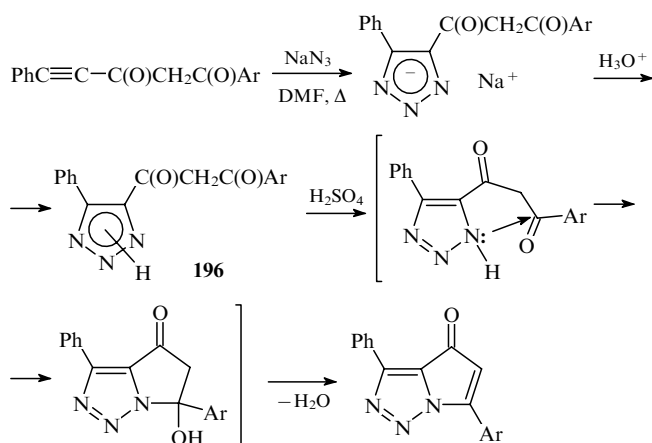
However, in the case of more labile 2-azidonitrobenzene, the reaction with alkyne is usually carried out at a lower temperature to prevent the azide from decomposition and, hence, the reactivity of diacetal **192** is insufficient. The removal of the acetal protection from one aldehyde group allows one to transform (benzene, 55 °C) alkyne **105d** and 2-azidonitrobenzene into a mixture of two monosubstituted triazole-4,5-dicarboxaldehyde diethyl acetals **193** and **194** (R = 2-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>) in which isomer **193** predominates.<sup>375</sup> Similar mixtures were obtained from other azides under the same conditions. Acid hydrolysis of the mixtures (with azeotropic distillation of water with benzene) gives rise to 1-substituted dialdehydes **195**, which react with hydrazine hydrate yielding triazolo[4,5-*d*]pyridazines. These products can also be obtained directly from mixtures of compounds **193** and **194**.





R = Bn, Ph, 2-MeC<sub>6</sub>H<sub>4</sub>, 4-MeC<sub>6</sub>H<sub>4</sub>, 2-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>.

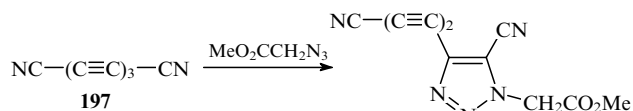
The addition of the azide anion to acetylene  $\beta$ -diketones carried out under drastic conditions (heating in DMF) is also chemospecific, involving the triple bond.<sup>165</sup> The yield of the resulting triazole diketones **196** reaches 60%–70%. As triazole dialdehydes, these polyfunctional compounds can be used in the synthesis of annelated heterocyclic systems. For example, on heating in sulfuric acid, compound **196** undergoes dehydration to give an annelated pyrrolone ring.



Ar = Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>.

The condensation of 1-aryl-2-phenylacetylenes (Ar = Ph, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>) with aryl azides (Ar = 2-ClC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 2-MeOC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>) takes place in boiling toluene to give mixtures of 4,5-regioisomers in which 1-aryl-4-aryl-5-phenyltriazole predominates.<sup>376, 377</sup> Only *o*-nitrophenyl azide does not enter into this reaction.<sup>377</sup>

It was shown that the addition of benzyl azide to diacetylene compounds in which triple bonds are separated by alkyl or aryl groups affords ditriazolyl derivatives as the only products. If the triple bonds are separated by a carbonyl group, NaN<sub>3</sub> adds to only one triple bond; benzyl azide taken in an equivalent amount forms the monoadduct, while a twofold amount results in the formation of mono- and diadduct isomers (Ref. 378).<sup>†</sup> However, terminal dicyanopolynes (for example, compounds **197**) with conjugated triple bonds react regioselectively with methyl azidoacetate to give the product of cycloaddition only to the terminal triple bond.<sup>379</sup>



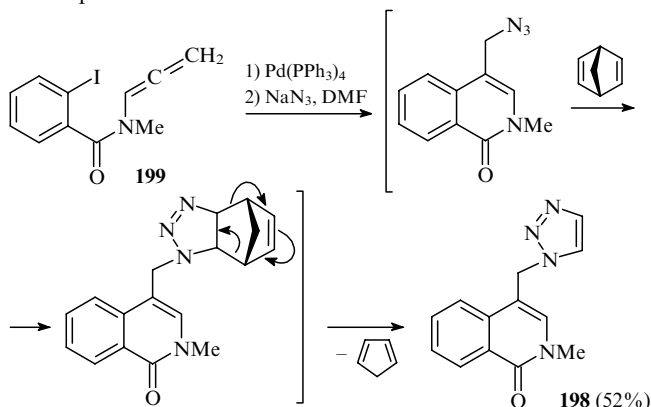
## 2. Reactions of azides with alkenes

Compounds with double C=C bonds can also undergo 1,3-dipolar cycloaddition with azides, the reaction being highly regioselective.<sup>264</sup> This strategy is a key route to 4,5-dihydro-1*H*-1,2,3-triazoles (or  $\Delta^2$ -1,2,3-triazolines) including those labelled by <sup>13</sup>C and <sup>15</sup>N isotopes.<sup>380</sup> The preparation and chemical transformations of these heterocycles are the subjects of numerous

papers and several reviews (for example Refs 4, 25, 381). The systems containing a triazoline fragment are usually unstable and can decompose under ambient conditions being converted into aziridines (with elimination of a nitrogen molecule), diazo compounds, imines or enamines, or undergo intramolecular rearrangements.<sup>381</sup> For this reason, the formation of triazolines often cannot be detected during cyclocondensation. The stability of the triazoline ring can be increased by introducing stabilising substituents or by synthesising fused systems or conformationally stable complex structures.

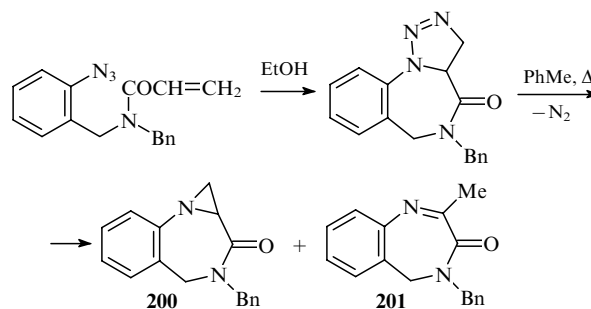
When phenyl azide reacts with the simplest allene, propa-1,2-diene, the resulting methylenetriazolines are aromatised to 4- and 5-methyltriazolines formed in very low yields.<sup>345</sup>

Cascade synthesis of 1-substituted triazoles **198** starting from aryl iodide **199** containing an allene fragment has been performed. The process includes the following reaction sequence: palladium complex-catalysed cyclisation of allene into the iodomethyl derivative, reaction with sodium azide, cyclocondensation of the resulting organylmethyl azide with norbornadiene to an unstable triazoline and the retro-diene decomposition of the last-mentioned product.<sup>272</sup>



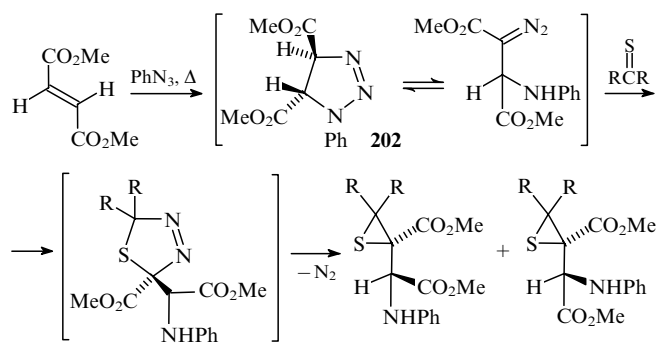
Examples of using other aryl iodides<sup>272</sup> and alkoxymethyl azides and their *S*-analogues<sup>292</sup> in a similar reaction with norbornadiene are also known.

The reaction of methyl azide with acrylic and crotonic acid derivatives is not stereospecific, resulting in triazolines which occur in equilibrium with their open forms, *i.e.*, aminodiazo compounds. In some cases, this reaction is complicated by the reactions of the latter compounds with the starting alkenes.<sup>382</sup> The presence of an electron-releasing substituent at the N(1) atom of the triazoline ring stabilises the molecule, while that at C(4) or C(5) has a destabilising effect.<sup>4</sup> The formation of unstable triazolines with electron-withdrawing substituents and easy opening of the triazoline ring is used to obtain new interesting structures, for example, compounds **200** and **201**.<sup>383, 384</sup>



Heating of thiobenzophenone or 9*H*-fluorene-9-thione with dimethyl fumarate and excess phenyl azide gave a mixture of diastereoisomeric thiiranes.<sup>385</sup> The researchers believe that this transformation involves triazoline derivative **202** as a reactive intermediate.

<sup>†</sup> The reactions of diacetylenes and their derivatives with sodium azide and organic azides are also considered in the review by I A Maretina, B A Trofimov *Adv. Heterocycl. Chem.* **82** 158 (2002).



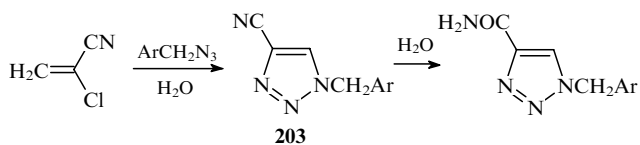
R = Ph, R-R = *o,o'*-biphenylene.

The regioselectivity of the cycloaddition of aromatic azides to 5-substituted furan-2-ones was studied.<sup>386</sup> In those cases where thermally stable triazolines are formed, they can be dehydrogenated by treatment with oxidants such as  $\text{KMnO}_4$ ,<sup>387, 388</sup>  $\text{NiO}_2$ ,<sup>382</sup>  $\text{Br}_2$ <sup>389</sup> and  $\text{O}_2$ <sup>390</sup> to be converted into the corresponding triazoles. The presence in the same molecule of an azido group and a double bond bridged by several carbon atoms is favourable for intramolecular cyclisation.<sup>389, 391</sup>

The presence of a good leaving group, for example, Hal (Cl, Br), RO (R = H, Alk, Ar, Ac),  $\text{RSO}_n$  ( $n = 0, 1, 2$ ),  $\text{Alk}_2\text{N}$ ,  $\text{NO}_2$  or CN at the olefin double bond is favourable for regiospecific cycloaddition to azide. When the carbon atom next to the double bond bears a hydrogen atom (*i.e.*, in the presence of a  $\text{H}-\text{C}=\text{C}-\text{X}$  fragment, which is a latent alkyne), the formation of triazoline during the reaction is often followed by spontaneous ejection of this group with aromatisation of the triazole ring.

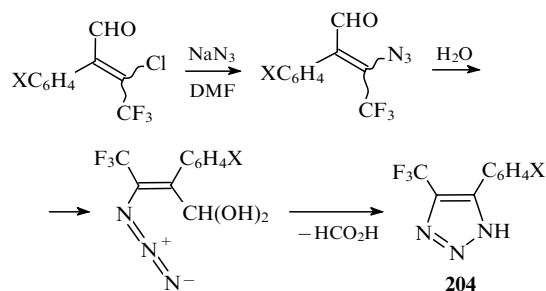
Below we consider reactions with azides classified according to the nature of the leaving group in the alkene.

The reaction of substituted benzyl azides with 2-chloroacrylonitrile, which is accompanied by HCl elimination, leads to 1-benzyltriazole-4-carbonitriles.<sup>392, 393</sup> The discovery of high biological activity and the possibility of practical use of 1-(2,6-difluorobenzyl)triazole-4-carboxamides<sup>194</sup> brought about the task of optimisation of the synthesis of their precursor, 4-cyano derivative **203** (Ar = 2,6- $\text{F}_2\text{C}_6\text{H}_3$ ), whose yield was increased to 98% by conducting the reaction in a two-phase system.<sup>392</sup> This procedure was extended to the synthesis of other 1-benzyl-4-cyanotriazoles **203** and 1-(het)aryl-4-cyanotriazoles.



Ar = Ph, 4-NCC $_6\text{H}_4$ , 2,6- $\text{F}_2\text{C}_6\text{H}_3$ .

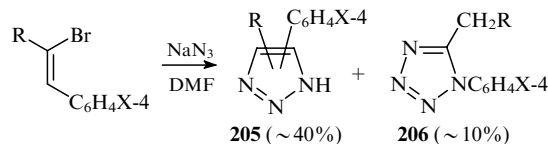
The reaction of sodium azide with 2-aryl-4,4,4-trifluoro-3-chlorobut-2-enal yields 5-aryl-4-trifluoromethyltriazoles **204**.<sup>394</sup> The reaction mechanism proposed includes substitution of the azido group for the chlorine atom followed by attack by the terminal nitrogen of the azido group on the double bond of the aldehyde hydrate with elimination of formic acid.



X = H, 4-Br, 3- $\text{CF}_3$ , 4- $\text{CF}_3$ .

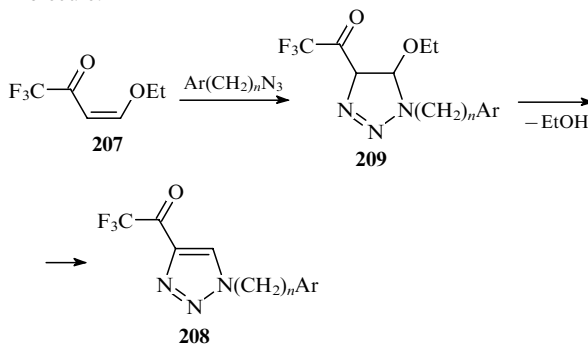
When the substrate contains two chloroacrolein groups connected by a *p*-phenylene bridge, the reaction gives 1,4-bis(4-trifluoromethyltriazol-5-yl)benzene.<sup>394</sup>

The reaction of (*Z*)-2- $\alpha$ -bromostyrylchromones with  $\text{NaN}_3$  in boiling DMF gives, in addition to the expected 4(5)-aryl-5(4)-(2-chromonyl)triazoles **205**, minor amounts of tetrazole derivatives **206**.<sup>395</sup> The latter products result from the reaction of the ketene imines, formed as side products, with  $\text{NaN}_3$ .



R = ; X = H, Cl.

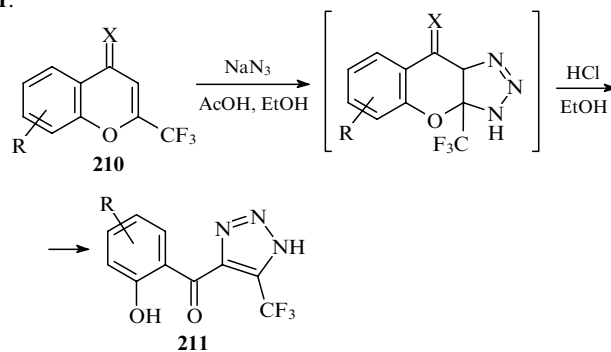
1,3-Dipolar cycloaddition of aryl (or benzyl) azides to activated alkene **207** proceeds on moderate heating without solvents to give the corresponding 4-trifluoroacetyltriazoles **208** in high yields.<sup>396</sup> The presence of an active vicinal hydrogen atom in the intermediate triazoline **209** promotes elimination of the EtOH molecule.



$n = 0$ : Ar = 2-Me $\text{C}_6\text{H}_4$ , 4-Cl $\text{C}_6\text{H}_4$ ;  $n = 0, 1$ : Ar = Ph, 4-MeOC $_6\text{H}_4$ , 4-O $_2\text{NC}_6\text{H}_4$ .

Elimination of the EtOH molecule to give a triazole derivative was also observed on heating a mixture of azidothymidine and vinyl ethyl ether.<sup>185</sup>

5-Trifluoroacetyl-3,4-dihydro-2*H*-pyran proved to be inert with respect to benzyl azide even on strong heating.<sup>396</sup> However, when heated with  $\text{NaN}_3$  in AcOH, 2-trifluoromethylchromones substituted at the benzene ring and similar imines **210** give cycloadducts that are cleaved in an acid medium to give 4-aryltriazoles **211**.<sup>397</sup>

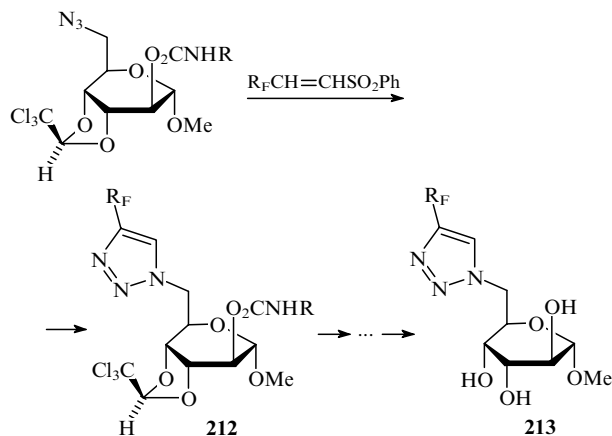


X = O, NH; R = Me, Cl,  $\text{NO}_2$ .

1-Pyridyltriazoles have been prepared in low yields by heating mixtures of vinyl acetate with various Cl- and  $\text{CF}_3$ -substituted isomeric azidopyridines.<sup>248</sup>

Reactions with a sulfur-containing leaving group are known. The parent triazole can be obtained in a yield of up to 55% on

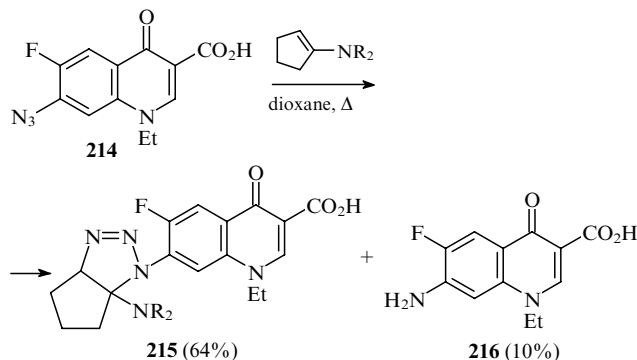
heating an alkali metal azide or  $\text{Me}_3\text{SiN}_3$  with vinyl sulfoxide or vinyl sulfone ( $\text{RSO}_n\text{CH}=\text{CH}_2$ ;  $n = 1, 2$ ) in toluene.<sup>398</sup> A similar approach has been used to prepare 5-(4-hydroxyphenyl) derivatives of triazole-4-carboxamides<sup>399, 400</sup> and 4-perfluoroalkyltriazoles, containing residues of D-galactose and D-altrose derivatives (compounds **212**, **213**).<sup>401</sup>



$R = \text{Cy}$ ;  $R_F = n\text{-C}_4\text{F}_9, n\text{-C}_6\text{F}_{13}$ .

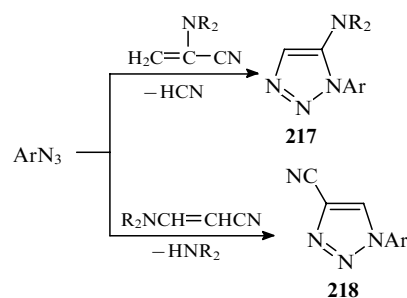
It was shown that a similar reaction can be carried out between 5-azidoxyfuranose and vinyl phenyl sulfoxide. The use of 1-(5-deoxy- $\alpha$ -D-xylofuranosyl)triazole azide grafted on a polymer (polyethylene glycol monomethyl ether) makes it possible to increase the yield from 68% to 94%.<sup>306</sup>

Examples of using various enamines with azides are encountered rather often in the literature. The 7-azido derivative of 6-fluoroquinolone-3-carboxylic acid **214** reacts with alkenes (norbornene, dicyclopentadiene and some enamines) to afford thermally unstable triazolyl adducts; only in the case of 1-morpholinocyclopentene, was the triazoline derivative **215** isolated together with side product 7-aminofluoroquinolone **216**.<sup>241</sup>



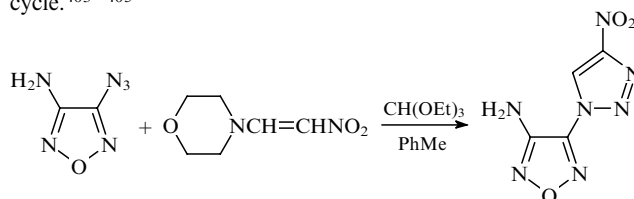
$R-R = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$ .

Aryl azides readily react with  $\alpha$ - and  $\beta$ -aminoacrylonitriles, but give different cycloaddition products. In the former case, spontaneous ejection of HCN from the intermediate triazoline takes place to give 1-aryl-5-aminotriazole **217**, and in the latter case, the corresponding amine is evolved and 1-aryl-4-cyanotriazole **218** is formed.<sup>402</sup> Fragments of secondary cyclic amines (pyrrolidine, piperidine and morpholine) were used as substituents in aminoacrylonitriles. In all cases, the yields of triazoles were 75%–95%. Despite the captodative character of  $\alpha$ -aminoacrylonitriles, their dipolarophilic properties in the cycloaddition are comparable with those of  $\beta$ -aminoacrylonitriles, which is inconsistent with their possible participation in the cyclisation of biradical intermediate species and confirms the one-step concerted Huisgen mechanism.<sup>402</sup>



$\text{Ar} = \text{Ph}, \text{MeC}_6\text{H}_4, 3\text{-ClC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4, 3\text{-O}_2\text{NC}_6\text{H}_4, 4\text{-O}_2\text{NC}_6\text{H}_4$ ;  
 $R-R = (\text{CH}_2)_4, (\text{CH}_2)_5, (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$ .

When the nitroethylene molecule contains a morpholine residue, cycloaddition to the azide is accompanied by morpholine elimination with retention of the nitro group in the heterocycle.<sup>403–405</sup>



To prevent decomposition of the starting azide under the action of the evolved morpholine, the reaction is carried out in the presence of triethyl orthoformate.

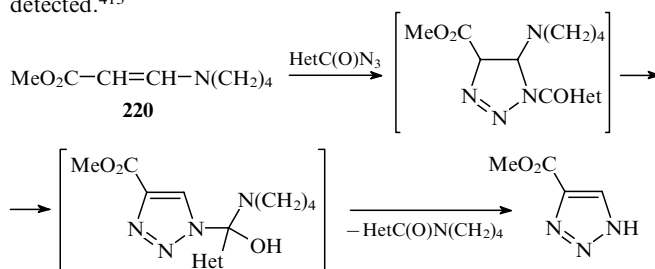
In the reaction of 3-dimethylaminocrotonic acid, its esters or amides with mono-, di- or trinitrophenyl azides, the dimethylamine molecule is eliminated during cyclisation to give the corresponding 1-[( $\text{O}_2\text{N}$ ) $_n\text{C}_6\text{H}_{5-n}$ ]-triazole-4-carboxylic acid derivatives ( $n = 1-3$ ).<sup>406</sup>

The reactions of thiazole azides **219a–c** with enamines have been studied.<sup>264</sup> The reaction of 2-morpholinoprop-1-enyl phenyl ketone with 2-(2-thienyl)-5-azidothiazole **219a** occurs under very mild conditions with evolution of morpholine to yield 5-(triazol-1-yl)thiazole. Using derivatives **219b,c** as examples, it was shown that in the absence of a hydrogen atom at the enamine double bond, the triazoline ring easily loses a nitrogen molecule yielding a mixture of 5-aminothiazole derivatives. The reaction of methyl acrylate with azide **219c** affords 5-aziridinotriazole (Scheme 7).

Acyl azides react with alkenes in a similar way, although in some cases, the products of the Curtius rearrangement are formed in parallel.<sup>356</sup>

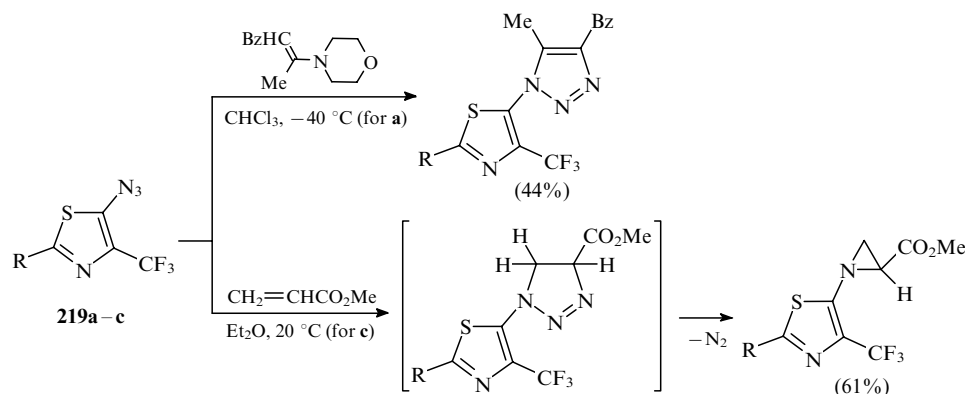
In some cases, a compound with the enamine fragment is used in the cyclisation as the dipolarophile.<sup>407–409</sup> 1,4-Disubstituted triazoles are formed as the result of ejection of the amine molecule from the triazoline that has already formed.<sup>410, 411</sup> Study of the kinetics of the reaction of aryl azides with methyl 3-pyrrolidinocrotonate **220** has shown that cycloaddition is a concerted asynchronous process controlled by the LUMO of the azide and the HOMO of the dipolarophile.<sup>412</sup>

An unusual rearrangement was found for the products of cycloaddition of heterocyclic acyl azides to aminoacrylate **220**, whereas in the reaction of the latter with methyl crotonate or methyl propiolate, no products of such a transformation were detected.<sup>413</sup>



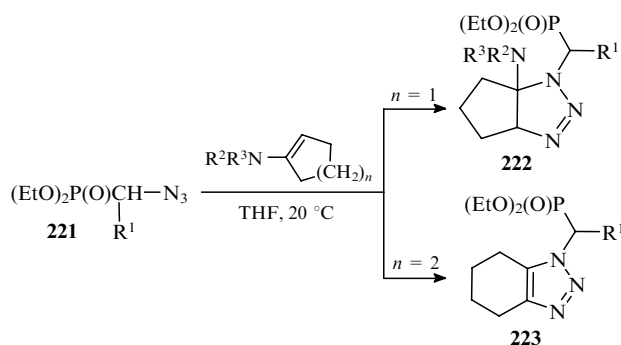
Het = 2-furyl, 2-thienyl, selenophen-2-yl, thieno[3,2-*b*]thiophen-2-yl.

Scheme 7



R = 2-thienyl (**a**), 2-furyl (**b**), 4-MeC<sub>6</sub>H<sub>4</sub> (**c**).

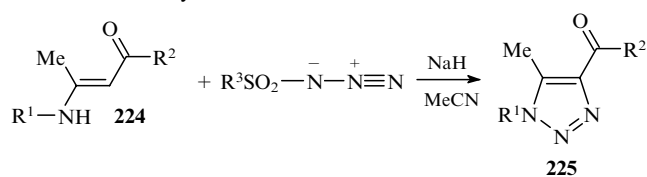
A number of publications have been devoted to the cycloaddition of azidoalkylphosphonates **221** to enamines.<sup>282, 283, 414</sup> It was shown that, depending on the enamine structure, the reaction can either stop after the formation of 1-phosphorylmethyl-5-amino- $\Delta^2$ -triazolines **222** or afford bicyclic 1-phosphorylmethyl-triazole **223** via elimination of the amine molecule.<sup>414</sup>



R<sup>1</sup> = H, Me, Ph; R<sup>2</sup>–R<sup>3</sup> = (CH<sub>2</sub>)<sub>4</sub>, (CH<sub>2</sub>)<sub>2</sub>O(CH<sub>2</sub>)<sub>2</sub>.

Upon reaction with enamines — amino derivatives of unsaturated acid esters R<sup>1</sup>R<sup>2</sup>NCH=CHCO<sub>2</sub>Alk — substrates **221** are converted into 4-alkoxycarbonyl-1-phosphoryl-methyltriazoles.<sup>414</sup>

β-Amino-α,β-unsaturated carbonyl compounds **224** have been proposed for the synthesis of 4-acyltriazoles and alkyl triazole-4-carboxylates.<sup>415</sup>

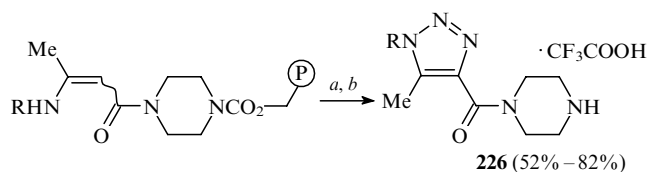


R<sup>1</sup> = Bu<sup>n</sup>, n-C<sub>10</sub>H<sub>21</sub>, Bn, Ph, *p*-Tol; R<sup>2</sup> = Me, EtO; R<sup>3</sup> = Me, *p*-Tol.

|                                  |                 |                                   |    |    |               |                 |     |
|----------------------------------|-----------------|-----------------------------------|----|----|---------------|-----------------|-----|
| R <sup>1</sup>                   | Bu <sup>n</sup> | n-C <sub>10</sub> H <sub>21</sub> | Bn | Ph | <i>p</i> -Tol | Bu <sup>n</sup> | Bn  |
| R <sup>2</sup>                   | Me              | Me                                | Me | Me | Me            | EtO             | EtO |
| Yield of <b>225</b> (%)          | 79              | 87                                | 97 | 20 | 37            | 83              | 72  |
| (R <sup>3</sup> = Me)            |                 |                                   |    |    |               |                 |     |
| Yield of <b>225</b> (%)          | 40              | 30                                | 50 | 40 | 10            | 2               | 23  |
| (R <sup>3</sup> = <i>p</i> -Tol) |                 |                                   |    |    |               |                 |     |

It was shown that reactions of **224** with tosyl (mesyl) azide are accompanied by the 'diazo transfer', *i.e.*, elimination of sulfonylamine and an attack by the diazo group on the enamine nitrogen. The reaction affords only one regioisomer of triazole **225**, whose yield depends on the reactant structure. It is noteworthy that the product yields are higher with mesyl azide.<sup>415</sup>

This strategy is also applicable for the solid-state synthesis of 4-carbamoyltriazoles **226**.<sup>416</sup>



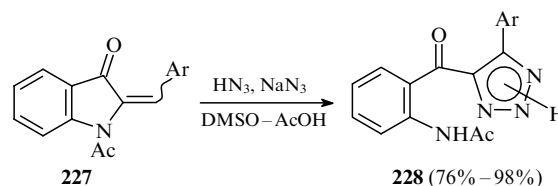
(a)  $\text{TsN}_3$ ,  $\text{Pr}_4\text{NEt}$ ,  $\text{DMF}$ ; (b)  $\text{TFA}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $20^\circ\text{C}$ ;

(P) is the polymer support;

R = CH<sub>2</sub>CO<sub>2</sub>Bn, CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>OMe-4, (CH<sub>2</sub>)<sub>2</sub>C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>-4.

It has been shown<sup>417</sup> that methyl 3-pyrrolidino-3-formylcrotonate dimethyl acetal is much more reactive in cycloaddition to 4-nitrophenyl azide than the cyclic analogue, namely, enaminofuranone.

The reaction of arylidene derivatives of *N*-acetylindoxyl **227** with hydrazoic acid proceeds as the nucleophilic addition of the N<sub>3</sub><sup>−</sup> anion to the C=C double bond accompanied by cleavage of the C–N bond followed by closure of the triazole ring.<sup>418–420</sup> The reaction takes place on heating substrate **227** with sodium azide in a DMSO–acetic acid mixture to give 4-(2-acetylaminobenzoyl)-5-aryltriazoles **228**.



R = Ph, 4-Pr<sup>i</sup>C<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-Py.

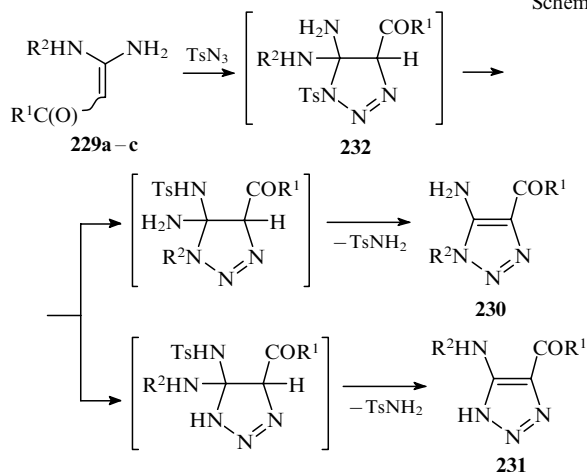
However, benzylideneacetophenone and 1,2-dibenzoyl ethylene, which do not differ much in structure from enamide **227**, do not form triazole or triazoline derivatives when reacted with 2-(4-pyridyl)ethyl azide, the corresponding enaminoketones being formed instead.<sup>293</sup>

Acyl ketene amins can also act as active dipolarophiles in dipolar cycloaddition.<sup>421</sup> By reactions of acylketene amins **229** with tosyl azide, a series of 5-amino-4-acetyl-1,2,3-triazoles **230** and **231** substituted at the endo-N(1)- or exocyclic nitrogen have been synthesised (Scheme 8).<sup>422</sup>

The reaction takes place in THF at room temperature (only substrates **229b** require refluxing). The researchers believe that the reaction is accompanied by the Dimroth rearrangement of cycloadduct **232** formed initially with subsequent elimination of the TsNH<sub>2</sub> molecule. In the case of amins **229b,c**, the reaction is regioselective to give 5-R<sup>2</sup>NH-4-acyltriazoles **231**; in other cases, isomer mixtures were obtained.<sup>422</sup>

The reactions of similar morpholine or piperidine enaminals containing various electron-withdrawing groups with *p*-nitrophenyl azide resulted in the preparation of only 1-aryltriazoles

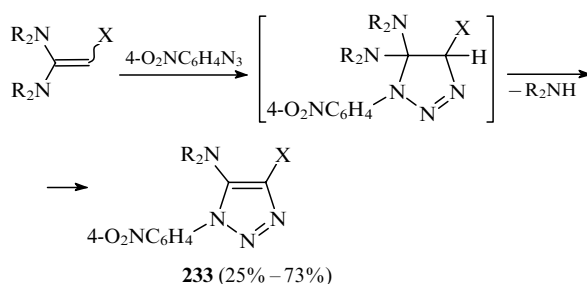
Scheme 8



R<sup>1</sup> = Me, Ph; R<sup>2</sup> = Ph (a), PhCO (b), 4,6-dimethylpyrimidin-2-yl (c).

| Aminal | R <sup>1</sup> | Yield (%) |     |
|--------|----------------|-----------|-----|
|        |                | 230       | 231 |
| 229a   | Me             | 73        | 13  |
|        | Ph             | 53        | 33  |
| 229b   | Me             | —         | 70  |
| 229c   | Me             | —         | 94  |

with the functional substituent at the 4-position of the heterocycle (compounds **233**).<sup>423</sup>

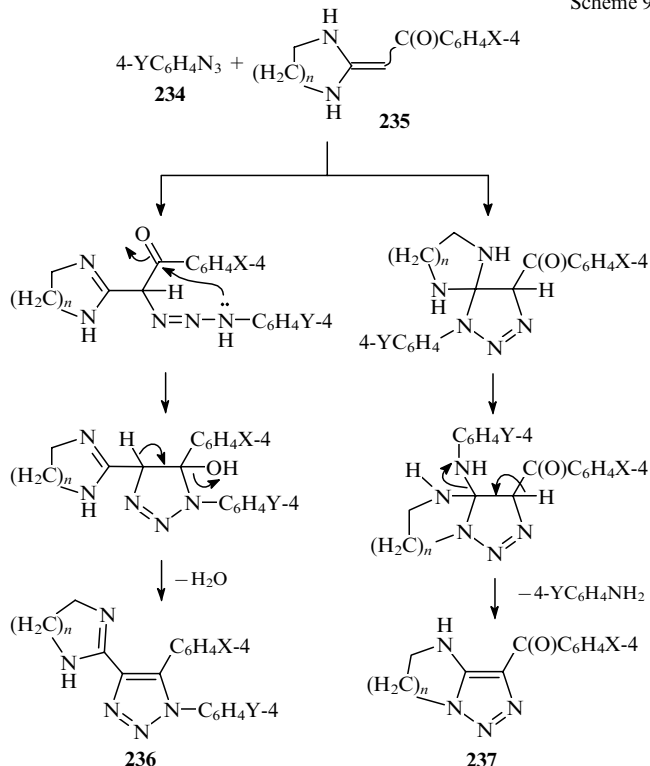


X = COMe, CPh, CO<sub>2</sub>Me, CO<sub>2</sub>Et, CO<sub>2</sub>Bn, Ts, NO<sub>2</sub>;  
R–R = (CH<sub>2</sub>)<sub>5</sub>, (CH<sub>2</sub>)<sub>2</sub>O(CH<sub>2</sub>)<sub>2</sub>.

In the general case, the reaction of aryl azides with cyclic acyl ketene amins can follow two pathways to give triazoles of two structural types: annelated and/or fully substituted,<sup>424, 425</sup> the product ratio being dependent on the nature of substituents in the reactants. These dependences were studied qualitatively for the reaction of *para*-substituted phenyl azides **234** with amins **235**, containing a *para*-substituted benzoyl fragment at the double bond. The reaction rate decreases with a decrease in the electron-withdrawing properties of the *para*-substituent Y in aryl azide in the series: NO<sub>2</sub> > Cl > H > OMe and in the electron-releasing properties of the substituent X in the enamine in the series OMe > Me > H > Cl (Scheme 9).<sup>424</sup>

All the enaminals studied react with 4-nitrophenyl azide very easily to give only fully substituted triazoles with two aryl groups **236** (yields 87%–97%) even at room temperature in dioxane. With other azides, the reaction is much slower; refluxing of reactants in dioxane gives product mixtures. In addition to triazoles **236** (yields 8%–71%), compounds **237** are formed, which include a fused triazole system with a bridgehead nitrogen atom (yields 6%–31%). On the basis of the results obtained, the researchers cited proposed a sequence of transformations (see Scheme 9) and concluded that enaminals of this structure react with aryl azides both as nucleophiles and as 1,3-dipolarophiles. In the former case, the terminal nitrogen atom of the azide group

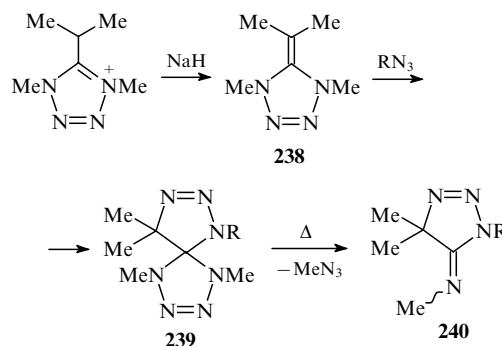
Scheme 9



X = H, Me, MeO, Cl; Y = H, MeO, Cl, NO<sub>2</sub>; n = 1, 2.

attacks the β-carbon atom of enamine to give an adduct whose subsequent cyclisation and dehydration afford 1,4,5-trisubstituted triazole **236**. In the alternative process, enaminals react as usual dipolarophiles. The resulting adducts undergo the Dimroth rearrangement followed by deamination to give fused triazoles **237**.<sup>424</sup> The reaction with amins of benzoyl-substituted heterocyclic ketenes was also carried out using 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide,<sup>426, 427</sup> while protected ribosyl azide was used in the reaction with aryl ketene amins.<sup>428</sup>

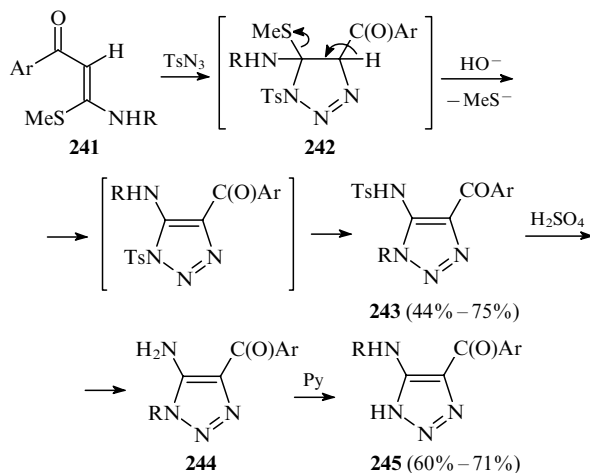
Isopropylidenedihydrotetrazoles **238**, which contain an enamine fragment, also react with alkyl azides to give spiro compounds **239**. These products undergo [3 + 2]-cyclo-reversion during thermolysis to eject methyl azide. The final products **240** exist as mixtures of iminodihydrotriazole geometric isomers in which the *E*-isomer predominates.<sup>429</sup>



R = Me, CD<sub>3</sub>, CH<sub>2</sub>Bu<sup>t</sup>.

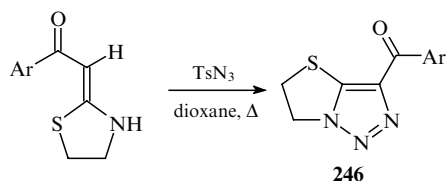
The aroyl derivatives of *S,S*- and *S,N*-acetals of polarised ketenes are also able to react with azides: on heating in DMSO with NaN<sub>3</sub>, the former are converted into 4-aroyle-5-methylthio-triazoles, while the latter give only 5-aroyletriazoles under the same conditions.<sup>430</sup> In addition, the aroyl derivatives of ketene *S,N*-acetals of ketenes **241** do not react with tosyl azide in boiling dioxane,<sup>431</sup> but they react in ethanol in the presence of alkali even

at room temperature. In this case, intermediate triazolines **242** eliminate MeSH and undergo the Dimroth rearrangement, resulting in 1-aryl-4-aryl-5-tosylaminotriazoles **243**. On treatment with sulfuric acid, the products give off the tosyl group, while the 5-aminotriazoles **244** thus produced undergo one more Dimroth rearrangement on refluxing in pyridine, being converted into substituted 5-anilinothiazoles **245**.<sup>431</sup>



R = Me, Et, Pr<sup>n</sup>, Pr<sup>i</sup>, Bu<sup>n</sup>, Cy, Bn, (EtO)<sub>2</sub>CHCH<sub>2</sub>, Ph;  
Ar = Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>.

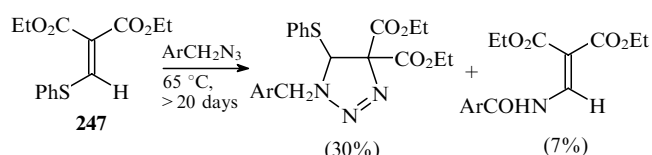
The reaction of tosyl azide with aroyl derivatives of cyclic ketene *S,N*-acetals carried out under the same conditions (NaOH, EtOH) is accompanied by resinification, but this reaction performed by refluxing in dioxane gives annelated triazoles **246** in good yields.<sup>431</sup>



Ar = Ph (69%), 4-ClC<sub>6</sub>H<sub>4</sub> (60%), 4-MeOC<sub>6</sub>H<sub>4</sub> (65%).

If cyclic ketene *N,X*-acetals (X = Me<sub>2</sub>C, MeN, O, S) react with azides that possess enhanced electrophilicity, this yields unstable triazoline adducts, which immediately eliminate N<sub>2</sub>. Simultaneously, the triazoline ring is cleaved giving rise to other nitrogen-containing heterocycles.<sup>432</sup>

In the case of two geminal acceptor groups at the double bond (*e.g.*, alkene **247**), the reaction with organic azide proceeds with difficulty and gives, in addition to dihydrotriazole, a side acyclic enamine product, which is apparently formed upon rearrangement rather than upon triazoline decomposition.<sup>433</sup>

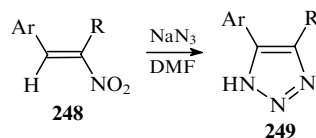


Ar = 4-MeOC<sub>6</sub>H<sub>4</sub>.

Alkenes that contain an electron-withdrawing nitro group at the double bond readily react with azides. Furan- and indole-based α,β-unsaturated ketones containing an α-nitro group have been used to prepare 4-hetaryl-5-acyltriazoles.<sup>434</sup> The reaction of α-nitroalkenes (R<sup>1</sup>CH = CR<sup>2</sup>NO<sub>2</sub>) with methyl and phenyl azides was found<sup>435, 436</sup> to give only 1-Me(Ph)-4-R<sup>2</sup>-4-NO<sub>2</sub>-5-R<sup>1</sup>-triazolines, which are converted into 1-Me(Ph)-4-R<sup>2</sup>-5-R<sup>1</sup>-triazoles after elimination of HNO<sub>2</sub>. The reactions of β-nitrostyrene and nitropropene homologues with the same azides give not only

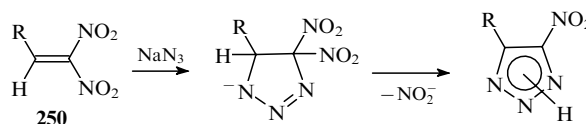
isomeric 1- and 3-substituted triazoles containing no nitro group but also 1-substituted 4-nitrotriazole.<sup>437</sup> Apparently, this product results from oxidative cyclisation of the intermediate diazo compound PhCHNHR<sup>1</sup>C(NO<sub>2</sub>)=N<sub>2</sub>, which is the open form of the corresponding triazoline.<sup>437</sup>

Recently, it has been shown that the double bond in β-nitrostyrenes **248** can be involved in dipolar cycloaddition with elimination of a nitro group. This gave triazoles **249** in high yields.<sup>438</sup>



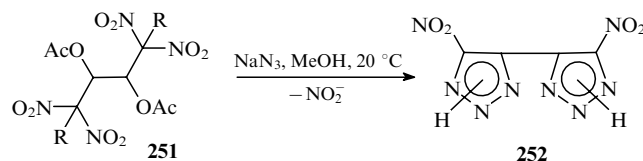
R is cyclohex-1-enyl; Ar = Ph, 4-MeOC<sub>6</sub>H<sub>4</sub>.

Of particular interest as the initial components for the synthesis of nitrotriazoles are *gem*-dinitroethylenes **250**, which are prepared either from alkyl dinitroacetate and the products of its transformation or starting from 1,1,1-trinitroalkanes.<sup>439–441</sup>



R = H, Me, Bu<sup>n</sup>, 4-MeC<sub>6</sub>H<sub>4</sub>, Me<sub>2</sub>N.

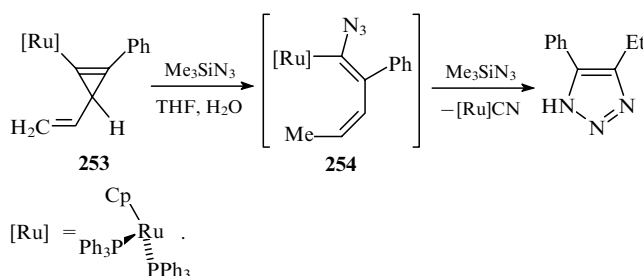
The reaction of tetranitrobutane-2,3-diol diacetates **251** with NaN<sub>3</sub> smoothly produces dinitro-substituted bis-triazole **252**, probably through the intermediate tetranitrobutadiene.<sup>440</sup>



R = H (67%), Br (34%).

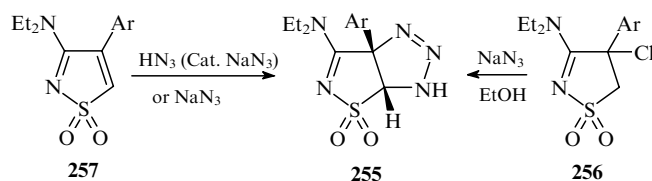
Unlike the diacetate, the monoacetate of tetranitrobutanediol forms only one triazole ring under these conditions, which is confirmed by the subsequent oxidation of the product to 5-nitrotriazole-4-carboxylic acid.<sup>440</sup>

The reaction of vinylcyclopropenylruthenium complex **253** with excess Me<sub>3</sub>SiN<sub>3</sub> follows an unusual route, resulting in 4-ethyl-5-phenyltriazole.<sup>442</sup> Presumably, the addition of Me<sub>3</sub>Si to an exocyclic double bond is accompanied by cyclopropenyl ring opening. The presence of traces of water in the solvent promotes elimination of the silyl group from the intermediate and the formation of complex **254**. The repeated attack by Me<sub>3</sub>SiN<sub>3</sub> on the double bond of the intermediate results in the [3+2]-cycloaddition product, which is converted into a triazole ring after elimination of the cyanoruthenium fragment.<sup>442, 443</sup>



Cyclocondensation has been carried out for 3-aminoisothiazole 1,1-dioxide.<sup>444</sup> The reaction of these cyclic sulfones containing an amidine fragment yields a mixture of several products depending on the conditions. The highest yield (70%) of the bicyclic adduct, namely, dihydrogenated isothiazolo[4,5-*d*]tri-

azole **255**, was attained by using isothiazoline **256** or isothiazole **257** as the starting compounds.



Ar = 4-MeOC<sub>6</sub>H<sub>4</sub>.

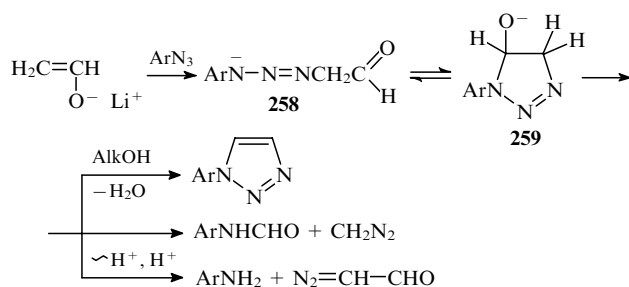
Cations of nitrogen-containing heteroallenes (1,3-diaza-2-azoniaallene salts) can be introduced in cycloadditions as the 1,3-dipolar component; they react stereoselectively, for example, with glycals.<sup>445</sup>

### 3. Reactions of azides with CH-active compounds

Depending on the reaction mechanism and the nature of the activating groups [most often, C(O)R or C≡N], the key stages of these reactions can formally be considered as either ionic (the nucleophilic addition of a carbanion to the azide group) or azide cycloaddition to the olefin intermediate (enol or enolate) or to the C=C=NH fragment.

Back in 1902, Dimroth<sup>446</sup> performed the reaction of phenyl azide with ethyl acetoacetate in ethanol in the presence of EtONa and obtained 1-phenyl-5-methyltriazole-4-carboxylic acid. Subsequently, Huisgen *et al.*<sup>447</sup> successfully used ethyl formylacetate in this reaction and obtained 1-phenyltriazole-4-carboxylic acid.<sup>403</sup> Later, other organic azides and various dicarbonyl compounds containing CH-active groups (acetylacetone, ethyl malonate, acetoacetate and cyanoacetate, *etc.*) have been used to prepare substituted triazoles. Other examples of such reactions are documented in reviews.<sup>2,3,8</sup> The reaction of azides with cyanomethylenecarbonyl compounds has some specific features. Apart from aminotriazoles, products of reduction of the azido group were found in the reaction mixture; in several cases, these were the major components.

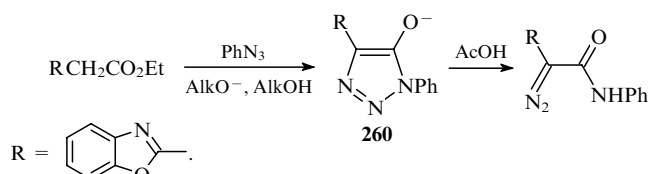
Previously, Olsen showed<sup>448</sup> that methyl (or benzyl) azide is capable of reactions with ketones in Bu<sup>t</sup>OH in the presence of Bu<sup>t</sup>OK to give 1-methyl(benzyl)-5-alkyl-5-hydroxytriazolines, which are readily dehydrated to the corresponding 5-alkyltriazoles. Later, acetaldehyde enolate was involved in cyclocondensation with some acetaldehyde arylazides to give 1-aryltriazoles in high yield (Scheme 10).<sup>449</sup>



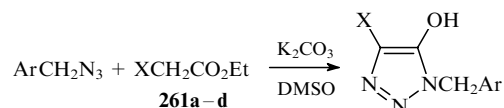
Ar = C<sub>6</sub>H<sub>4</sub>R; R = H, 2-Me, 4-Me, 3-OMe, 4-OMe, 2-SMe, 2-SEt.

Only phenyl azides with electron-releasing substituents in the aromatic ring can be used in this reaction. This increases the stability of the triazoline ring and, hence, the equilibrium shifts from triazene ketone **258** towards hydroxytriazoline **259**, which is dehydrated on treatment with MeONa or Bu<sup>t</sup>OK. The reaction is complicated by side reactant destruction processes.

The reactions of organic azides with arylacetic esters can be exemplified by the reaction of phenyl azide with ethyl benzoxazolyl-2-acetate. This affords 1-phenyltriazol-5-olate **260**; attempts to isolate the product as a neutral compound resulted in triazole ring opening.<sup>450</sup>



The reaction of diethyl malonate **261a** with benzyl azides in DMSO<sup>451</sup> gives the corresponding 1-benzyl-5-hydroxy-4-ethoxycarbonyltriazoles. However, with ethyl phenylacetate **261b**, the yield of triazole was relatively low (8%), and esters **261c,d** did not react at all.

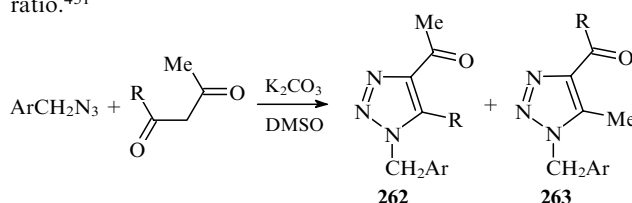


Ar = Ph, 4-MeOC<sub>6</sub>H<sub>4</sub>, 3,5-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>; X = CO<sub>2</sub>Et (**a**), Ph (**b**), F (**c**), NO<sub>2</sub> (**d**).

Diethyl malonate reacts with aryl azides in EtOH in a similar way;<sup>187</sup> 4-nitrophenyl and tosyl azide react with alkyl malonates in HMPT to give 2-diazomalonates.<sup>452</sup>

Ethyl alkylidenemalonates react with NaN<sub>3</sub> in DMSO to give triazoles *via* intermediate 4,5-dihydrotriazoles and with benzyl azide to give 1-benzyl-4,5-dihydrotriazole. On treatment with Bu<sup>t</sup>OK in DMSO, the latter products undergo either aromatisation to triazoles, or deethoxycarbonylation without aromatisation, or lose nitrogen, being converted into ethyl (benzylamino)methylidenemalonates.<sup>453</sup>

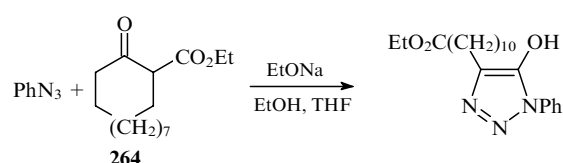
The reaction of azides with 1,3-diketones allows the synthesis of triazole ketones. For example, benzyl azides react with acetylacetone to afford 1-substituted 4-acetyl-5-methyltriazoles in high yields (at R = Me **262** ≡ **263**); the reaction with benzoylacetone gives mixtures of two regioisomers, **262** and **263**, in a ~1:1.5 ratio.<sup>451</sup>



Ar = Ph, 3,5-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>; R = Me, Ph.

Analogous reactions between 4-nitrophenyl azide and various 1,3-diketones and alkyl acetoacetates in HMPT resulted in the synthesis of carbonyl compounds with a triazole ring.<sup>452,454</sup> Ethyl 1-aryl-5-methyltriazole-4-carboxylates, formed upon reactions of the aryl azides  $\text{RC}_6\text{H}_4\text{N}_3$  (R = H, 2-Me, 3-Me, 4-Me, 2-MeO, 4-MeO, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br) with ethyl acetoacetate in the presence of EtONa, were subjected to alkaline hydrolysis giving rise to a series of the corresponding acids in 43%–80% yields.<sup>455</sup>

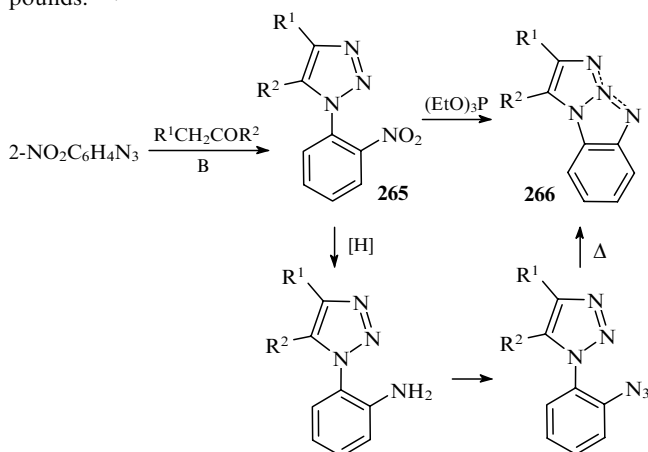
Phenyl azide reacts with methyl γ-methoxyacetoacetate in the presence of Et<sub>3</sub>N in boiling MeOH (the yield of methyl 5-methoxy-1-phenyltriazole-4-carboxylate is ≤24%<sup>201</sup>) and reacts with macrocyclic oxo ester **264** yielding 5-hydroxytriazole due to opening of the macrocycle.<sup>456</sup>



The reaction of 2-nitrophenyl azide with ethyl benzoylacetate affords the 1-nitrophenyl derivative of triazole **265**, which was used to prepare the triazolo[1,2-a]benzotriazole system **266**.<sup>457</sup>

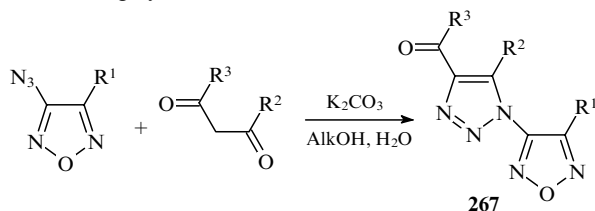


A similar protocol was also realised for other carbonyl compounds.<sup>458, 459</sup>



$R^1 = \text{COPh}$ ,  $R^2 = \text{OEt}$ ;  $R^2 = \text{Me}$ :  $R^1 = \text{COMe}$ ,  $\text{CO}_2\text{Et}$ ,  $\text{Ph}$ .

The reaction of azides with CH-activated compounds has found wide use in the synthesis of polynuclear heterocyclic structures. The reactions of substituted azidofurazans with  $\beta$ -dicarbonyl compounds furnished a series of (triazol-1-yl)furazans **267** in high yields.<sup>460, 461</sup>



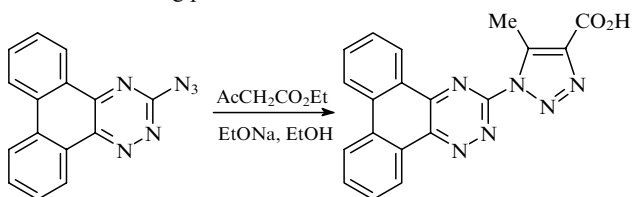
$R^1 = \text{Me}$ ,  $\text{Ph}$ ,  $\text{MeO}$ ,  $\text{NH}_2$ ;  $R^2 = \text{Me}$ ,  $\text{Et}$ ,  $\text{Pr}^n$ ,  $\text{MeOCH}_2$ ,  $\text{ClCH}_2$ ,  $\text{Ph}$ ;  
 $R^3 = \text{Me}$ ,  $\text{Ph}$ ,  $\text{MeO}$ ,  $\text{EtO}$ .

The predominant formation of one regioisomer is in line with the data on the reaction of 2-azidothiazoles with 1,3-dicarbonyl compounds.<sup>462</sup>

By condensing various  $\text{CF}_3$ -substituted 2- and 4-azidopyrimidines with  $\text{RC(O)CH}_2\text{CO}_2\text{Et}$  ( $R = \text{Me}$ ,  $\text{Ph}$ , 4-Py), a broad range of 1-pyridyl-5-methyl(or aryl)triazole-4-carboxylates have been prepared.<sup>247</sup>

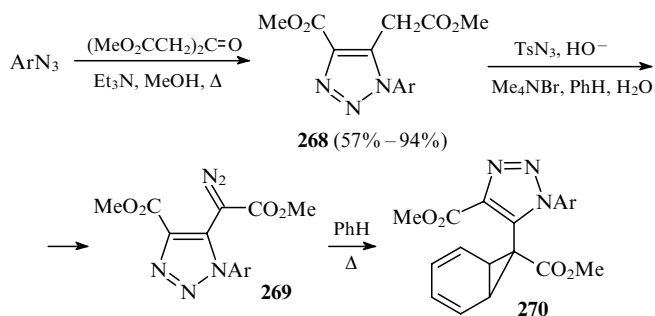
Starting from 4-azidoquinolines, ethyl *p*-nitrobenzoylacetate and other  $\text{CH}_2$ -active compounds, a series of 1-(4-quinolyl)triazoles have been synthesised.<sup>463, 464</sup> 1-(Acridin-9-yl)-4-methoxycarbonyl-5-*R*-triazoles [ $R = \text{Me}$ ,  $\text{Et}$ ,  $\text{Pr}$ ,  $(\text{CH}_2)_4\text{Cl}$ ,  $\text{CH}_2\text{CO}_2\text{Me}$ ,  $\text{Ph}$ ] have been prepared from 9-azidoacridines. The regioselectivity of the base-catalysed reaction may be indicative of an ionic mechanism of the successive steps.<sup>36</sup>

Refluxing 3-azidophenanthro[9,10-*e*][1,2,4]triazine and ethyl acetoacetate produces, in a high yield, 1-hetaryl-5-methyltriazole-4-carboxylic acid, which is readily decarboxylated on heating above the melting point.<sup>338</sup>



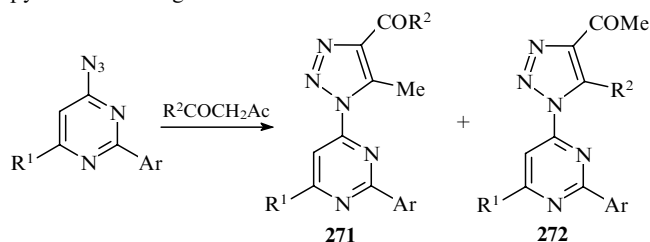
The reaction of aryl azides with dimethyl acetonedicarboxylate carried out by refluxing the reactants in  $\text{MeOH}$  in the presence of  $\text{Et}_3\text{N}$  gave disubstituted triazoles **268**. Repeated treatment of these esters with tosyl azide under phase transfer catalysis conditions resulted in diazo derivatives at the methylene

group, triazoles **269**, which were converted into triazolylnorcaradienes **270** (in the *endo*-hetaryl, *exo*-methoxycarbonyl configuration) on heating in benzene.<sup>465</sup>



$\text{Ar} = \text{Ph}$ , 4- $\text{ClC}_6\text{H}_4$ , 4- $\text{BrC}_6\text{H}_4$ , 4- $\text{NO}_2\text{C}_6\text{H}_4$ , 4- $\text{MeCOC}_6\text{H}_4$ , 2,4- $\text{Cl}_2\text{C}_6\text{H}_3$ .

It has been shown<sup>466</sup> that the reaction of 2- and 4-azidopyrimidines with  $\beta$ -dicarbonyl compounds (acylacetones) in  $\text{EtOH}$  or dioxane in the presence of  $\text{Et}_3\text{N}$  gives 1-pyrimidinyl-4-acyl-1,2,3-triazoles in good yields. In the case of acetylacetone, the reaction of 2-aryl-4-azidopyrimidines gives rise to 4-acetyl-5-methyltriazoles (at  $R^2 = \text{Me}$ , **271**  $\equiv$  **272**), whereas in the case of benzoylacetone, mixtures containing equal amounts of regioisomers **271** and **272** are formed. The reaction rate depends on the nature of the substituent in the 2-aryl groups of pyrimidine. On the one hand, electron-releasing substituents retard the process; on the other hand, the most pronounced accelerating effect was noted for *o*-hydroxyphenyl derivatives, which form a strong intramolecular hydrogen bond between the hydroxyl group and the neighbouring pyrimidine nitrogen.<sup>466</sup>



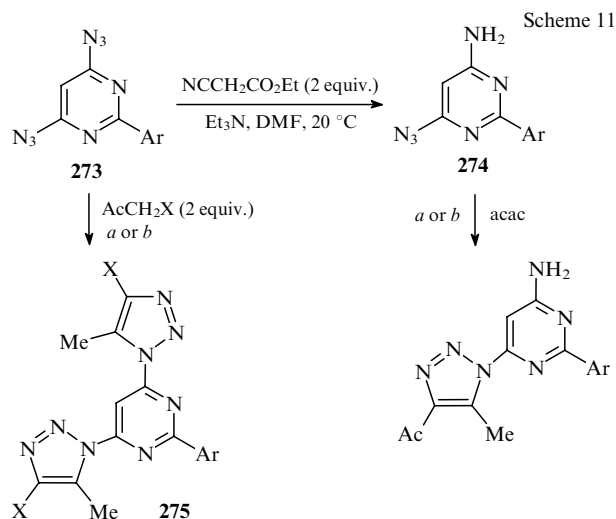
$R^1 = \text{H}$ ,  $\text{Ph}$ ;  $\text{Ar} = \text{Ph}$ , 4- $\text{BrC}_6\text{H}_4$ , 2- $\text{HOC}_6\text{H}_4$ , 2- $\text{MeOC}_6\text{H}_4$ , 4- $\text{MeOC}_6\text{H}_4$ ;  
 $R^2 = \text{Me}$ ,  $\text{Ph}$ .

The reactions of (het)aryl azides with alkyl cyanoacetates give in some cases (het)arylamines as side products (the formal reduction of the azido group to the amino group). One factor directing the reaction along this pathway is the enhanced  $\text{CH}$ -acidity of the dipolarophile. When interpreting the experimental results, researchers consider two possible reaction pathways. Azide cycloaddition to the double bond of the enol form of the dipolarophile gives 5-hydroxytriazoline, while its open form, unstable triazene of type **258** (see Scheme 10), spontaneously decomposes to amine and diazo ketone (or diazo ester).<sup>38, 467, 468</sup>

When two azide groups are present at the 4- and 6-positions of the pyrimidine ring (compound **273**), the reaction with cyanoacetate does not lead to triazoles but stops after the formation of 4-azido-6-aminopyrimidine **274** (Scheme 11).<sup>469</sup>

When other  $\beta$ -dicarbonyl compounds are used (acetylacetone, ethyl acetoacetate and ethyl benzoylacetate), diazidopyrimidine **273** is converted into bis(triazolyl)pyrimidines, although completion of the reaction requires long-term refluxing. Only in one case, when 1 equivalent of acetylacetone is made to react with diazidopyrimidine **273**, 4-amino- and 4-azido-6-(triazol-1-yl)pyrimidines were detected in minor amounts apart from bis(triazolyl)pyrimidine **275**.<sup>469</sup>

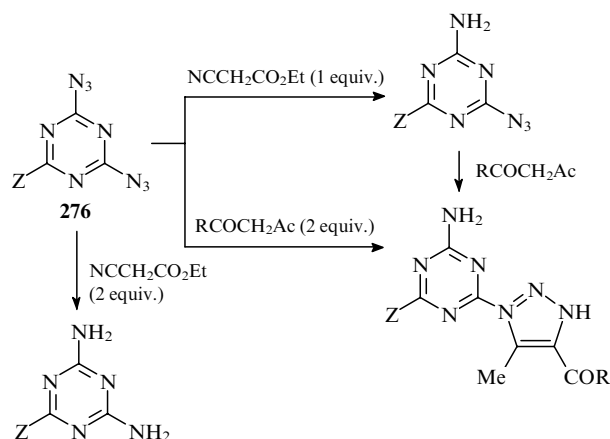
However, in the reaction of diazido-1,3,5-triazines **276** with compounds having a reactive  $\text{CH}_2$  group, both azide substituents



Ar = 4-MeOC<sub>6</sub>H<sub>4</sub>; X = CO<sub>2</sub>Et, Ac;

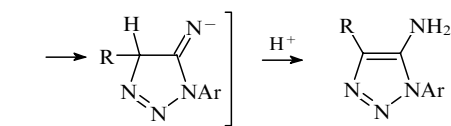
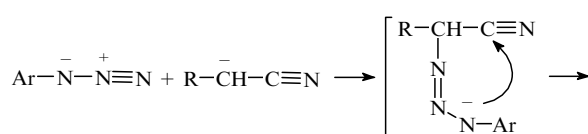
(a) Et<sub>3</sub>N, DMF, 20 °C; (b) Et<sub>3</sub>N, EtOH, Δ.

can be transformed into amino groups due to the better acceptor properties of the heterocycle.<sup>468</sup>



Z = MeO, EtO, NH<sub>2</sub>; R = Me, EtO.

For azides with fragments having lower electron-withdrawing ability than pyrimidine and 1,3,5-triazine rings, 'diazo transfer' processes in the triazene and its decomposition (see Scheme 10) do not play a crucial role, the reaction being directed along the usual route to give 5-aminotriazoles. The reaction of phenyl azide with CH<sub>2</sub>-active compounds containing a cyano group was first performed by Dimroth.<sup>470</sup> The reaction does not follow a concerted mechanism; it starts with attack of the electrophilic terminal nitrogen atom of the azide on the anion derived from the cyanomethylene component, resulting in the formation of the intermediate triazene, in which the anionic nitrogen atom attacks the electrophilic carbon atom of the cyano group in the same molecule. 'Quenching' (protonation) of the anion and isomerisation of the imine produce the final product, namely, amino-triazole.<sup>3</sup>

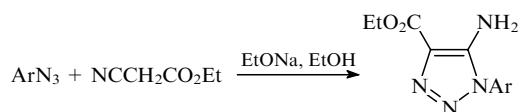


R = Ph, CO<sub>2</sub>Alk, CONH<sub>2</sub>, CN.

This route is important from the synthetic standpoint;<sup>4</sup> however, its use is restricted due to the lability of both the starting compounds and the reaction products under the given conditions. For example, it is known that 1-substituted 5-aminotriazoles readily undergo the Dimroth rearrangement; therefore, to prevent this transformation, the reaction is usually carried out at a lower temperature. In some cases, the optimal condition is to perform the process at room temperature in the presence of Bu<sup>t</sup>OK in Bu<sup>n</sup>OH or anhydrous K<sub>2</sub>CO<sub>3</sub> in DMSO.<sup>451</sup>

The substituents of choice in the RCH<sub>2</sub>CN molecule are Ph, CO<sub>2</sub>Alk, CONH<sub>2</sub> and CN. Aryl and vinyl azides readily react with these cyano derivatives (examples are documented<sup>3,6,34,471</sup>), while HN<sub>3</sub> and acyl azides do not react. Benzyl and alkyl azides give ambiguous results. For example, in the above-mentioned reaction of benzyl azide with ethyl cyanoacetate (EtONa, EtOH, 20 °C), the yield of ethyl 1-benzyl-5-aminotriazole-4-carboxylate did not exceed 5%.<sup>472</sup> The yield was increased by increasing the reaction time (30%)<sup>473</sup> or by conducting it under an elevated pressure of 5 kbar (53%). The attempt to replace the solvent by DMSO was unsuccessful.<sup>451</sup> On refluxing phenylethyl azide in ethanol in the presence of EtONa, the yield of 5-aminotriazole was low.<sup>474</sup>

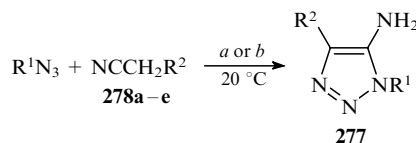
Various substituted phenyl azides were used for the synthesis of *N*-aryl-5-aminotriazoles.<sup>475</sup>



Ar = 3-ClC<sub>6</sub>H<sub>4</sub>, 3-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, 3-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 3-F<sub>3</sub>CSC<sub>6</sub>H<sub>4</sub>, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-FC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>, 4-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 2,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 2,5-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 3,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 2,4,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>2</sub>, 2-Cl-3-F-4-F<sub>3</sub>CC<sub>6</sub>H<sub>2</sub>.

Similar products have been obtained from hetaryl azides, for example, 4-azidopyridine and its *N*-oxide,<sup>26</sup> 6-azido-2,3-diphenyl-indole,<sup>239</sup> 5-azido-2-trifluoromethylpyrimidine.<sup>475</sup> Most often, the reaction is carried out at 0–20 °C to prevent the Dimroth rearrangement.

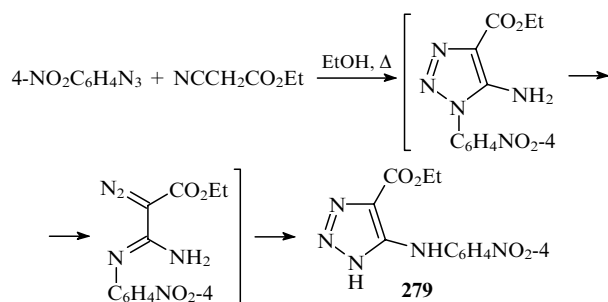
Other acetonitriles have also been used in reactions with azides. For example, 1,4-disubstituted 5-aminotriazoles **277** were prepared by the reaction of 4-nitrophenyl and 4-pyridyl azides with nitriles **278a–c** (condition *a*)<sup>26,76</sup> and benzyl azide with nitriles **278d,e** (condition *b*).<sup>476,477</sup>



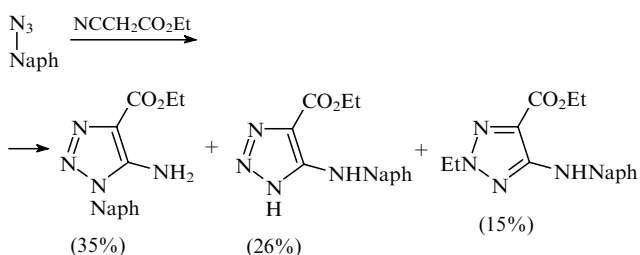
R<sup>1</sup> = Bn, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 4-Py, 4-Py-*N*-oxide; R<sup>2</sup> = CO<sub>2</sub>Me (**a**), Ph (**b**), 4-ClC<sub>6</sub>H<sub>4</sub> (**c**), 4-MeOC<sub>6</sub>H<sub>4</sub> (**d**), 4-MeC<sub>6</sub>H<sub>4</sub> (**e**);  
(a) MeONa, MeOH; (b) Bu<sup>t</sup>OK, THF.

1-(Acridin-9-yl)-5-amino-4-aryltriazoles (Ar = Ph, 2-ClC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>, 2-Py) and analogous 4-carbamoyltriazoles have been synthesised on the basis of 9-azido-acridines and cyano derivatives.<sup>36</sup>

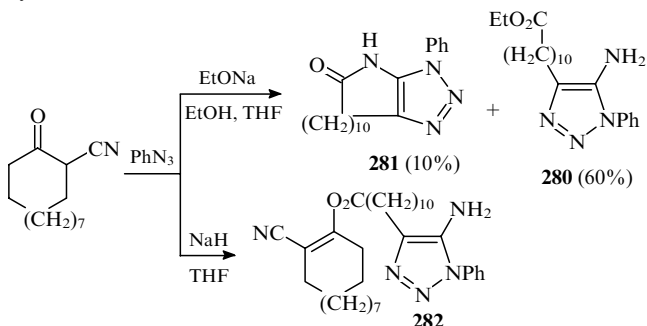
Refluxing a mixture of 4-nitrophenyl azide and ethyl cyanoacetate in EtOH yielded the Dimroth rearrangement product, 5-arylamino derivative **279**.<sup>26</sup>



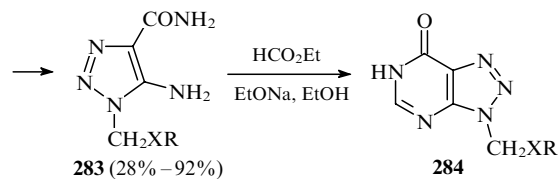
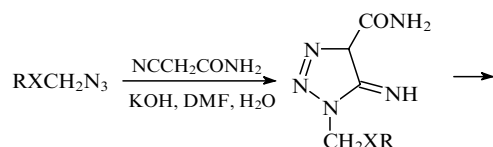
An analogous compound has been isolated, together with the product of its alkylation, in pronounced amounts in addition to the expected 5-amino-4-ethoxycarbonyl-1,2,3-triazole, upon the reaction of 1-naphthyl azide with ethyl cyanoacetate.<sup>478</sup>



The chemoselectivity of the reaction of phenyl azide with the cyanoketone group incorporated in a macrocyclic system depends on the type of the base.<sup>456</sup> In the presence of EtONa, the macrocycle in the intermediate adduct is cleaved to give 5-amino-4-ethoxycarbonyl-1,2,3-triazole **280** and the product of its intramolecular N-acylation **281** as an impurity. When NaH is used, acylation is intermolecular, giving rise to the product of O-acylation of the enol form of the starting cyanoketone **282**.<sup>456</sup>



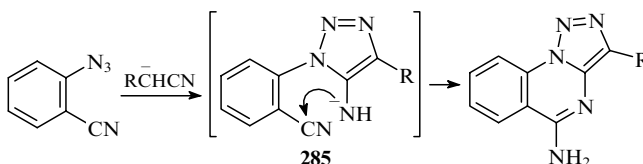
The reaction of azides with cyanoacetamide proceeds smoothly giving the corresponding 5-amino-4-carboxamidotriazoles in high yields. Depending on the nature of the azide, the reaction is carried out in EtOH in the presence of EtONa at various temperatures (0–5 °C,<sup>479</sup> 20 °C<sup>474</sup> or 70 °C<sup>138</sup>), in DMF in the presence of KOH (0 °C)<sup>292</sup> or in DMSO in the presence of K<sub>2</sub>CO<sub>3</sub> (35–40 °C).<sup>451</sup> The resulting 5-amino-4-carbamoyl-1,2,3-triazoles are of interest as biologically active compounds<sup>480,481</sup> and the starting compounds for the synthesis of fused heterocyclic systems.<sup>8,482</sup> The preparation of these derivatives (**283**) by the reaction of substituted methyl azides with cyanoacetamide and their further transformation into 8-azapurines **284**, which are acyclic analogues of nucleosides, have been reported.<sup>292,483</sup>



R = BnO(CH<sub>2</sub>)<sub>2</sub>, (BnOCH<sub>2</sub>)<sub>2</sub>CH, BnO(BnOCH<sub>2</sub>)CHCH<sub>2</sub>; X = O, S.

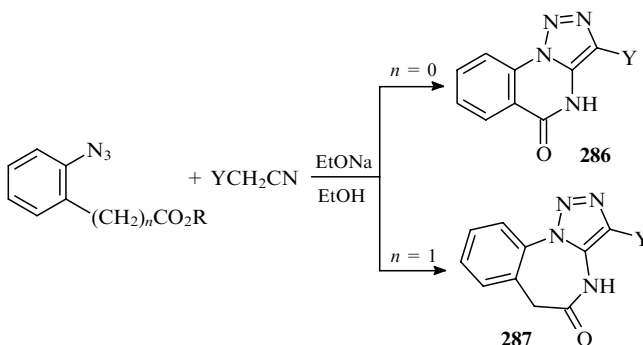
5-Amino-4-carbamoyl-1,2,3-triazole 1-β-ribozide has been prepared in a similar way; it can be used to prepare 9-β-ribozides of 8-azahypoxanthines.<sup>484,485</sup> 2,9-Disubstituted 8-azapurin-6-ones were synthesised without isolation of intermediate triazoles.<sup>486</sup>

Of special interest from the synthetic standpoint is the reaction of the cyano carbanions RCH<sup>−</sup>CN with *ortho*-substituted aryl azides (substituents CN, NO<sub>2</sub>, CO<sub>2</sub>H). Previously, it was found that aminotriazole **285** formed *in situ* is involved in the formation of the new ring:<sup>487–489</sup> the amide anionic centre attacks the electrophilic centre of the *ortho*-substituent.



R = Ph, CO<sub>2</sub>Et, CONH<sub>2</sub>, CN.

When aryl azide (or benzyl azide) contains a carbonyl group, the cyclisation ends with the formation of substituted 4*H*-triazolo[1,5-*a*]quinazolinones **286** and their seven-membered analogues **287**, respectively.<sup>490–492</sup>

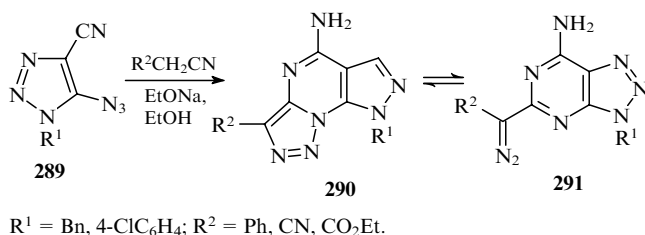
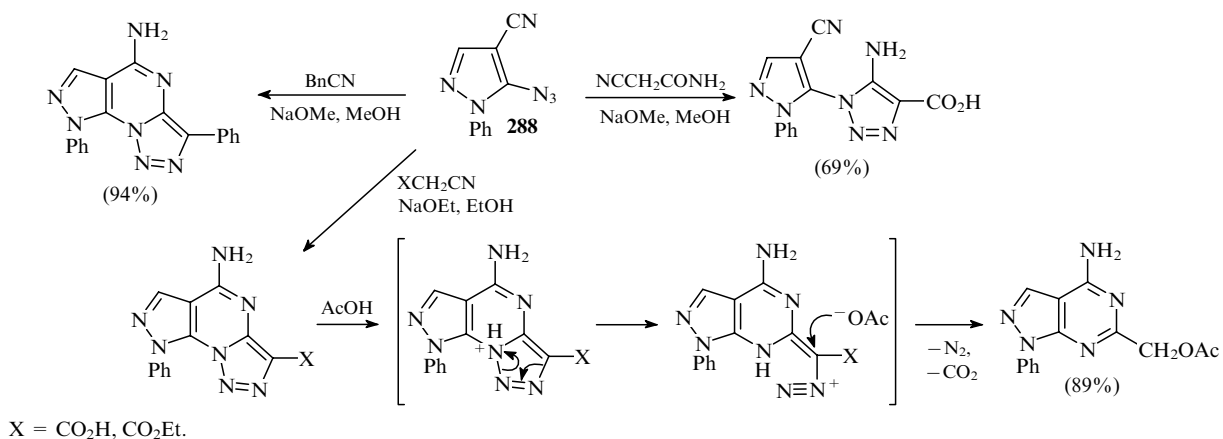


R = H, Et; Y = Ph, CONH<sub>2</sub>, CONHMe, CO<sub>2</sub>Et.

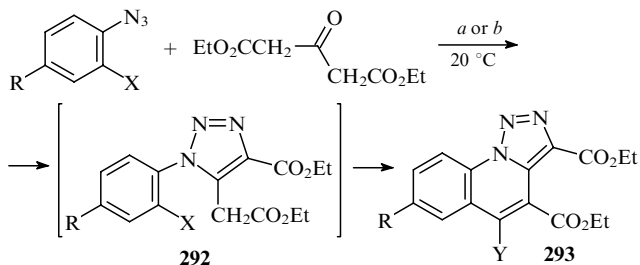
Azidocyano derivatives of five-membered nitrogen heterocycles react in this way with the anions derived from substituted acetamides, the subsequent transformations of the compounds formed being dependent on the nature of the heterocycle and the acetamide. For example, 5-azido-4-cyanopyrazole **288** is converted into different products when reacted with phenylacetone, cyanoacetamide and cyanoacetic acid and its esters.<sup>493</sup> Interestingly, the mechanism of the last-mentioned transformation includes opening of the triazole ring at the N–N bond, ejection of the nitrogen molecule and decarboxylation (Scheme 12).

In the reaction of 5-azido-4-cyanotriazoles **289** with substituted acetonitriles, it is possible to detect both tautomers of the product, namely, cyclic **290** and open **291** tautomers, whose ratio depends on the polarity of the medium and the nature of the substituent.<sup>494,495</sup>

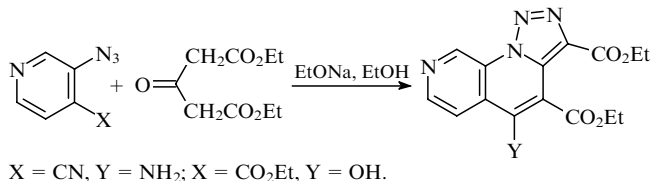
Scheme 12



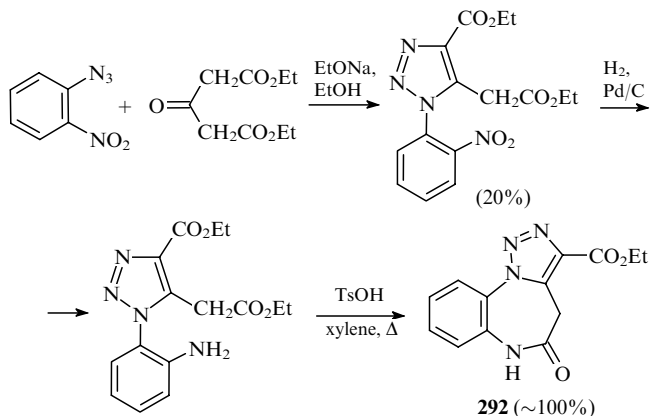
Subsequently, the scope of this reaction was extended. The reactions of various *ortho*-substituted aryl azides with the diethyl acetonedicarboxylate carbanion generated under the action of bases or an ion exchange resin in the OH-form have been studied.<sup>489</sup> The reactions take place in ethanol at room temperature. The side fragment in the intermediate 1-aryltriazole **292** interacts immediately with the *ortho*-substituent. The closure of the additional ring affords tricyclic system **293**.



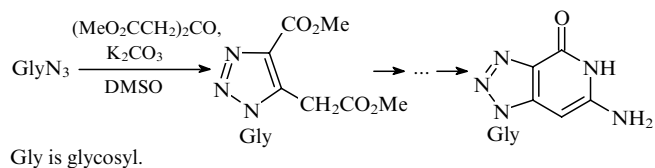
The amino or hydroxy derivative of 1,2,3-triazolo[1,5-*a*][1,7]naphthyridine is formed in a similar way from azidopyridine containing a CN or a CO<sub>2</sub>Et group, respectively, when made to react with diethyl acetonedicarboxylate.<sup>489</sup>



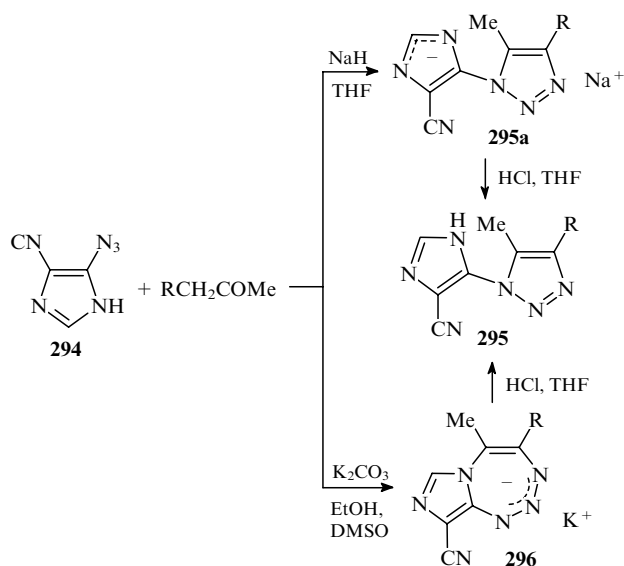
Only in the case of 2-nitrophenyl azide, was 1-(2-nitrophenyl)-triazole isolated; it was reduced to the corresponding *o*-amino-phenyl derivative, which was refluxed in xylene containing some *p*-toluenesulfonic acid to give 1,2,3-triazolo[1,5-*a*]benzo[1,5]diazepin-6-one **292** in a quantitative yield<sup>489</sup>



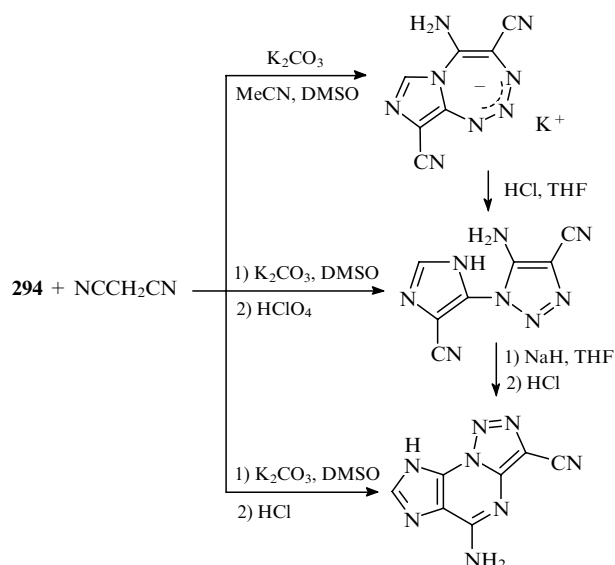
Similar transformations have been employed in the synthesis of 8-aza-3-deazaguanine nucleosides; the reaction between protected glycosyl azides and dimethyl acetonedicarboxylate was carried out in DMSO in the presence of K<sub>2</sub>CO<sub>3</sub>.<sup>496</sup>



The behaviour of 5-azido-4-cyanoimidazole **294** in the reaction with compounds containing an active CH<sub>2</sub>-group differs from that presented above for the benzene and pyridine analogues. It was shown that, depending on the conditions of reactions with β-dicarbonyl compounds, either imidazolate (**295a**) or tetrazepinate salts (**296**) can be isolated; on treatment with HCl in tetrahydrofuran, these products are converted into the corresponding imidazolytriazole **295** in high yields.<sup>497</sup>

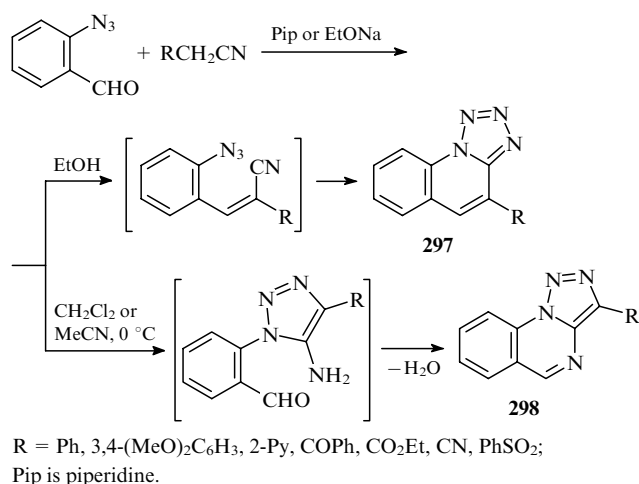


The outcome of the reaction of the same azide with malononitrile depends on the conditions of product isolation. It has been assumed<sup>497</sup> that imidazo[5,1-*d*][1,2,3,5]tetrazepinate salts play a key role in these transformations.



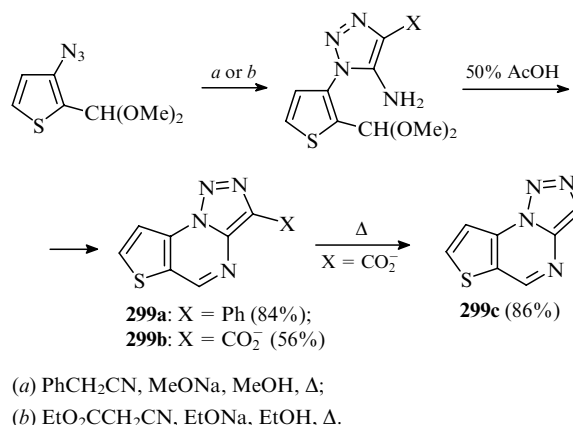
When the phenyl azide molecule contains an *o*-CHO group, the reaction pathway is determined by the conditions, in particular, by the solvent used. The reaction of 2-azidobenzaldehyde with substituted acetonitriles in EtOH in the presence of piperidine or EtONa results in tetrazolo[1,5-*a*]quinolines **297** (first, the Knoevenagel condensation takes place at the aldehyde group and only after that, does the 1,3-cycloaddition of the azide group to the  $C\equiv N$  bond of the intermediate nitrile occur). However, the same reaction in an aprotic solvent at 0 °C yields triazolo[1,5-*a*]quinazolines **298**.<sup>498</sup> With the protected aldehyde function (as the oxime or *N*-methylnitron), this reaction produces only triazolo[1,5-*a*]quinazolines **298**, irrespective of the conditions.<sup>498</sup>

The attempts to induce a regioselective attack by cyano carbanions on the carbonyl group in 2-azidoacetophenone failed, 5-methyltriazolo[1,5-*a*]quinazolines being isolated as the only products.<sup>489</sup>

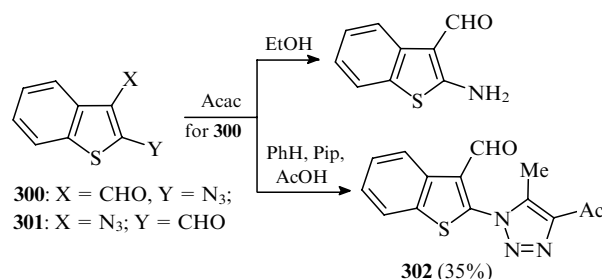


The behaviour of mono- and dimethyl-6-azido-5-formyluracils towards ethyl cyanoacetate and malononitrile in ethanol is similar to that of 2-azidobenzaldehyde: in the presence of piperidine, only the corresponding tetrazolo[1',5':1,6]pyrido[2,3-*d*]pyrimidines are formed.<sup>499</sup>

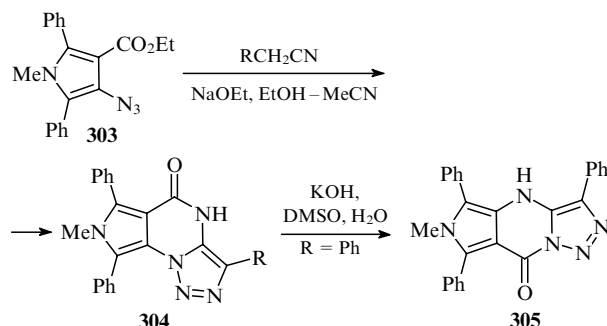
The reaction of 3-azidothiophene-2-carboxaldehyde with substituted acetonitriles was carried out using the acetal protection of the aldehyde group in order to prevent the aldol-crotonic condensation. The protection was removed after the formation of aminotriazole; the condensation of the free aldehyde group with the amino group gave a pyrimidine ring in the tricyclic system **299**.<sup>488</sup>



The behaviour of two isomeric azido derivatives of benzo[*b*]thiophenealdehydes **300** and **301** towards 1,3-dicarbonyl compounds has been studied.<sup>500</sup> It was shown that only the 2-azido isomer **300**, does form triazole **302** (benzene, piperidine acetate as the catalyst) when made to react with acetylacetone, while in EtOH, reductive deazotisation takes place. The 3-azido isomer reacts with diethyl malonate, ethyl acetoacetate and acetylacetone to give 2-alkylidene derivatives of 3-azidobenzothiophene.<sup>500</sup>



If the (het)aryl azide molecule contains an ester group, instead of the aldehyde group, an amide fragment is formed in the resulting ring. This was shown using azidopyrrole **303** as an example. It was noted that the reaction products did not undergo the Dimroth rearrangement under classical conditions; only upon refluxing in the DMSO–water system, did phenyl derivative **304** rearrange to heterocycle **305** in a quantitative yield.<sup>501, 502</sup>



R = Ph, CN, CONH<sub>2</sub>.

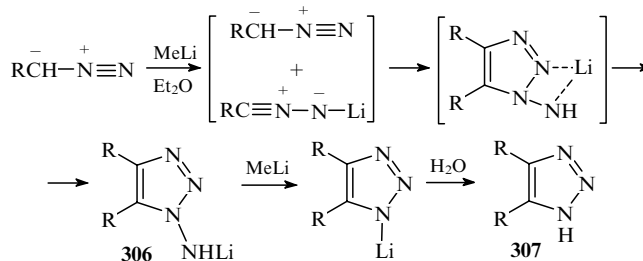
To conclude the Section devoted to the methods of synthesis of triazoles from azides, it is pertinent to list once again the most advanced modifications of the experimental conditions used to carry out dipolar cycloaddition. Apart from the dependence on the nature of reactants, solvents and temperature, the rate and completeness of the reaction were found to depend markedly on the pressure in the reaction system.<sup>214, 216, 242, 291, 473</sup>

The use of ionic liquids as the reaction media allows one to sharply reduce the reaction time.<sup>268</sup> Cascade synthesis of 1-substituted triazoles from allene derivatives of aryl iodides, NaN<sub>3</sub> and norbornene has been carried out.<sup>272</sup> The reactions of organic azides with acetylene amides, azidomethylphosphonates with low-activated acetylenes and enamines and aryl azides with methyl-enephosphoranes have been successfully carried out in the absence of solvents on exposure to microwave radiation.<sup>179, 233, 283, 335</sup>

New methods the regiocontrol of dipolar cycloaddition include encapsulation conditions for the reactants<sup>237</sup> or the 'chemical recognition' principle (for example, the presence of the crown-ether fragment in the azide molecule and the terminal ammonium group in the substituted acetylene).<sup>238</sup> A series of substituted triazoles with a high degree of purity have been prepared by solid-state synthesis using polymer-supported 3-aminocrotonamides and tosyl azide,<sup>416</sup> 2-azidocarboxylic acids,<sup>503, 504</sup> 5-azido-4-hydroxyvaleric acid.<sup>505</sup> However, in this version, it is impossible to use low-reactivity compounds and it is inconvenient to monitor the reaction. It has been proposed to avoid these difficulties by using soluble polymers with grafted dipolarophiles.<sup>306, 506</sup> As a polymer of this type, monomethyl ether of polyethylene glycol with a molecular mass of 5000 (MeO-PEG 5000) was proposed. This polymer is soluble in many organic solvents, which allows one to monitor the cycloaddition using spectral methods. The removal of the target products from the polymer is accomplished under mild conditions by treatment with NaBH<sub>4</sub> in ethanol. Using this procedure, several carbohydrate triazole derivatives have been prepared.<sup>306, 506</sup> Another variant implies attachment of the azide function to a polymer and carrying out cyclocondensation with DMAD or terminal acetylenes containing Ph, CO<sub>2</sub>Me, CH<sub>2</sub>Cl, CH<sub>2</sub>Br, CH<sub>2</sub>OH or CH<sub>2</sub>CH<sub>2</sub>OH group. The reaction mixture is then treated with formic acid to isolate the regioisomers, namely, 4- and 5-substituted triazoles.<sup>507</sup> The solid-state combinatorial synthesis of substituted carboxamidotriazoles by successive treatment of supported 3-oxobutyramide with triethyl orthoformate and tosyl azide has been described.<sup>508</sup>

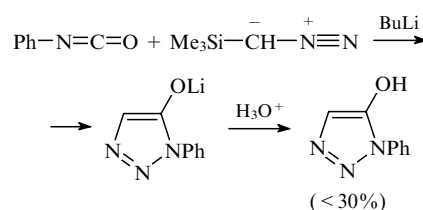
## V. Methods of formation of the C(4)–C(5) and N(1)–N(2) bonds

This line of research is not very popular in triazole synthesis. This is mainly limited to the condensation of diazo derivatives with compounds containing activated C=N bonds. It was found in the mid-20th century that metallated derivatives of diazoethane and phenyldiazomethane form 4,5-dimethyl- or 4,5-diphenyltriazoles, respectively.<sup>509, 510</sup> Some suggestions have been made concerning the reaction mechanism and the structures of intermediates but they have long remained unproved. In a recent publication,<sup>511</sup> the reaction of trimethylsilyldiazomethane with butyllithium was studied, the structure of the dimerisation product formed was determined and theoretical calculations were performed that made it possible to correct the existing views on the structure of the reacting species and the dimerisation mechanism. The general scheme includes the reaction between two dipolar diazomethane molecules, the formation of the lithium derivative of *N*-amino-triazole **306** and cleavage of the exocyclic N–N bond. Treatment of the reaction mixture with water results in disubstituted triazoles **307**.<sup>511</sup>



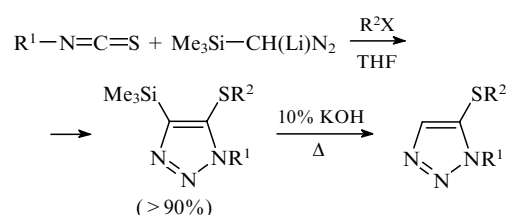
R = Me, Ph, Me<sub>3</sub>Si.

Phenyl isocyanate reacts with trimethylsilyldiazomethane in the presence of butyllithium to give 5-hydroxy-1-phenyltriazole.<sup>512</sup>



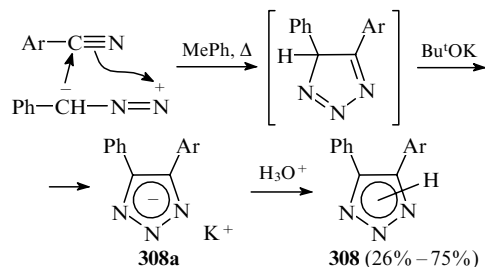
C-Metallated diazoalkanes are also capable of this type of cyclocondensation. Indeed, the  $\alpha$ -diazomethylzirconium complex reacts with phenyl and naphthyl isocyanates to give triazole derivatives.<sup>513</sup>

Isothiocyanates easily react with the lithium salt of trimethylsilyldiazomethane but the reaction pathway depends on the solvent used: 2-amino-1,3,4-thiadiazoles are formed in Et<sub>2</sub>O; only conducting the reaction in THF, does allow one to prepare 1-substituted 5-alkylthio-4-trimethylsilyltriazoles.<sup>514</sup> The Me<sub>3</sub>Si group is readily removed by refluxing of the reaction products with 10% KOH.



R<sup>1</sup> = Me, Bu<sup>n</sup>, Bn, Ph, CH<sub>2</sub> = CHCH<sub>2</sub>; R<sup>2</sup>X = MeI, BnBr.

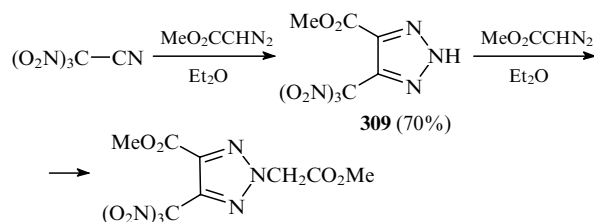
4,5-Diaryltriazoles **308** are formed in the reaction of phenyl-diazomethane with substituted benzonitriles in the presence of Bu<sup>t</sup>OK according to the dipolar cycloaddition pattern to an activated C≡N bond.<sup>515</sup> The function of a base is to eliminate a proton in the cycloadduct to give anion **308a**, the treatment of which with an aqueous solution of an acid gives the corresponding triazole.



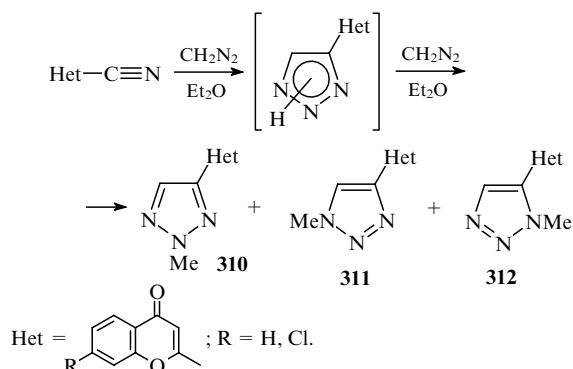
Ar = Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 2-BrC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>.

It is noteworthy that azines of aromatic aldehydes (Bu<sup>t</sup>OK, DMSO, 20 °C) enter into a similar reaction to give symmetric 4,5-diaryltriazoles (Ar = Ph, 3-MeOC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>), but the product yield does not exceed 40%.<sup>515</sup>

Other cyano derivatives in which the C≡N bond is activated can also react with diazo compounds. For example, cyanotrinitromethane reacts with methyl diazoacetate in ether at room temperature to give 5-methoxy-4-trinitromethyl-2*H*-triazole **309**, which undergoes N-alkylation on long-term storage in the reaction mixture.<sup>516, 517</sup>

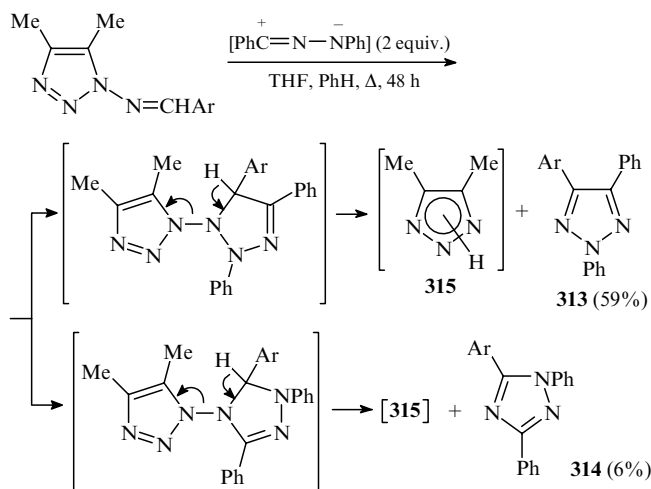


2-Cyanochromone and its 7-chloro derivative reacts with excess diazomethane to give a set of three *N*-methylated triazoles **310–312** in which the 2-methyl derivatives **310** predominate.<sup>518</sup> Presumably, prototropic triazole is first formed and then it undergoes N-methylation. The reaction of diazomethane with nitrophthalonitriles proceeds in a similar way, but involving only one cyano group.<sup>519</sup>



In order to obtain N–N' bonded triazole rings, attempts have been made to involve *N*-arylideneaminotriazoles and diphenylnitrile imine in cycloaddition.<sup>520</sup> However, the C=N bond in *N*-arylideneaminotriazoles proved to be inactive and only in the case of Ar = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, did the reaction give triaryltriazole isomers in satisfactory yields. Diphenylnitrile imine was generated *in situ* by treatment of *N*-phenylbenzoylhydrazonoyl chloride with triethylamine in an aprotic solvent (THF–benzene), and the suspension obtained in this way was kept at the boiling point of

the solvent mixture. Presumably, the reaction proceeds *via* isomeric cycloadducts, each of them decomposing with cleavage of the exocyclic N–N bond to give 1,2,3-triazole derivatives **313** and 1,2,4-triazole derivatives **314**, respectively.<sup>520</sup> The intermediate 4,5-dimethyltriazole **315** adds a second nitrile imine molecule (at the 1- or 2-position).



Ar = 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>.

## VI. Conclusion

The methods of synthesis of substituted 1,2,3-triazoles described in the review were used in the last decade to prepare a great diversity of compounds, the properties of which proved to be rather attractive for practical purposes, in particular, for the development of drugs and plant protection and growth control agents.

For example, it has been proposed to use polyunsaturated conjugated systems containing terminal 5-hydroxytriazole groups as dyes for photographic materials,<sup>512</sup> and bis(triazol-2-yl)-substituted arylenes with different bridging fragments, in organic electroluminescence devices.<sup>81</sup> (2*H*-Benzotriazol-2-yl)-4-methylphenol is known as the Benazol-P light stabiliser.<sup>135</sup> Fluorescing bleaching agents can be prepared on the basis of triazole derivatives.<sup>521</sup> In view of the substantial energy content of nitrogen derivatives, it has been proposed to use nitrotriazoles as components of explosive mixtures,<sup>107, 108, 522</sup> and 1,1'-bitriazole,<sup>115</sup> 1*H*-triazole and its 1-amino derivatives can be used as nitrogen generators for the automobile safety bags.<sup>523–526</sup>

1-Benzyl-4,5-dibenzoyl- and -4,5-dialkoxycarbonyltriazoles inhibit the corrosion of some metals in acid media,<sup>527–530</sup> 4-alkyl(hydroxy, nitroso, mercapto)-triazoles can also be used to protect aluminium and its alloys.<sup>531</sup>

In recent years, 1-hydroxy-1*H*-triazoles and their *O*-derivatives have attracted the attention of researchers engaged in the search for new coupling reagents for peptide synthesis to suppress racemisation.<sup>46, 102</sup> For instance, ethyl 1-hydroxytriazole-4-carboxylate can be used in combination with diisopropylcarbodiimide in solid-state peptide synthesis<sup>46, 532, 533</sup> and in combination with peptide hydrazides for the assembly of peptide segments.<sup>534, 535</sup>

Data on the biological action of triazole derivatives and the possible use of these compounds in agrochemistry, veterinary and medicine have been reported in a number of publications and patents. Particular aspects of the activity are considered in special reviews.<sup>14, 536–539</sup> 1-Aryl-5-phenoxytriazoles have been proposed as herbicides,<sup>187</sup> while a number of 2-[2-alkyl- and cycloalkyl(2*H*-triazol-4-yl)]acrylonitriles have been proposed as insecticides, nematocides and acaricides.<sup>540</sup> Some (het)aryltriazoles have shown high insecticide and pesticide activities,<sup>96, 247, 248, 541–543</sup> and halogen and haloalkyl derivatives of 1-(diarylmethyl)triazoles have exhibited insecticide properties.<sup>544</sup>

Triazolyl analogues of natural antibiotics have shown excellent antibacterial action.<sup>545, 546</sup> Antibacterial properties have also been found for triazolyl derivatives of esters of  $\beta$ -enamino acids,<sup>547</sup> 7 $\beta$ -(triazolyl-4-formamido)cephalosporins,<sup>548–550</sup> 4-aryl-1-[5-methyl-1-(4-chlorophenyl)triazole-4-carbonyl]thiosemicarbazides and their heterocyclic derivatives.<sup>551</sup> Antiinflammatory activities have been found for carboxamidotriazoles,<sup>400</sup> while sterically hindered 5-(4-hydroxyphenyl) derivatives of triazole-4-carboxylic acids and amides have proved active in the therapy of arthritis.<sup>399</sup> For 5-amino-4-carbamoyltriazoles,<sup>481</sup> dimethyl triazole-4,5-dicarboxylate with *N*-arylacetamide substituents<sup>552</sup> and some bistriazoles,<sup>553</sup> various types of antimicrobial activities have been found. 1-Benzyl-5-aminotriazoles constitute a new class of antiproliferative agents for the therapy of psoriasis and coccidiosis.<sup>554–557</sup>

1-Aryltriazole-4,5-dimethanol derivatives<sup>180</sup> and 1-(1-phenyltriazol-5-yl)alkyl-4(1*H*)-quinolones<sup>558</sup> possess a cytotoxic action, while 5-amino-1-[[3,5-dichloro-4-(chlorobenzoyl)phenyl]-methyl]-4-carboxamidotriazole exhibited anti-HIV action, along with cytotoxic properties.<sup>559–561</sup> Clinical investigations of the last-mentioned compound have demonstrated that it is well tolerated in the case of oral administration, decreases a tumour, and stabilises the patient's condition.<sup>537</sup> Some 5-amino-4-carboxamidotriazoles inhibit metastases,<sup>562–564</sup> and one of the 4 $\beta$ -(1-triazolyl)podophyllotoxins has demonstrated even stronger cytotoxic properties *in vivo* than the anticancer drug etoposide used in clinical practice.<sup>340</sup> Some triazole *N*-nucleosides also possess antitumour and antiviral properties.<sup>426, 565</sup> 17-(Triazol-1-yl)steroids induce a decrease in testosterone and dihydrotestosterone levels and can be used for the therapy of benign hypertrophy and prostatic cancer.<sup>566–568</sup>

Some substituted 1-(4-quinolyl)triazoles are analgesics, being superior to indometacin as regards this type of activity.<sup>463, 464</sup> For the series of fused diazepine systems, it has been shown that the neuroleptic properties are due to the presence of the 1,2,3-triazole fragment in the structure.<sup>569</sup> 1-Aryl-5-pyridyltriazoles have formed a new structural group of anticonvulsants, which are comparable in action with known clinical drugs and, in addition, possess a very low neurotoxicity.<sup>570, 571</sup> Fluorinated 1-arylalkyltriazoles also exhibit an antispasmodic action,<sup>193</sup> 4(5)-carboxamide and -alkylcarbamoyl derivatives have been recommended for the therapy of neuropathic diseases, in particular, epilepsy,<sup>572–575</sup> while triarylmethyltriazoles have been proposed for treatment of central nervous system diseases.<sup>176</sup>

A series of substituted 5-dimethylaminomethyltriazoles with (thio)morpholino groups in the heterocycle or in the side chain are antagonists of neurokinin receptors and exhibit the properties of opioid analgesics.<sup>576</sup> Preparations of this type have been proposed for the curing and prevention of inflammations, headaches and neuralgias.<sup>166, 347–349</sup> Some 4-piperidyl-substituted triazoles<sup>270</sup> and substituted triazolo[1,5-*a*]quinazolines<sup>577</sup> are active with respect to muscarin receptors and are of particular interest as drugs against Alzheimer's disease. Tricyclic benzoazepine compounds containing a carbamoyltriazole fragment can be used as antiallergic drugs.<sup>192, 578, 579</sup> Substituted amidinotriazoles showed an antihypertensive effect, while having low toxicity.<sup>141</sup> 5-(2-Nitroanilino)triazoles and 1-(4-carbamidotriazol-5-yl)benzotriazoles possess a vasodilatory action caused by activation of potassium channels.<sup>137, 480</sup>

Some 1-( $\beta$ -D-ribofuranosyl)-5-alkylcarbamoyltriazole derivatives<sup>337, 580, 581</sup> and carbocyclic analogues of ribavirin containing a 4-carbamoyltriazole fragment<sup>315</sup> showed high anti-HIV and antihepatitis activities.

Many publications are devoted to the interaction of functional derivatives of 1,2,3-triazole with various bioreceptors and enzymes but these studies are beyond the scope of this review. We would only like to note that triazole compounds are attractive components in biochemical and medical investigations, as they are formed in high yields in aqueous or aqueous-organic media from organic azides and terminal alkynes *via* Cu(I)-catalysed cyclo-

addition and are readily bound to biological targets through hydrogen bonds and dipole interactions, while still remaining chemically inert linkers.<sup>582, 583</sup>

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# Plant alkaloids of the polymethyleneamine series

L N Rogoza, N F Salakhutdinov, G A Tolstikov

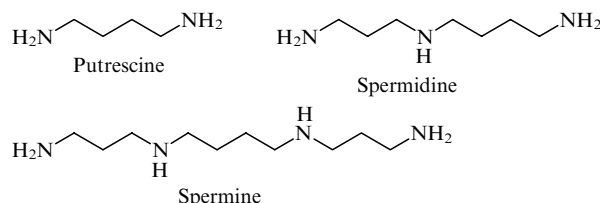
## Contents

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**Abstract.** The published data on the structures and biological activities of the plant alkaloids of the biogenic polymethyleneamine series, *viz.*, putrescine (1,4-diaminobutane), spermidine (1,8-diamino-4-azaoctane), and spermine (1,12-diamino-4,9-diazadodecane), are considered and systematised. The structures and biological activities of some synthetic analogues of these alkaloids are also presented. The bibliography includes 84 references.

## I. Introduction

The biogenic polymethylenepolyamines putrescine, spermidine and spermine have been identified in detectable amounts in all living cells.



These are natural amino acid metabolites in plants and animals<sup>1,2</sup> and are involved in many biological processes.<sup>1,3</sup> Valuable biological activities of biogenic polymethylenepolyamines gave impetus to the development of methods for their synthesis and the synthesis of their analogues.<sup>†</sup>

The natural polyamines occur as free aliphatic bases and structural elements of alkaloids commonly referred to as secondary metabolites.

This review is devoted to plant alkaloids with putrescine, spermidine or spermine fragments as their constituents. They play an essential role in different stages of plant development (flowering, fruit ripening, ageing, *etc.*), as well as in miscellaneous interactions of plants with the environment.<sup>4,5</sup> Depending on the nature of the parent polyamine, the alkaloids can be divided into

three groups, *viz.*, putrescine-borne polyamines, spermidine-borne polyamines and spermine-borne polyamines. Each of these groups is represented by both cyclic and linear compounds. A special group of alkaloids includes lactams.

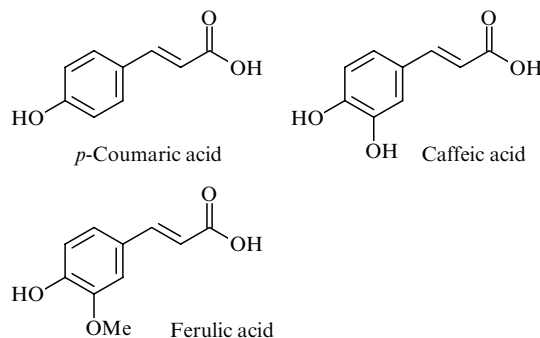
The present review covers the literature published in 1992–2003 dealing with the description of methods for the isolation of this group of alkaloids from plants, determination of their structures and biological activities and structural modification aimed at the design of targeted-action medicines. References to previous publications are given where necessary.

It is common practice that trivial names of natural compounds derive from the names of plants they are isolated from. Some linear polymethyleneamine derivatives have no such names and the substitutive nomenclature is used where putrescine, spermidine or spermine are taken as parent compounds and the locants of the nitrogen atoms indicate their positions in the chain.

## II. Linear polymethyleneamine alkaloids

Linear alkaloids containing spermine, spermidine, putrescine or guanidinoputrescine fragments are represented by amides of various carboxylic acids (*N*-acylpolyamines). As a rule, these compounds contain only one polyamine constituent. The only exception is alkaloid tenuilobine isolated from plants of the *Oncinotis* genus (Apocynaceae), with contains both spermine and spermidine fragments.

The carboxylic acids most commonly found in linear spermine and spermidine derivatives include cinnamic acid and its derivatives, *e.g.*, *p*-coumaric (*p*-hydroxycinnamic), caffeic (3,4-dihydroxycinnamic), ferulic (4-hydroxy-3-methoxycinnamic), 3,4-dimethoxycinnamic and, less frequently, dihydrocinnamic acids.



L N Rogoza, N F Salakhutdinov, G A Tolstikov, N N Vorozhtsov  
Novosibirsk Institute of Organic Chemistry, Siberian Branch of  
the Russian Academy of Sciences, prosp. Akad. Lavrent'eva 9, 630090  
Novosibirsk, Russian Federation. Fax (7-3832) 30 49 80,  
tel. (7-3832) 30 97 33, e-mail: rogoza@nioch.nsc.ru (L N Rogoza),  
anvar@nioch.nsc.ru (N F Salakhutdinov), gtolstik@nioch.nsc.ru  
(G A Tolstikov)

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<sup>†</sup> Since recently, synthetic polymethyleneamine derivatives are considered as promising antitumour and anti-infectious agents.<sup>1</sup>

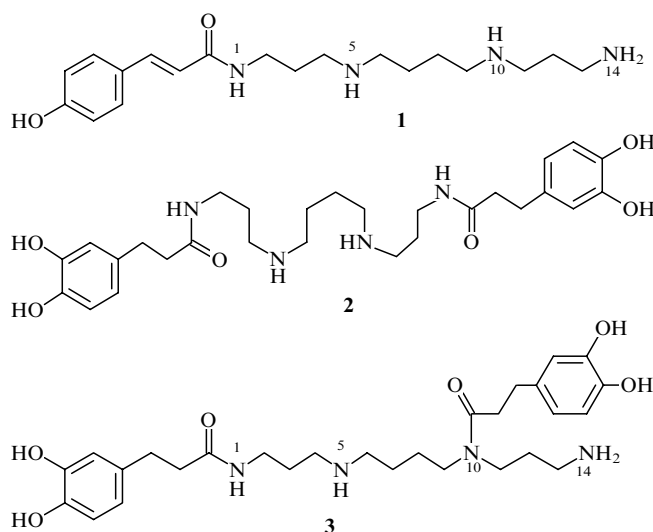


Some alkaloids contain benzoic and hexadecanedioic acids as carboxylic acid components. In addition to the foregoing carboxylic acids, linear putrescine derivatives contain aliphatic acids and carboxy derivatives of flavaglines,<sup>6</sup> cyclopenta[*bc*]benzopyrans (aglaines and aglaforbesines) and benzo[*b*]oxepins (forbaglines).

Cinnamamides are present in many higher plants.<sup>7,8</sup> They were found in the reproductive organs (anthers) as the main structural components of pollen and in some other parts of the plants. Their presence is associated with responses of plants to pathogenic factors, *e.g.*, viral or fungal infections.<sup>9</sup>

### 1. Linear spermine derivatives

Linear spermine derivatives are few in number. 1-(*N*-*p*-Coumaroyl)spermine (**1**) is the simplest representative of natural spermine amides.<sup>10</sup> Kukoamines A (**2**) and B (**3**) isolated from the root bark of *Lycium chinense* also belong to this group. These compounds contain dihydrocaffeic acid fragments.<sup>11</sup>



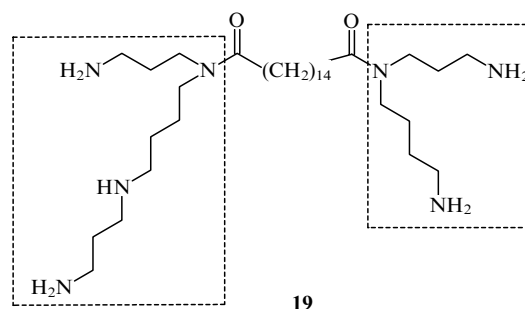
### 2. Linear spermidine derivatives

Linear spermidine derivatives include mono- (**4–6**), di- (**7–10**) and triacyl (**11–18**) derivatives of cinnamic acids.<sup>7,9,10,12–15</sup> Some spermidine amides isolated from plants are listed in Table 1. The monoamide **4** and its synthetic isomer (compound **5**) differing in the position of the central nitrogen atom in the chain result from acylation of the primary amino group. Diamides include compounds with all possible combinations of pairwise substitutions, *viz.*, N<sup>1</sup> and N<sup>5</sup>; N<sup>1</sup> and N<sup>10</sup>; N<sup>5</sup> and N<sup>10</sup>. In these compounds, fragments of the same acid (compounds **7–9**) or of different acids (compound **10**) serve as the substituents. Trisubstituted spermidine derivatives are the most numerous; in this case, too, the role of substituents is played by the same acid (compounds **11–13**) or two different acids (compounds **14–17**). The alkaloid **18** is the only spermidine alkaloid containing three different acyl substituents (coumaric, caffeic and ferulic acid fragments).

In addition to fragments of cinnamic acids, some linear spermidine derivatives contain fragments of other acids. Thus 5-*N*-benzoylspermidine (**6**)<sup>12</sup> (monoamide) and tenuilobine (**19**) (diamide), were isolated from the leaves of *Oncinotis tenuiloba* Stapf (Apocynaceae).<sup>16</sup> Compound **19** represents a diamide of hexadecanedioic acid and contains one spermine and one spermidine fragment. This was also isolated from the Central Asian plant *Salsola subaphylla*<sup>17</sup> and was named subaphylline.

**Table 1.** Linear alkaloids derived from spermidine.

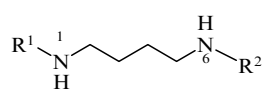
| Alkaloid                           | R <sup>1</sup>      | R <sup>2</sup>      | R <sup>3</sup>      | Plant source                                                                            | Ref.     |
|------------------------------------|---------------------|---------------------|---------------------|-----------------------------------------------------------------------------------------|----------|
| <b>Monosubstituted derivatives</b> |                     |                     |                     |                                                                                         |          |
| <b>4</b>                           | <i>p</i> -coumaroyl | H                   | H                   | —                                                                                       | 10       |
| <b>5</b>                           | H                   | H                   | <i>p</i> -coumaroyl | synthetic                                                                               | 10       |
| <b>6</b>                           | H                   | benzoyl             | H                   | <i>Oncinotis tenuiloba</i> Stapf                                                        | 12       |
| <b>Disubstituted derivatives</b>   |                     |                     |                     |                                                                                         |          |
| <b>7</b>                           | <i>p</i> -coumaroyl | <i>p</i> -coumaroyl | H                   | <i>Pterocarya fraxinifolia</i> , <i>Aphelandra tetragona</i> , <i>A. chamissoniana</i>  | 13, 14   |
| <b>8</b>                           | <i>p</i> -coumaroyl | H                   | <i>p</i> -coumaroyl | <i>A. tetragona</i> , <i>A. chamissoniana</i>                                           | 14       |
| <b>9</b>                           | feruloyl            | feruloyl            | H                   | <i>Betula verrucosa</i>                                                                 | 13       |
| <b>10</b>                          | caffeyl             | H                   | feruloyl            | <i>Corylus avellana</i>                                                                 | 13       |
| <b>Trisubstituted derivatives</b>  |                     |                     |                     |                                                                                         |          |
| <b>11</b>                          | <i>p</i> -coumaroyl | <i>p</i> -coumaroyl | <i>p</i> -coumaroyl | <i>Quercus dentata</i> , <i>Q. alba</i> , <i>A. tetragona</i> , <i>A. chamissoniana</i> | 7, 9, 14 |
| <b>12</b>                          | caffeyl             | caffeyl             | caffeyl             | <i>Q. dentata</i> , <i>Q. alba</i>                                                      | 7, 9     |
| <b>13</b>                          | feruloyl            | feruloyl            | feruloyl            | <i>Hippeastrum hortorum</i>                                                             | 15       |
| <b>14</b>                          | <i>p</i> -coumaroyl | <i>p</i> -coumaroyl | caffeyl             | <i>Q. dentata</i>                                                                       | 7, 13    |
| <b>15</b>                          | <i>p</i> -coumaroyl | caffeyl             | <i>p</i> -coumaroyl | <i>Q. alba</i>                                                                          | 9        |
| <b>16</b>                          | <i>p</i> -coumaroyl | caffeyl             | caffeyl             | <i>Q. dentata</i>                                                                       | 7        |
| <b>17</b>                          | feruloyl            | caffeyl             | caffeyl             | <i>Q. dentata</i>                                                                       | 13       |
| <b>18</b>                          | <i>p</i> -coumaroyl | caffeyl             | feruloyl            | <i>Q. dentata</i>                                                                       | 13       |



### 3. Linear putrescine derivatives

A characteristic feature of mono- and diacyl putrescine derivatives is diversity of substituents. Putrescine mono- and diamides isolated from plants are listed in Table 2.<sup>5,6,18–27</sup>

The aminoamides **20**, **21** and the diamides **22–25** contain 'standard' fragments of cinnamic, ferulic, coumaric and benzoic acids. The alkaloid **24** is known under two names, *viz.*, pyramidine (being isolated from *Aglaia pyramidata* Hance, syn. *Aglaia*

**Table 2.** Linear alkaloids derived from putrescine.

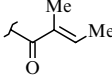
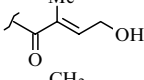
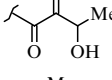
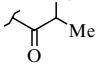
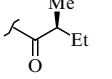
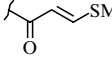
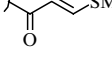
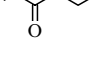
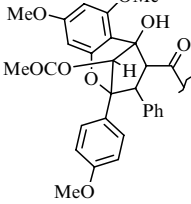
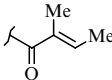
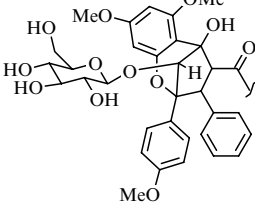
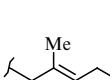
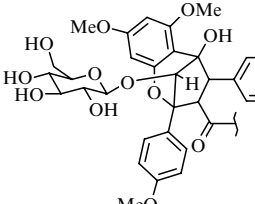
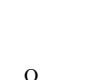
| Alkaloid | Trivial name                                 | R <sup>1</sup>                                                                      | R <sup>2</sup>                                                                      | Plant source                                                        | Ref.          |
|----------|----------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------|---------------|
| 20       | —                                            | <i>p</i> -coumaroyl                                                                 | H                                                                                   | <i>Hordeum vulgare</i>                                              | 5             |
| 21       | —                                            | feruloyl                                                                            | H                                                                                   | <i>H. vulgare</i>                                                   | 5             |
| 22       | —                                            | feruloyl                                                                            | feruloyl                                                                            | cereals, maize                                                      | 18, 19        |
| 23       | —                                            | <i>p</i> -coumaroyl                                                                 | feruloyl                                                                            | cereals, maize                                                      | 18, 19        |
| 24       | haplamidine<br>(pyramidine)                  | cinnamoyl                                                                           | benzoyl                                                                             | <i>Haplophyllum latifolium</i><br>( <i>Aglaia pyramidata</i> Hance) | 20            |
| 25       | haplamide                                    | benzoyl                                                                             | benzoyl                                                                             | <i>H. latifolium</i>                                                | 22            |
| 26       | grandiamide B                                | cinnamoyl                                                                           |    | <i>Aggl. grandis</i> Korth.                                         | 21, 23        |
| 27       | dasyclamide                                  | cinnamoyl                                                                           |    | <i>Aggl. dasyclada</i>                                              | 24            |
| 28       | grandiamide C                                | cinnamoyl                                                                           |    | <i>Aggl. grandis</i> Korth.                                         | 21, 23        |
| 29       | secopirifrine                                | cinnamoyl                                                                           |    | <i>Aggl. gracilis</i> A.C.Smith                                     | 21, 25        |
| 30       | (+)-secoodorine                              | cinnamoyl                                                                           |   | <i>Aggl. gracilis</i> A.C.Smith                                     | 21, 25        |
| 31       | aglaithioduline                              |  |  | <i>Aggl. edulis</i> A.Gray,<br><i>Aggl. leptantha</i> Miq.          | 21, 26,<br>27 |
| 32       | aglaithioduline                              |  |  | <i>Aggl. edulis</i> A.Gray,<br><i>Aggl. leptantha</i> Miq.          | 21, 26,<br>27 |
| 33       | edulimide <sup>a</sup>                       | cinnamoyl                                                                           |  | <i>Aggl. edulis</i> (synonym<br><i>Aggl. pirifera</i> Hance)        | 6             |
| 34       | grandiamide A                                |  |  | <i>Aggl. grandis</i> Korth.                                         | 21, 23        |
| 35       | bisamide of the aglaine<br>type <sup>b</sup> |  |  | <i>Aggl. dasyclada</i>                                              | 24            |
| 36       | bisamide of the<br>aglaine type <sup>b</sup> |  |  | <i>Aggl. dasyclada</i>                                              | 24            |

Table 2 (continued).

| Alkaloid | Trivial name                                 | R <sup>1</sup>                                                                                                                      | R <sup>2</sup> | Plant source           | Ref. |
|----------|----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|----------------|------------------------|------|
| 37, 38   | bisamide of the forbagline type <sup>b</sup> | <p>37: R<sup>3</sup> = R<sup>4</sup> = R<sup>5</sup> = H;<br/>38: R<sup>3</sup> = R<sup>4</sup> = Me; R<sup>5</sup> = glucosyl.</p> |                | <i>Agla. dasyclada</i> | 24   |

<sup>a</sup> Edulimide is a triamide with an additional Ac substituent at N<sup>6</sup>. <sup>b</sup> The names for structure types are indicated.

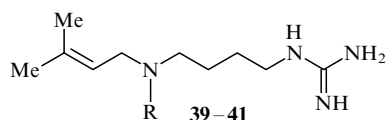
*silvestris*)<sup>6,21</sup> and haplamidine (being isolated from *Haplophyllum latifolium*).<sup>20</sup> It is noteworthy that haplamide (**25**) (putrescine dibenzoate) was isolated from the same plant.<sup>22</sup>

Putrescine diamides containing various aromatic and aliphatic acids were identified in plants of the *Aglaia* genus (Meliaceae). This genus comprises 130 dioecious arboreal and shrub species occurring predominantly in tropical and subtropical climatic zones. Depending on the structures of the substituents R<sup>1</sup> and R<sup>2</sup>, these compounds are categorised into two types. One of them includes compounds **26–30**,<sup>21,23–25</sup> which contain cinnamic acid or its derivatives as the substituent R<sup>1</sup> as well as two sulfur-containing methylthioacrylic acid diamides<sup>21,26</sup> [aglaithioduline (**31**) and aglaithioduline (**32**)] and edulimide (**33**).<sup>21,26</sup> The latter contains an acetyl group at the nitrogen atom as a third substituent and is the only representative of dihydrocinnamic acid imides in this group of compounds. Compounds containing aglaine (**34**, **35**), aglaforbesine (**36**) and forbagline (**37**, **38**) are related to the second type of diamides.<sup>21,23,24</sup> Diamides of the former type are accumulated predominantly in plant leaves, while structurally more complex amides are usually present in the bark.

The presence, in the same plant species, of different types of amides, which occurs quite often, suggests close biogenetic relationships between them. Thus the ability of dasyclamide **27** to be converted into diamides **35–38** upon cycloaddition with flavonoids suggests its role as a biosynthetic precursor of these compounds.<sup>24</sup>

#### 4. Linear guanidinoputrescine derivatives

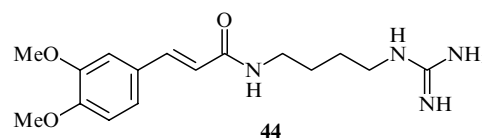
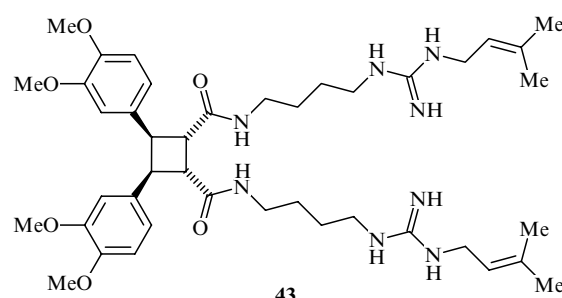
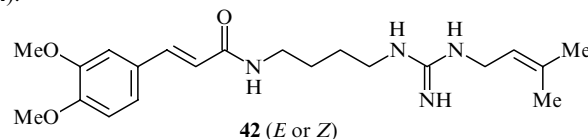
Guanidinoputrescine, which is most likely formed upon enzymatic decarboxylation of arginine, undergoes further transformations. Sphaerophysine (**39**), the first guanidinoputrescine derivative with a simple structure, was isolated from the Central Asian plants *Sphaerophysa salsula* and *Smirnovia turkestanica*.<sup>28</sup> Sphaerophysine acetate and malonate, named smirnovine (**40**) and smirnovinine (**41**),<sup>29</sup> were also isolated from *Smirnovia turkestanica*.



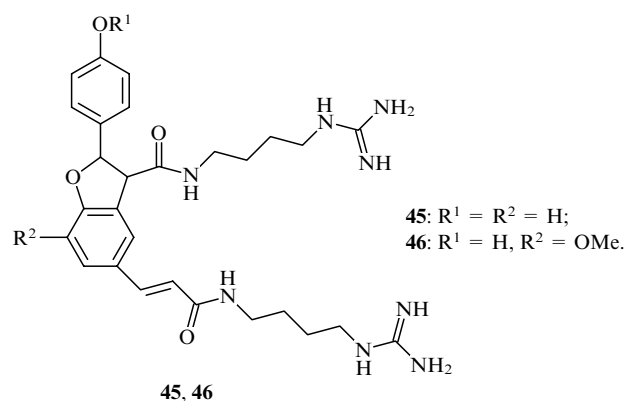
R = H (**39**), C(O)Me (**40**), C(O)CH<sub>2</sub>CO<sub>2</sub>H (**41**).

More complex guanidinoputrescine derivatives containing a 3,4-dimethoxycinnamic acid fragment were found in the Venezuelan plant *Verbesina caracasana* Fries. One of them, viz., caracasanamide (**42**), was isolated as a mixture of *E*- and *Z*-forms.<sup>30,31</sup> The second compound, viz., caracasanediamide (**43**), represents a cyclobutane-type dimer of caracasanamide **42**<sup>31,32</sup> and yet

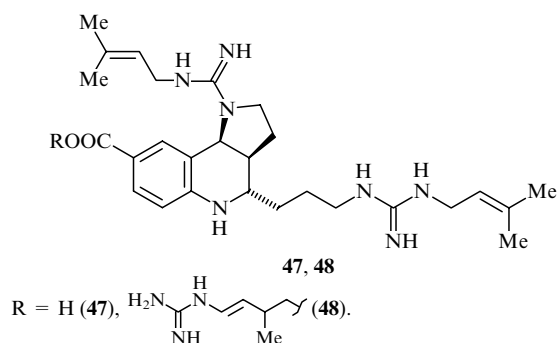
another is 1-(3,4-dimethoxycinnamoylamino)-4-guanidinobutane (**44**).<sup>33</sup>



The alkaloids (+)-hordatines A (**45**) and B (**46**), which contain a benzofuran core with two guanidinoputrescine residues as substituents, were isolated from barley (*Hordeum vulgare* L.) sprouts.<sup>34</sup>



Martinellinic acid (**47**) and its ester, martinelline (**48**), isolated from the roots of the tropical liana *Martinella iquitensis* have even more complex structures.<sup>35</sup> They contain a pyrroloquinoline backbone and several guanidino groups including a guanidinoputrescine group.

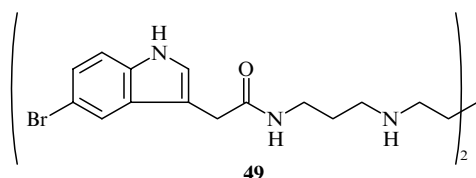


Of special note is the fact that no natural compounds with such a backbone have been reported hitherto.

### 5. Biological activities of linear alkaloids

Linear alkaloids manifest diverse kinds of biological activities. Thus the hypotensive activity kukoamine A (**2**) gave an impetus to the synthesis and assay of all of its regioisomers as potential hypotensive drugs.<sup>36</sup> Besides, this compound causes mixed-type inhibition of trypanothione reductase ( $K_i = 1.8 \mu\text{mol litre}^{-1}$  and  $K_{ii} = 13 \mu\text{mol litre}^{-1}$ ), a unique specific enzyme of protozoan parasites (trypanosomes, *Leishmania*). It is of note that kukoamine A has no effect on the human enzyme endowed with a similar protective function.

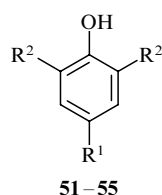
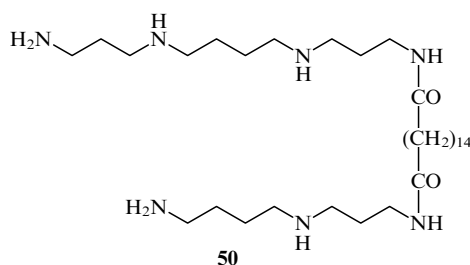
Synthetic mono- and diacyl, analogues kukoamine A based on spermine and spermidine also inhibit trypanothione reductase, however, with much lesser efficiency ( $K_i = 11-607 \mu\text{mol litre}^{-1}$ ).<sup>37</sup> Studies of inhibiting activities of a panel of kukoamine A-based inhibitors prepared by solid-phase combinatorial chemical synthesis have shown that the highest inhibiting activity is manifested by bis(5-bromoindol-3-ylacetyl)spermine (compound **49**) ( $K_i = 0.076 \mu\text{mol litre}^{-1}$ ).<sup>38</sup>



The monosubstituted alkaloids 1-(*N*-*p*-coumaroyl)spermine (**1**) and 1-(*N*-*p*-coumaroyl)spermidine (**4**) cause reversible dose-dependent inhibition of neuromuscular synapses in insects ( $IC_{50} = 70$  and  $60-200 \mu\text{mol litre}^{-1}$ , respectively), which opens a way to a better understanding of their role as a means of chemical self-protection of plants against pests. Structural analogues of these alkaloids, *viz.*, polyamines isolated from the toxins of *Nephila* spiders, produce irreversible blocking effects ( $IC_{50} = 0.1 \mu\text{mol litre}^{-1}$ ).<sup>10</sup>

The triamides **11**, **12** and **15** manifest fungicidal activities: they inhibit mycelial growth in the pathogenic fungus *Pyrenophora avenae* affecting oats leaves and protect barley seedlings against mildew.<sup>9</sup>

Among synthetic derivatives of tenuilobine **19**, isotenuilobine (**50**)<sup>39</sup> and the aromatic derivatives **51-55** are worthy of note.<sup>39</sup> The structural similarity of tenuilobine **19** to spider and wasp toxins widely known as potent inhibitors of CNS glutamate



**51:**  $\text{R}^1 = \text{Bu}^t$ ,  $\text{R}^2 = (\text{CH}_2)_2\text{C}(\text{O})\text{N}[(\text{CH}_2)_3\text{NH}_2](\text{CH}_2)_4\text{NH}_2$ ;

**52:**  $\text{R}^1 = \text{Bu}^t$ ,  $\text{R}^2 = (\text{CH}_2)_2\text{C}(\text{O})\text{N}[(\text{CH}_2)_3\text{NH}_2](\text{CH}_2)_4\text{NH}(\text{CH}_2)_3\text{NH}_2$ ;

**53:**  $\text{R}^1 = \text{Bu}^t$ ,  $\text{R}^2 = (\text{CH}_2)_2\text{C}(\text{O})\text{NH}(\text{CH}_2)_3\text{NH}(\text{CH}_2)_4\text{NH}_2$ ;

**54:**  $\text{R}^1 = \text{R}^2 = (\text{CH}_2)_2\text{C}(\text{O})\text{N}[(\text{CH}_2)_3\text{NH}_2](\text{CH}_2)_4\text{NH}_2$ ;

**55:**  $\text{R}^1 = \text{R}^2 = (\text{CH}_2)_2\text{C}(\text{O})\text{N}[(\text{CH}_2)_3\text{NH}_2](\text{CH}_2)_4\text{NH}(\text{CH}_2)_3\text{NH}_2$ .

receptors provided a rationale for their biological testing as candidate inhibitors of ionotropic glutamate receptors. These studies are currently under way.<sup>40</sup>

Presumably symmetrical and non-symmetrical tenuilobine derivatives of hexadecanedioic acid and spermidine, spermine and their shorter-chain analogues inhibit polyamine transport. At present, methods for the synthesis of these compounds are developed and investigations into their ability to control polyamine metabolism are underway.<sup>41</sup>

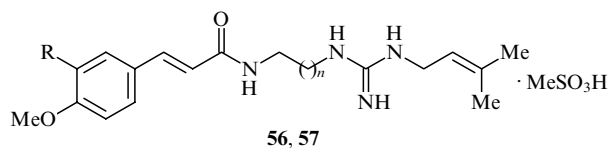
Some disubstituted putrescines also possess biological activity. Thus compounds **22** and **23** cause reversible inhibition of  $\alpha$ -glucosidase,<sup>‡</sup> which is involved in carbohydrate catabolism. Studies on structure-activity relationships have shown that inhibiting activities of these compounds are determined by the presence of a hydroxy group in the aromatic ring.<sup>25</sup>

Non-cytotoxic concentrations of the sulfur-containing bis-amides aglaithioduline (**31**) and aglaithioduline (**32**) have little effect on the herpes simplex virus (types 1 and 2);<sup>26</sup> pyrimidine (**24**) manifests antileukemic activity *in vivo*.<sup>42</sup>

The identification of sphaerophysine (**39**) and the discovery of its hypotensive activity were of great consequence for the therapy of a hypertonic disease, being the first demonstration of high potential of guanidinoputrescine derivatives as efficient hypotensive drugs. Sphaerophysine benzoate<sup>8</sup> is successfully used in the therapy of hypertony and as a labour-stimulating agent in obstetrical-gynecological practice.<sup>43</sup> Smirnovine (**40**) also possesses hypotensive activity.<sup>45</sup>

Worthy of notice are water-soluble guanidinoputrescine derivatives caracasamide (**42**, *Z*-form) and caracasenediamide (**43**) endowed with hypotensive properties. Caracasamide (**42**) can be used in the therapy of moderate arterial hypertension; its therapeutic effect is commensurate with those of reserpine and papaverine. Caracasenediamide (**43**) exceeds compound **42** in hypotensive and antihypertensive activities and has no adverse side effects (*e.g.*, reflexive tachycardia or low cardiac inotropism) manifested by the majority of antihypertensive and vasodilating agents.<sup>31</sup>

Candidates for hypotensive drugs were also found among synthetic derivatives of compound **44** containing a modified diaminoalkane chain or a modified acyl moiety.<sup>33</sup> The derivative **56** containing an (*E*)-*p*-methoxycinnamic acid fragment produces a stronger hypotensive effect than compound **44**. The number of methylene groups in the diaminoalkyl chains of compounds of the type **57** does not influence their therapeutic activity. In pharma-



**56:**  $\text{R} = \text{H}$ ,  $n = 3$ ; **57:**  $\text{R} = \text{OMe}$ ,  $n = 1-5$ .

‡ In the past decade,  $\alpha$ -glucosidase inhibitors have been widely used as peroral hypoglycemic drugs in the therapy of diabetes, but a search for novel, safer inhibitors remains a topical task.

§ At present, sphaerophysine benzoate has no wide application.<sup>44</sup>

cological doses, all these compounds produced hypotensive and slightly positive inotropic effects devoid of substantial chronotropic and respiratory effects.

Hordatines A (**45**) and B (**46**) possess fungicide activities.<sup>34</sup>

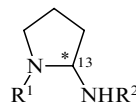
There is evidence that the sap of two tropical liana species (of the genus *Martinea* Bignoniaceae), viz., *M. iquitosensis* A. Sampayo and *M. obovata* (HBK) Bureau et K. Schum, is used by representatives of thirteen different ethnolinguistic groups in nine countries of South America as a folk remedy against various eye diseases. Some native tribes residing in the Amazonian Region of Peru extract this sap from the root bark of *M. obovata*. One or two drops of such potion immediately eliminate inflammation in the eye infected by a parasitic microorganism (or a group of microorganisms, including Gram-positive and Gram-negative bacteria). Studies have shown that this effect is provided by martinellinic acid (**47**) and martinelline (**48**), the only natural non-peptide antagonists of B<sub>1</sub>- and B<sub>2</sub>-receptors of bradykinin (BK). It is noteworthy that martinelline (**48**) exceeds martinellinic acid (**47**) in activity. Thus, the sap from the root bark of *M. obovata* possess antiinflammatory and analgesic effects. Martinelline (**48**) is an antagonist of histaminergic,  $\alpha$ -adrenergic and muscarinic receptors, manifests moderate antibiotic activity and has little or no cytotoxic or lytic effect with respect to red blood cells. Such a happy combination of antiinflammatory, analgesic and antimicrobial actions makes this compound a valuable tool in the treatment of conjunctivitis.<sup>35</sup>

### III. Cyclic polymethyleneamine alkaloids

Yet another important class of polyamine alkaloids comprises cyclic compounds with polyamine backbones. These compounds can be divided into two main subtypes, viz., cycloputrescine derivatives (2-aminopyrrolidines) and macrocyclic (8–22-membered) lactams containing biogenic bases (mostly spermine and spermidine). Putrescine, spermidine and spermine are present in the ring systems either as a whole molecule or as a part thereof.

### 1. Cycloputrescine derivatives

Cycloputrescine derivatives are represented by pyrrolidine bisamide alkaloids, which rarely occur in nature and contain a 2-aminopyrrolidine group. By present, pyrrolidine bisamides have been identified only in plants of the *Aglaia* genus (Meliaceae). Some aminopyrrolidine bisamides isolated from these plants are listed in Table 3.



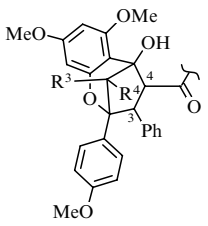
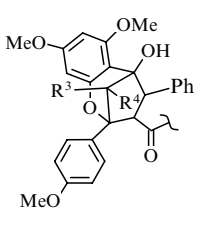
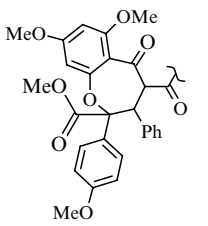
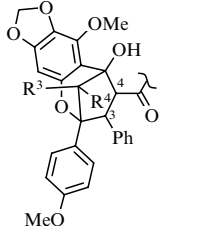
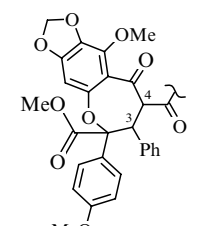
Depending on the structures of their substituents R<sup>1</sup> and R<sup>2</sup>, all aminopyrrolidine bisamides are divided into two types. Compounds **58**–**65** have simple structures and contain various carboxylic acid fragments as substituents R<sup>1</sup> and R<sup>2</sup>. In structurally more complex bisamides, the role of the substituent R<sup>2</sup> is played by carboxylic acids, while that of substituent R<sup>1</sup> is played by structural fragments, of the aglaine (**66**–**69**), aglaforbesine (**70**, **71**), forbagline (**72**, **73**), tapsakine (**74**) or tapoxepin types (**75**). Such complex bisamides are related to flavaglines and represent typical secondary metabolites of 30 investigated species of the genus *Aglaia*.<sup>6</sup> Presumably, the flavagline molecule consists of a flavonoid and a fragment of cinnamic acid. Flavaglines are represented by three structural types, viz., cyclopenta[*b*]benzofurans (rocaglamides,<sup>49</sup> aglaroxin A, pannelline), cyclopenta[*bc*]benzopyrans (aglaines, aglaforbesines, tapsakins) and benzo[*b*]oxepins (forbaglines, tapoxepins). The latter two types are related to polyamine derivatives. Possible biogenetic relationships between different types of flavaglines and putative mechanisms of their formation have been discussed.<sup>48</sup>

As a rule, the same plant species produces different types of bisamides. Different compositions of linear and cyclic bisamides in plants of the same species is interpreted as a 'survival strategy' preventing the adaptation of herbivores and microorganisms to the common chemical profile of the plant.<sup>27</sup> The presence of different forms of bisamides in the same plant species suggests close biogenetic relationships between them. Cycloaddition of the pyrrolidine bisamide odorine (**58**) to a flavonoid affords aglaines

**Table 3.** Aminopyrrolidine bisamides from plants of the genus *Aglaia* (Meliaceae).

| Alkaloid  | Name           | R <sup>1</sup> | R <sup>2</sup>          | Plant source                                                                                                                                                                                | Ref.  |
|-----------|----------------|----------------|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| <b>58</b> | odorine        |                | C(O)Bu <sup>s</sup>     | <i>Aglaia odorata</i> Lour, <i>Aglaia elaeagnoidea</i> , <i>Aglaia argentea</i> Blume, <i>Aglaia forbesii</i> King, <i>Aglaia elliptica</i> Blume (synonym <i>Aglaia harmsiana</i> Perkins) | 6     |
| <b>59</b> | odorine        |                | C(O)C(Me)(Et)OH         | <i>Aglaia odorata</i> Lour, <i>Aglaia elaeagnoidea</i>                                                                                                                                      | 6     |
| <b>60</b> | dehydroodorine |                |                         | <i>Aglaia tomentosa</i> , <i>Aglaia formosana</i>                                                                                                                                           | 6, 46 |
| <b>61</b> | piriferine     |                | C(O)CMe <sub>2</sub> OH | <i>Aglaia edulis</i> (synonym <i>Aglaia pirifera</i> Hance), <i>Aglaia elaeagnoidea</i>                                                                                                     | 6     |
| <b>62</b> | piriferinol    |                | C(O)Pr <sup>i</sup>     | <i>Aglaia elaeagnoidea</i>                                                                                                                                                                  | 6     |
| <b>63</b> | agleptin       |                | C(O)Bn                  | <i>Aglaia leptantha</i> Miq.                                                                                                                                                                | 27    |
| <b>64</b> | isoagleptin    | BnC(O)         |                         | <i>Aglaia leptantha</i> Miq.                                                                                                                                                                | 27    |
| <b>65</b> | leptantine     |                |                         | <i>Aglaia leptantha</i> Miq.                                                                                                                                                                | 27    |

Table 3 (continued).

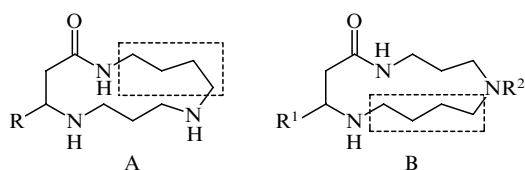
| Alkaloid       | Name                     | R <sup>1</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | R <sup>2</sup>                                                                      | Plant source               | Ref. |
|----------------|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------|------|
| 66<br>67<br>68 | aglaïnes<br>A<br>B<br>C  |  <p>A: R<sup>3</sup> = OAc, R<sup>4</sup> = H; H-3β, H-4α, 13S<br/> B: R<sup>3</sup> = H, R<sup>4</sup> = OH; H-3β, H-4α, 13S<br/> C: R<sup>3</sup> = H, R<sup>4</sup> = OH; H-3α, H-4β, 13S</p>                                                                                                                                                                                                                                                                                                              | C(O)Bu <sup>s</sup>                                                                 | <i>Agl. argentea</i> Blume | 47   |
| 69             | deacetylaglaine A        | R <sup>3</sup> = OH, R <sup>4</sup> = H; H-3β, H-4α, 13S                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                     | <i>Agl. gracilis</i>       | 25   |
| 70<br>71       | aglaforbesines<br>A<br>B |  <p>A: R<sup>3</sup> = OH, R<sup>4</sup> = H; 13R;<br/> B: R<sup>3</sup> = H, R<sup>4</sup> = OH; 13R</p>                                                                                                                                                                                                                                                                                                                                                                                                     | C(O)Bu <sup>s</sup>                                                                 | <i>Agl. forbesii</i>       | 47   |
| 72<br>73       | forbaglines<br>A<br>B    |  <p>13R (A), 13S (B)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | C(O)Bu <sup>s</sup>                                                                 | <i>Agl. forbesii</i>       | 47   |
| 74             | tapsakines               |  <p>R<sup>3</sup> = H, R<sup>4</sup> = OH, R<sup>5</sup> = Me; H-3β, H-4α, 13S (A); 13R (B);<br/> R<sup>3</sup> = OH, R<sup>4</sup> = H, R<sup>5</sup> = Me; H-3β, H-4α, 13S;<br/> R<sup>3</sup> = H, R<sup>4</sup> = OH, R<sup>5</sup> = Et; H-3α, H-4β, 13S;<br/> R<sup>3</sup> = H, R<sup>4</sup> = OCOMe, R<sup>5</sup> = Me; H-3α, H-4β, 13S;<br/> R<sup>3</sup>-R<sup>4</sup> = O, R<sup>5</sup> = Me; H-3α, H-4β, 13S;<br/> R<sup>3</sup>-R<sup>4</sup> = O, R<sup>5</sup> = Me; H-3β, H-4α, 13S</p> |  | <i>Agl. edulis</i>         | 48   |
| 75             | tapoxepines              |  <p>R<sup>3</sup> = Me; H-3α, H-4β; 13S (A); 13R (B);<br/> R<sup>3</sup> = Et; H-3α, H-4β, 13S;<br/> R<sup>3</sup> = Me; H-3β, H-4α; 13S (A); 13R (B)</p>                                                                                                                                                                                                                                                                                                                                                   |  | <i>Agl. edulis</i>         | 48   |

A, B and C (66–68) as well as agloforbesines A and B (70 and 71).<sup>47</sup> Simultaneous presence of pyrrolidine bisamides and the corresponding linear analogues [e.g., odorine (58) and secoodorine (30),<sup>25</sup> pirifirine (61) and secopirifirine (29),<sup>25</sup> agleptine (63), isoagleptine (64), leptantine (65) and aglaithioduline (31) or aglaithioduline (32)],<sup>27</sup> in the same plant species prompts a conclusion that all alkaloids containing a 2-aminopyrrolidine fragment have a biogenetic linear putrescine bisamide precursor;<sup>25</sup> its cyclisation is effected by an enzymatic system of its own.<sup>21</sup>

## 2. Cyclic spermidine alkaloids

### a. 13-Membered cyclic spermidine alkaloids

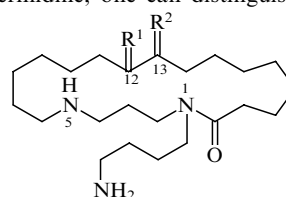
Palustrine (76), the first alkaloid in this series, was isolated from marsh horsetail *Equisetum palustre* L. in 1936.<sup>50</sup> The asymmetry of spermidine structure enables the formation of two types of cyclic alkaloids, viz., type A (compounds 76–84) and type B (compounds 85–98).<sup>51</sup>



Both types of alkaloids occur in plants (Table 4). Mayfoline (98) belonging to the B-type alkaloid contains a hydroxy substituent at the secondary nitrogen atom of the spermidine chain; this feature has been observed for the first time in this type of a compound. Plants containing this kind of an alkaloid may contain its analogue the N-hydroxy group in which is replaced by the N-acetyl group.<sup>8</sup>

### b. Spermidine alkaloids isolated from various species of plants of the genera *Oncinotis*, *Lunaria* and *Codonocarpus*

Polyamine alkaloids present in plants of the genus *Oncinotis* (Apocynaceae) are classified into two groups, viz., linear and macrocyclic. All macrocyclic keto lactams contain a 16-membered hydrocarbon chain linked to the neighbouring nitrogen atoms of spermidine. Depending on the mode of attachment of the chain to spermidine, one can distinguish monocyclic inandenines (com-



Inandenines, inandeninols

$R^1 = \text{O or OH, H; } R^2 = \text{H}_2;$   
 $R^1 = \text{H}_2; R^2 = \text{O or OH, H.}$

**Table 4.** 13-Membered spermidine macrocyclic lactam alkaloids.

| Alkaloid | Name                                       | Structure | Plant source                                 | Ref. |
|----------|--------------------------------------------|-----------|----------------------------------------------|------|
| Type A   |                                            |           |                                              |      |
| 76       | palustrine                                 |           | <i>Equisetum palustre</i> L.                 | 50   |
| 77       | dihydropalustrine                          |           | <i>E. palustre</i> L.                        | 52   |
| 78       | cannabisativine                            |           | <i>Cannabis sativa</i> L.<br>(roots, leaves) | 53   |
| 79       | anhydrocannabisativine                     |           | <i>C. sativa</i> L. (roots, leaves)          | 53   |
| 80       | (–)-(4 <i>R</i> )-dihydroisomyricoidine    |           | synthetic                                    | 51   |
| 81       | periphylline<br>( <i>trans</i> -cinnamoyl) |           | <i>Periptygia marginata</i> (Baill.) Loes.   | 54   |



Table 4 (continued).

| Alkaloid | Name                                                       | Structure | Plant source                                                                                                                                                                                                                                        | Ref.      |
|----------|------------------------------------------------------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Type A   |                                                            |           |                                                                                                                                                                                                                                                     |           |
| 82       | isoperiphylline<br>( <i>cis</i> -cinnamoyl)                |           | <i>P. marginata</i> (Baill.) Loes.                                                                                                                                                                                                                  | 54        |
| 83       | (+)-(S)-dihydro-periphylline<br>( <i>trans</i> -cinnamoyl) |           | <i>P. marginata</i> (Baill.) Loes.                                                                                                                                                                                                                  | 54        |
| 84       | neoperiphylline<br>( <i>trans</i> -cinnamoyl)              |           | <i>P. marginata</i> (Baill.) Loes.                                                                                                                                                                                                                  | 54        |
| Type B   |                                                            |           |                                                                                                                                                                                                                                                     |           |
| 85       | (+)-(2S)-myricoidine                                       |           | <i>Clerodendrum myricoides</i> Vatke<br>(Verbenaceae)                                                                                                                                                                                               | 55        |
| 86       | (+)-(2S)-dihydro-myricoidine                               |           | <i>C. myricoides</i> Vatke,<br><i>Maytenus loeseneri</i> Urb. (Celastraceae)                                                                                                                                                                        | 51,<br>55 |
| 87       | (+)-(2R)-loesenerine                                       |           | <i>M. loeseneri</i> Urb.                                                                                                                                                                                                                            | 55        |
| 88       | (+)-(2R)-17,18-didehydroloesenerine                        |           | <i>M. loeseneri</i> Urb.                                                                                                                                                                                                                            | 55        |
| 89       | (+)-(2R)-16,17-didehydroloesenerin-18-ol                   |           | <i>M. loeseneri</i> Urb.                                                                                                                                                                                                                            | 55        |
| 90       | celacinnine<br>( <i>trans</i> -cinnamoyl)                  |           | <i>M. arbutifolia</i> ( <i>M. serrata</i> ) (Hochst., ex A.Rich)<br><i>R. Wilczek</i> (Celastraceae) (branches); <i>Tripterygium wilfordii</i> Hook (Celastraceae) (roots);<br><i>M. heterophylla</i> (bark), <i>Pleurostulia africana</i> (leaves) | 8, 56     |
| 91       | celalocinnine<br>( <i>cis</i> -cinnamoyl)                  |           | <i>M. arbutifolia</i> (Hochst., ex A.Rich )<br><i>R. Wilczek</i> (Celastraceae) (branches)                                                                                                                                                          | 56        |
| 92       | celafurine                                                 |           | <i>T. wilfordii</i> Hook<br>(Celastraceae) (roots)                                                                                                                                                                                                  | 56        |
| 93       | celabensine                                                |           | <i>M. mossambicensis</i> (Klotzsch) Blakelock<br>var. <i>mossambicensis</i> ; <i>T. wilfordii</i> Hook<br>(Celastraceae) (roots)                                                                                                                    | 56,<br>57 |

**Table 4** (continued).

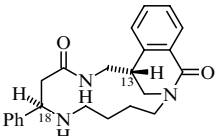
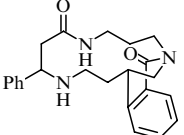
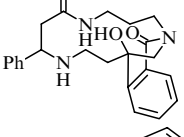
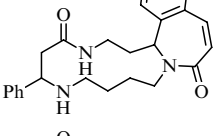
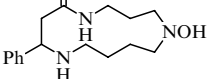
| Alkaloid | Name                                              | Structure                                                                          | Plant source                                                                | Ref. |
|----------|---------------------------------------------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|------|
| Type B   |                                                   |                                                                                    |                                                                             |      |
| 94       | (+)-(18 <i>S</i> ,13 <i>R</i> )-cyclo-celabensine |   | <i>M. mossambicensis</i> (Klotzsch)<br>Blakelock var. <i>mossambicensis</i> | 57   |
| 95       | (+)-isocyclo-celabensine                          |   | <i>M. mossambicensis</i> (Klotzsch)<br>Blakelock var. <i>mossambicensis</i> | 57   |
| 96       | (+)-hydroxyiso-cyclocelabensine                   |   | <i>M. mossambicensis</i> (Klotzsch)<br>Blakelock var. <i>mossambicensis</i> | 57   |
| 97       | pleurostiline                                     |   | <i>P. africana</i> (leaves)                                                 | 8    |
| 98       | mayfoline                                         |  | <i>M. buxifolia</i> (superterrestrial parts)                                | 8    |

**Table 5.** Spermidine alkaloids from plants of the genus *Oncinotis* (Apocynaceae).

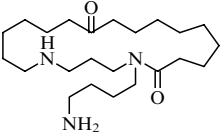
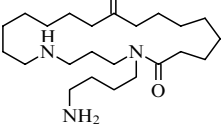
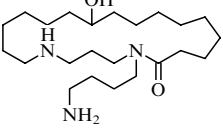
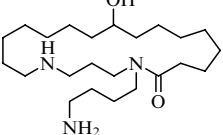
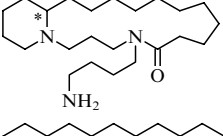
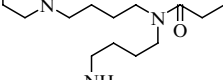
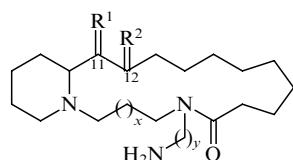
| Alkaloid | Name              | Structure                                                                           | Plant source                                                                                       | Ref.     |
|----------|-------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|----------|
| 99       | inandenin-12-one  |  | <i>Oncinotis tenuiloba</i> Stapf<br><i>O. inandensis</i> Wood et Evans,<br><i>O. nitida</i> Benth. | 58<br>59 |
| 100      | inandenin-13-one  |  | <i>O. inandensis</i> Wood et Evans,<br><i>O. nitida</i> Benth.<br><i>O. tenuiloba</i> Stapf        | 59<br>58 |
| 101      | inandenin-12-ol   |  | <i>O. tenuiloba</i> Stapf<br><i>O. nigra</i> Pich.                                                 | 58<br>59 |
| 102      | inandenin-13-ol   |  | <i>O. tenuiloba</i> Stapf<br><i>O. nigra</i> Pich.                                                 | 58<br>59 |
| 103      | (-)-oncinotine    |  | <i>O. nitida</i> Benth.                                                                            | 59       |
| 104      | (-)-neooncinotine |  | <i>O. nitida</i> Benth.                                                                            | 59       |

Table 5 (continued).

| Alkaloid | Name              | Structure | Plant source              | Ref. |
|----------|-------------------|-----------|---------------------------|------|
| 105      | (-)-isooncinotine |           | <i>O. nitida</i> Benth.   | 59   |
| 106      | oncinotin-11-one  |           | <i>O. tenuiloba</i> Stapf | 59   |
| 107      | oncinotin-12-one  |           | <i>O. tenuiloba</i> Stapf | 59   |

pounds **99–102**, Table 5),<sup>58,59</sup> bicyclic oncinotines (compounds **103–107**, Table 5)<sup>59</sup> and linear tenuilobine (**19**).

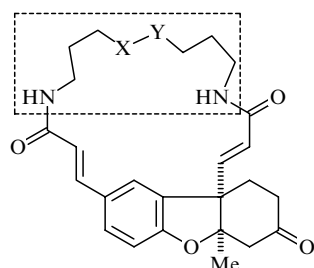


Oncinotines

$R^1 = O, R^2 = H_2; R^1 = H_2, R^2 = O;$   
 $x = 1, y = 4; x = 2, y = 3.$

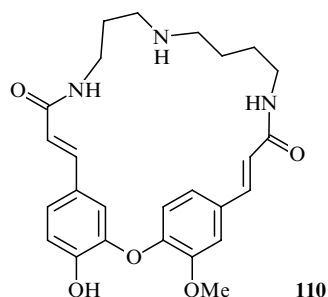
The specific content of an alkaloid in a plant depends on the species and the organ from which it was isolated. Thus the stem bark of the Nigerian species *O. nitida* Benth. predominantly contains oncinotine (**103**) and its isomers, viz., neooncinotine (**104**) and isooncinotine (**105**). Inandenines were found in this plant in only minor amounts and were isolated as a non-separable mixture of isomers. In contrast, leaves of *O. inandensis* Wood et Evans and *O. tenuiloba* are rich in inandenines. The concentration of inandeninols, i.e., the secondary alcohols formed upon reduction of the keto groups of inandenines, in these plant species is very small. However, in the leaves of *O. nigra* Pich. these compounds are present as major components.<sup>58,59</sup>

Lunarine (**108**) isolated from *Lunaria annua*<sup>60</sup> differs from lunaridine (**109**) which is present in *L. biennis* and *L. rediviva*<sup>8</sup>



108, 109

**108:** X = NH, Y = CH<sub>2</sub>;  
**109:** X = CH<sub>2</sub>, Y = NH.



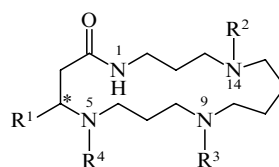
110

simultaneously with lunarine, in the mode of attachment of spermidine. Codonocarpine (**110**) was isolated from the bark of *Codonocarpus attenuatus* (Phytolaccaceae).<sup>8</sup>

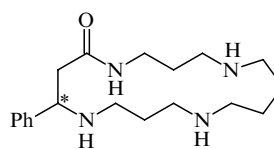
### 3. Cyclic spermine alkaloids

#### a. 17-Membered cyclic spermine alkaloids

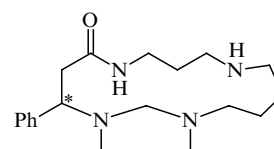
Compounds containing spermine and carboxylic acids constitute a large group of cyclic polyamine alkaloids. 17-Membered cyclic spermine alkaloids form a special group. Depending on the nature of the carboxylic acid and the substituents at the nitrogen atoms of the 17-membered macrocycle, these alkaloids are divided into two groups, viz., alkaloids from *Verbascum* (Scrophulariaceae), *Incarvillea sinensis*, *Clerodendrum buchneri* (Verbenaceae) (group A, compounds **111–128**, Table 6)<sup>61–67</sup> and budmunchiamines from plants of the *Albizia* genus (group B, compounds **129–148**, Table 7).<sup>68–72</sup>



The 17-membered rings of the group A alkaloids contain fragments of dihydrocinnamic acid or its 4-methoxy derivative and spermine ( $R^3 = R^4 = H$ , compounds **111–121**) or its cyclic analogue ( $R^3 - R^4 = -CH_2-$ , compounds **122–128**). The structures of (-)-protoverbine (**111**) and (+)-protomethine (**122**) are typical basic structures.



111

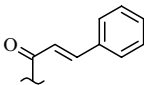
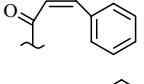
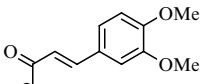
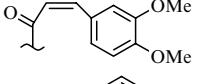
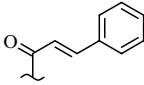
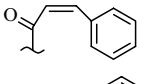
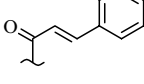
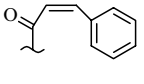
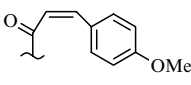
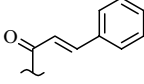
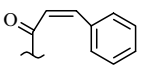
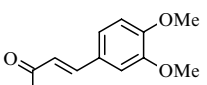
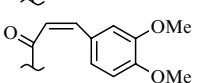
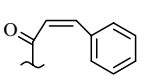
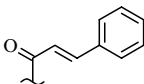


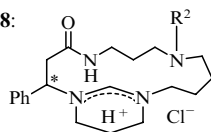
122

The alkaloids protoverbine **111** and (+)-protomethine (**122**) are thought to be putative biogenetic precursors of a large class of spermine alkaloids. Thus, compound **111** is a hypothetical precursor of verbacine (**112**) and verballoicine (**113**), while compound **122** is a precursor of (+)-verbamethine (**123**) and (+)-isoverbamethine (**124**).<sup>61</sup> Compounds **112** and **113** are often considered as biogenetic precursors of their *N*-acetylated derivatives verbasce-nine (**118**) and verballosceneine (**119**). Simultaneous isolation of all the four compounds provides supporting evidence in favour of this hypothesis.<sup>66</sup>

Fragments of cinnamic, 4-methoxycinnamic, 3,4-dimethoxy-cinnamic (*E*- or *Z*-forms), acetic and formic acids are typical

**Table 6.** Spermidine alkaloids from plants of the genus *Verbascum* (Scrophulariaceae), *Incarvillea sinensis* and *Clerodendrum buchneri* (Verbenaceae).

| Alkaloid | Name                                                         | R <sup>1</sup>                     | R <sup>2</sup>                                                                      | R <sup>3</sup>                  | R <sup>4</sup> | Plant source                                                                              | Ref.   |
|----------|--------------------------------------------------------------|------------------------------------|-------------------------------------------------------------------------------------|---------------------------------|----------------|-------------------------------------------------------------------------------------------|--------|
| 111      | (–)-protoverbine                                             | Ph                                 | H                                                                                   | H                               | H              | <i>Verbascum pseudonobile</i> Stoj. et Stef.                                              | 61     |
| 112      | (–)-verbacine ( <i>E</i> )                                   | Ph                                 |    | H                               | H              | <i>V. pseudonobile</i> Stoj. et Stef.                                                     | 61, 62 |
| 113      | (–)-verballocine ( <i>Z</i> )                                | Ph                                 |    | H                               | H              | <i>Incarvillea sinensis</i>                                                               | 63     |
| 114      | (–)-( <i>S</i> )-verbasitrine ( <i>E</i> )                   | Ph                                 |    | H                               | H              | <i>V. pseudonobile</i> Stoj. et Stef.                                                     | 64     |
| 115      | (–)-( <i>S</i> )-isoverbasitrine ( <i>Z</i> )                | Ph                                 |    | H                               | H              | <i>V. pseudonobile</i> Stoj. et Stef.                                                     | 64     |
| 116      | verbamedine ( <i>E</i> )                                     | Ph                                 |    | CHO                             | H              | <i>V. pseudonobile</i> Stoj. et Stef.                                                     | 65     |
| 117      | isoverbamedine ( <i>Z</i> )                                  | Ph                                 |    | CHO                             | H              | <i>V. pseudonobile</i> Stoj. et Stef.                                                     | 65     |
| 118      | verbascenine ( <i>E</i> )                                    | Ph                                 |    | Ac                              | H              | <i>V. phoeniceum</i> L.,<br><i>V. nigrum</i> L.,<br><i>V. pseudonobile</i> Stoj. et Stef. | 62     |
| 119      | verballoscenine ( <i>Z</i> )                                 | Ph                                 |   | Ac                              | H              | <i>V. phoeniceum</i> L.                                                                   | 66     |
| 120      | buchnerine                                                   | 4-MeOC <sub>6</sub> H <sub>4</sub> | H                                                                                   | H                               | H              | <i>Clerodendrum buchneri</i>                                                              | 67     |
| 121      | <i>N</i> -( <i>Z</i> )- <i>p</i> -methoxycinnamoylbuchnerine | 4-MeOC <sub>6</sub> H <sub>4</sub> |  | H                               | H              | <i>C. buchneri</i>                                                                        | 67     |
| 122      | (+)-protomethine                                             | Ph                                 | H                                                                                   | –CH <sub>2</sub> –              |                | <i>V. pseudonobile</i> Stoj. et Stef.                                                     | 61     |
| 123      | (+)-verbamethine ( <i>E</i> )                                | Ph                                 |  | –CH <sub>2</sub> –              |                | <i>V. pseudonobile</i> Stoj. et Stef.                                                     | 61     |
| 124      | (+)-isoverbamethine (incasine C) ( <i>Z</i> )                | Ph                                 |  | –CH <sub>2</sub> –              |                | <i>V. pseudonobile</i> Stoj. et Stef.,<br><i>I. sinensis</i>                              | 65     |
| 125      | (+)-( <i>S</i> )-verbametrine ( <i>E</i> )                   | Ph                                 |  | –CH <sub>2</sub> –              |                | <i>V. pseudonobile</i> Stoj. et Stef.                                                     | 64     |
| 126      | (+)-( <i>S</i> )-isoverbametrine ( <i>Z</i> )                | Ph                                 |  | –CH <sub>2</sub> –              |                | <i>V. pseudonobile</i> Stoj. et Stef.                                                     | 64     |
| 127      | incasine B' (or verdoline) ( <i>Z</i> ) (see <sup>a</sup> )  | Ph                                 |  | –CH <sub>3</sub> <sup>+</sup> – |                | <i>V. pseudonobile</i> Stoj. et Stef.                                                     | 65     |
| 128      | incasine B (or isoverdoline) ( <i>E</i> )                    | Ph                                 |  | –CH <sub>3</sub> <sup>+</sup> – |                | <i>I. sinensis</i>                                                                        | 63     |

<sup>a</sup> The structures of compounds **127** and **128**:

substituents at the nitrogen atoms in the macrocycles of the type A alkaloids. Alkaloids containing cinnamic and 3,4-dimethoxycinnamic acid fragments as substituents R<sup>2</sup> usually form *E/Z*-

isomeric pairs, e.g., **112/113**, **114/115**, **116/117**, **118/119**, **123/124**, **125/126**, **127/128** (see Table 6). The (*E*)-verbamedine/(*Z*)-isoverbamedine and (*E*)-verbacine/(*Z*)-verballoccine alkaloid pairs are

**Table 7.** Spermine alkaloids from plants of the genus *Albizia*.

| Alkaloid | Name                                     | R <sup>1</sup>                                                           | R <sup>2</sup> | R <sup>3</sup> | R <sup>4</sup> | Plant source                                    | Ref.      |
|----------|------------------------------------------|--------------------------------------------------------------------------|----------------|----------------|----------------|-------------------------------------------------|-----------|
| 129      | budmunchiamine A                         | C <sub>11</sub> H <sub>23</sub> -n                                       | Me             | Me             | Me             | <i>Albizia amara</i> ,<br><i>Alb. gummifera</i> | 68,<br>69 |
| 130      | budmunchiamine B                         | C <sub>9</sub> H <sub>19</sub> -n                                        | Me             | Me             | Me             | <i>Alb. amara</i>                               | 68        |
| 131      | budmunchiamine C                         | C <sub>13</sub> H <sub>27</sub> -n                                       | Me             | Me             | Me             | <i>Alb. amara</i>                               | 68        |
| 132      | 6,′ξ-hydroxybudmunchiamine C             | n-C <sub>5</sub> H <sub>10</sub> CH(OH)C <sub>7</sub> H <sub>15</sub> -n | Me             | Me             | Me             | <i>Alb. schimperana</i>                         | 70        |
| 133      | budmunchiamine D                         | n-C <sub>9</sub> H <sub>18</sub> C(O)C <sub>3</sub> H <sub>7</sub> -n    | Me             | Me             | Me             | <i>Alb. amara</i>                               | 68        |
| 134      | budmunchiamine E                         | n-C <sub>8</sub> H <sub>16</sub> C(O)C <sub>4</sub> H <sub>9</sub> -n    | Me             | Me             | Me             | <i>Alb. amara</i>                               | 68        |
| 135      | budmunchiamine F                         | C <sub>11</sub> H <sub>23</sub> -n                                       | Me             | Me             | H              | <i>Alb. amara</i>                               | 68        |
| 136      | budmunchiamine G                         | C <sub>13</sub> H <sub>27</sub> -n                                       | Me             | Me             | H              | <i>Alb. amara</i> ,<br><i>Alb. gummifera</i>    | 68,<br>69 |
| 137      | budmunchiamine H                         | n-C <sub>9</sub> H <sub>18</sub> C(O)C <sub>3</sub> H <sub>7</sub> -n    | Me             | Me             | H              | <i>Alb. amara</i>                               | 68        |
| 138      | budmunchiamine I                         | n-C <sub>8</sub> H <sub>16</sub> C(O)C <sub>4</sub> H <sub>9</sub> -n    | Me             | Me             | H              | <i>Alb. amara</i>                               | 68        |
| 139      | budmunchiamine K                         | C <sub>15</sub> H <sub>31</sub> -n                                       | Me             | Me             | Me             | <i>Alb. gummifera</i>                           | 69        |
| 140      | 5-normethylbudmunchiamine K              | C <sub>15</sub> H <sub>31</sub> -n                                       | Me             | Me             | H              | <i>Alb. schimperana</i>                         | 70        |
| 141      | 9-normethylbudmunchiamine K              | C <sub>15</sub> H <sub>31</sub> -n                                       | Me             | H              | Me             | <i>Alb. gummifera</i>                           | 69        |
| 142      | 14-normethylbudmunchiamine K             | C <sub>15</sub> H <sub>31</sub> -n                                       | H              | Me             | Me             | <i>Alb. schimperana</i>                         | 70        |
| 143      | 6′ξ-hydroxybudmunchiamine K              | n-C <sub>5</sub> H <sub>10</sub> CH(OH)C <sub>9</sub> H <sub>19</sub> -n | Me             | Me             | Me             | <i>Alb. gummifera</i>                           | 60        |
| 144      | 6′ξ-hydroxy-5-nor-methylbudmunchiamine K | n-C <sub>5</sub> H <sub>10</sub> CH(OH)C <sub>9</sub> H <sub>19</sub> -n | Me             | Me             | H              | <i>Alb. schimperana</i>                         | 70        |
| 145      | budmunchiamine L1                        | C <sub>16</sub> H <sub>33</sub> -n                                       | H              | H              | H              | <i>Alb. lebbek</i>                              | 71        |
| 146      | budmunchiamine L2                        | C <sub>14</sub> H <sub>29</sub> -n                                       | H              | H              | H              | <i>Alb. lebbek</i>                              | 71        |
| 147      | budmunchiamine L4                        | C <sub>13</sub> H <sub>27</sub> -n                                       | H              | H              | H              | <i>Alb. adinocephala</i>                        | 72        |
| 148      | budmunchiamine L5                        | C <sub>15</sub> H <sub>31</sub> -n                                       | H              | H              | H              | <i>Alb. adinocephala</i>                        | 72        |

the major components of *Verbascum pseudonobile* Stoj. et Stef. (Scrophulariaceae), while the (*E*)-verbacitrine/(*Z*)-isoverbactrine pair was isolated from this plant species in only minor amounts.<sup>65</sup> Incasines B and B′ isolated from *Incarvillea sinensis* were also found in *V. pseudonobile*. The (*E*)-verbamedine/(*Z*)-isoverbamedine pair was structurally identical to incasines A and A′, although in the authors' opinion<sup>65</sup> the structures of the latter were not established unambiguously.

The *E*:*Z* ratio of the isomeric pairs of alkaloids containing cinnamic acid fragments (**112**: **113** and **123**: **124**) is 5:4, that of the alkaloids containing a 3,4-dimethoxycinnamic substituent (**114**: **115** and **125**: **126**) is 1:9. Similar ratios were obtained after irradiation of these alkaloids with visible or UV light ( $\lambda = 365$  nm). It was thus concluded that *Z*-isomers represent photoisomerisation products of the corresponding *E*-isomers formed in intact plant tissues under the influence of solar irradiation.<sup>64</sup>

The 17-membered rings of the group B alkaloids, viz., budmunchiamines, isolated from plants of the genus *Albizia*, contain spermine and various fatty acid fragments (R<sup>1</sup>CH<sub>2</sub>COOH) [R<sup>1</sup> = C<sub>n</sub>H<sub>2n+1</sub>, where  $n \geq 9$ , or R<sup>1</sup> = C<sub>m</sub>H<sub>2m</sub>C(O)C<sub>p</sub>H<sub>2p+1</sub>, where  $m + p = 13$ ], the major part of the alkyl chains of the fatty acids (substituent R<sup>1</sup>) is not incorporated into the macrocycle. The classification of budmunchiamines (from A to L) is based on the length of the side alkyl chain (R<sup>1</sup>) and the degree of methylation of the nitrogen atoms in the macrocycle.

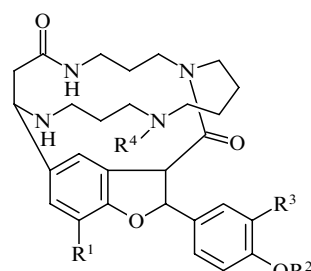
The lengths of the side alkyl chains of the alkaloids of the same series are constant; within the series, the differences reflect different degrees of methylation of the nitrogen atoms in the macrocycle or the presence of hydroxy groups in the side chain R as, e.g., in budmunchiamines C and K. Budmunchiamines L are an exception: all the four nitrogen atoms in the macrocycles in these alkaloids are non-methylated and differ from one another only in the length of the alkyl side chain.

Budmunchiamines are largely isolated from legumes (Leguminosae) and different species of mimosa (Mimosoidae): from seeds of *Albizia amara* Bolv. and an Indian plant (*Alb. lebbek* Benth.), from the stem skins of the Kenyan species *Alb. gummifera*

(J.F.Gmel.) C.A.Sm. and *Alb. schimperana* Oliv. and from the stem bark (budmunchiamines L4 and L5) and leaves (budmunchiamines L5) of the Panamanian plant *Alb. adinocephala* (J.D.Sm.) Britton et Rose ex Record.

#### b. Spermine bimacrocylic alkaloids of the aphelandrine type

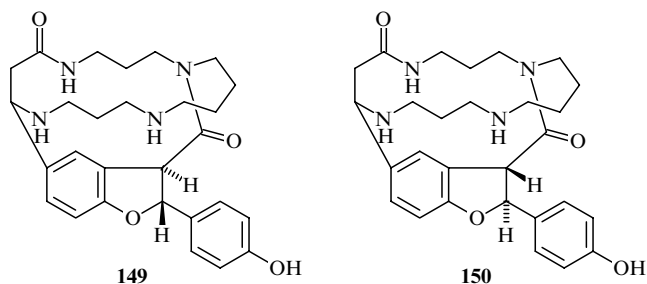
Spermine alkaloids of the aphelandrine type were isolated from the roots of plants of three families, viz., Acanthaceae, Scrophulariaceae and Ephedraceae. These alkaloids contain two macrocycles one of which is identical to the 17-membered lactam ring of the aforementioned group A spermine alkaloids, whereas the other (13-membered) macrocycle contains a fragment of the highly substituted dihydrobenzofuran core. Aphelandrine type alkaloids can also be regarded as compounds the spermine component in which is acylated by two fragments of *p*-coumaric acid.



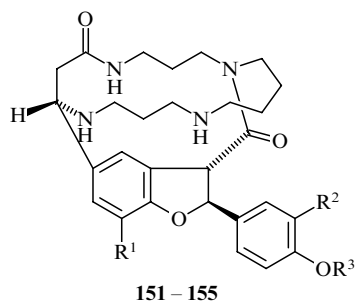
Alkaloids of the aphelandrine type

R<sup>1</sup> = H, OMe; R<sup>2</sup> = H, Me; R<sup>3</sup> = H, OMe; R<sup>4</sup> = H, OH, OAc.

Plants of the genus *Aphelandra* (Acanthaceae) occur on the territory extending from the south of Mexico to the north of Argentina and are represented by nearly 165 species. The roots of some representatives of this genus (*A. tetragona*, *A. squarrosa*, *A. sinclairiana*, *A. pepeparodii*, *A. aurantiaca*, *A. chamissoniana*, *A. fuscopunctata*) contain the bicyclic spermine alkaloid (+)-aphe-landrine (**149**) and its diastereoisomer (–)-oranthine (**150**) (syn. ephedradine A).

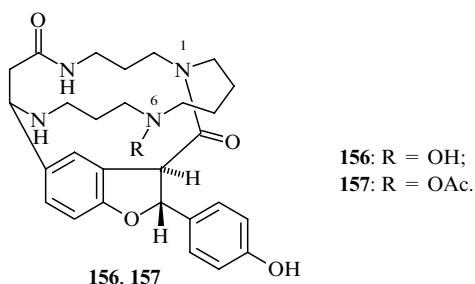


Aphelandrine was also isolated from *Encephalosphaera lasian-dra* also belonging to this family; oranthine was isolated from *Chaenorhinum minus*, *Schweinfurthia papilioacea* (Scrophulariaceae) and *Ephedra* (Ephedraceae). The alkaloid (–)-*O*-methylo-ranthine (**151**) was found in *C. minus* and *C. villosum* (Scrophulariaceae); (–)-epioranthine (**152**) was found in *S. papilioacea* (Scrophulariaceae). Representatives of yet another group of alkaloids structurally similar to aphelandrine, viz., (–)-ephe-dradines B, C and D (compounds **153–155**), were found in *Ephedra* (Ephedraceae).<sup>73, 74</sup>

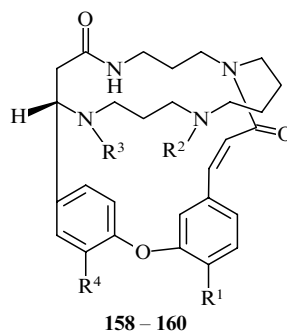


- 151:**  $R^1 = R^2 = H, R^3 = Me$ ;  
**152:**  $R^1 = R^2 = R^3 = H$ ;  
**153:**  $R^1 = R^3 = H, R^2 = OMe$ ;  
**154:**  $R^1 = H, R^2 = OMe, R^3 = Me$ ;  
**155:**  $R^1 = OMe, R^2 = R^3 = H$ .

The isolation of (+)-*N*(6)-hydroxyaphelandrines (**156**) and (+)-*N*(6)-acetoxyaphelandrine (**157**) from the roots of *A. fusco-punctata* confirmed that macrocyclic spermine alkaloids are typical of the genus *Aphelandra*.<sup>73</sup> However, in the upper (super-terrestrial) parts and in cell cultures of *A. tetragona* and *A. sinclairiana*, this type of alkaloid was not found.<sup>74</sup>



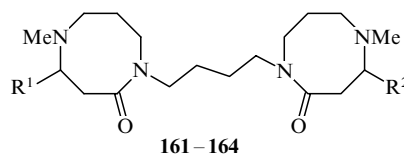
Besides oranthine and ephedradines B and C, the roots of some plants of the family Scrophulariaceae contain a variety of other macrocyclic spermine alkaloids. Thus chaenorine (**158**) and chaenorpine (**159**) were isolated from the plant *C. minus*, while 18-*O*-methylchaenorpine (**160**) was isolated from *A. tetragona*. The alkaloids **158–160** are structurally similar to the aphelandrine alkaloids **149–157**.<sup>75, 76</sup>



- 158:**  $R^1 = H, R^2 = Ac, R^3 = H, R^4 = OMe$ ;  
**159:**  $R^1 = OH, R^2 = R^3 = R^4 = H$ ;  
**160:**  $R^1 = OMe, R^2 = R^3 = R^4 = H$ .

### c. Spermine alkaloids from *Homalium* plants

The group of homaline alkaloids comprises four spermine derivatives, viz., homaline (**161**), hopromine (**162**), hoprominol (**163**) and hopromalinol (**164**), isolated from the leaves of plants of the genus *Homalium* and *Homalium pronyense* Guillaum (Flacourtiaceae) growing in the rainforests of New Caledonia.<sup>77, 78</sup>



- 161:**  $R^1 = R^2 = (S)\text{-Ph}$ ;  
**162:**  $R^1 = n\text{-C}_5\text{H}_{11}, R^2 = n\text{-C}_7\text{H}_{15}$ ;  
**163:**  $R^1 = n\text{-C}_5\text{H}_{11}, R^2 = \text{CH}_2\text{CH}(\text{OH})\text{C}_5\text{H}_{11}\text{-n}$ ;  
**164:**  $R^1 = \text{Ph}, R^2 = \text{CH}_2\text{CH}(\text{OH})\text{C}_5\text{H}_{11}\text{-n}$ .

## 4. Biological activities of cyclic alkaloids

In the past decade, plants of the genus *Aglaia* (Meliaceae) attracted keen attention as a novel source of unique natural compounds, primarily because of unusually high insecticidal activities of their lipophilic extracts. Non-nitrogenous flavaglines with a cyclopenta[*b*]benzofuran backbone manifest especially high insecticidal and antiproliferative activities;<sup>49</sup> their hypothetical biosynthetic intermediates are polyamine-containing taspakines devoid of insecticidal activity.<sup>48</sup>

Some bisamide alkaloids isolated from plants of the genus *Aglaia*, e.g., dehydroodrine (**60**), manifest cytotoxic activity.<sup>46</sup> The spermidine alkaloid lunarine (**108**) causes time-dependent inhibition of trypanthione reductase (presumably, this reaction is accompanied by the binding of the enzyme to one of the double bonds in the lunarine macrocycle).<sup>79</sup>

The arboreal plant *Alb. gummifera* (J.F.Gmel.) C.A.Sm. is widely used in the folk medicine of Kenya. Its bark possesses pronounced antipyretic properties and is a popular remedy against cold, dermatosis, gonorrhea, malaria, gastric pains (as aqueous extract) and wound contamination (as powder).<sup>69</sup> Yet another Kenyan plant, *Alb. schimperana* Oliv., is used for the treatment of bacterial and parasite-borne infections (pneumonias, infected injuries, malaria) and as a component of antipyretic and analgesic drugs.<sup>70</sup> The species *Alb. julibrissin* is a component of a patented herbal mix for regulation of the level of female hormones. The therapeutic activity of budmunchiamines is usually associated with their physiological effect on the human nervous system.<sup>80</sup>

Wide application of plants of the genus *Albizia* in folk medicine has given strong impetus to their comprehensive studies. It was found that budmunchiamines isolated from these plants

manifest different types of biological activity. A mixture of budmunchiamines A–C (compounds **129–131**) (4 : 1 : 1) has non-specific cytotoxic and antibacterial (*Salmonella typhimurium* TM677) effects; besides, it prevents platelet aggregation and transformation of human lymphocytes and inhibits cyclooxygenase activity.<sup>81</sup>

Budmunchiamines L4 (**147**) and L5 (**148**) induce moderate inhibition of plasmepsin II,<sup>¶</sup> a specific enzyme of the malaria pathogen *Plasmodium falciparum* ( $IC_{50} = 14$  and  $15 \mu\text{mol litre}^{-1}$ , respectively).<sup>72</sup> The currently observed increase in the gravity of the disease and its abundance due to appearance of novel drug- and insecticide-resistant parasites and mosquitos makes the development of newer treatment strategies and novel antimalarial drugs with enhanced properties and new in principle mechanisms of action a central task. This situation is further aggravated by the lack of efficient vaccines and the ambiguity of results of some clinical trials of novel antimalarial drugs.

Budmunchiamines **129**, **132** and **139–144** isolated from the Kenyan plants *Alb. gummifera* and *Alb. schimperana* possess antibacterial and cytotoxic properties.<sup>69</sup> Their antibacterial activities were tested in experiments with two Gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) and two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria; chloramphenicol was used as a standard. Cytotoxicity studies were carried out on sea shrimp larvae. It was found that the biological activities of budmunchiamines strongly depend on two factors, viz., the presence of hydroxy groups in the side alkyl chain R<sup>1</sup> and the degree of methylation of the nitrogen atoms in the macrocycle. A decrease in the degree of methylation of nitrogen atoms (from three to two groups) has no effect on the antibacterial activity, but causes significant reduction of the cytotoxic activity. Both antibacterial and cytotoxic activities decrease significantly, if the side alkyl chain R<sup>1</sup> contains hydroxy groups.<sup>69</sup> The decrease in antibacterial and cytotoxic activities of budmunchiamines A–I (**129–138**) in the presence of carbonyl groups in their side chains provide conclusive evidence in favour of this assumption.<sup>68</sup>

Budmunchiamine A (**129**) was examined for the ability to control the activity of calcium receptors, which are extremely sensitive to even minor changes in  $\text{Ca}^{2+}$  concentrations. It was found that compound **129** inhibits the effect of the extracellular  $\text{Ca}^{2+}$  ion on the cell containing the  $\text{Ca}^{2+}$  receptor. This finding led the authors to conclude<sup>82</sup> that budmunchiamine A is a helpful tool in structure–activity studies.

Ephedradines extracted from plant roots are used as essential components of the Oriental antiperspirant composition ‘mao-kon’. Pharmacological studies have shown that this preparation exhibits antitussive and antiallergic properties.<sup>83</sup> Intravenous injection of ephedradine dihydrochlorides or -bromides to mice produces a hypotensive effect.<sup>84</sup>

\* \* \*

The data presented in this review demonstrate the extreme structural diversity of plant polymethyleamine alkaloids. Many of them showed high activity in pharmacological tests (Table 8) and proved to be promising models in comprehensive structure–activity studies. The wealth of literature data on various biological activities of polymethyleamine alkaloids and the abundant experience in their synthesis open up broad opportunities for the development of novel, highly efficient drugs.

¶ Plasmepsin II is a representative of the plasmepsin family and plays a crucial role in the survival and proliferation of enzymes. It is extensively studied and readily available and is thereby used as a target of choice for screening a library of natural products.

**Table 8.** Biological activities of plant source alkaloids of the polymethyleamine series.

| Type of biological activity                                                 | Alkaloids                         |                     |
|-----------------------------------------------------------------------------|-----------------------------------|---------------------|
|                                                                             | natural                           | synthetic analogues |
| Antagonists of histaminergic, $\alpha$ -adrenergic and muscarinic receptors | <b>48</b>                         |                     |
| Antibacterial                                                               | <b>129–132, 139–144</b>           |                     |
| Antiherpetic                                                                | <b>31, 32</b>                     |                     |
| Antileukemic                                                                | <b>24</b>                         |                     |
| Hypotensive                                                                 | <b>2, 39, 40, 42, 43, 153–155</b> | <b>56</b>           |
| Inhibitor of:                                                               |                                   |                     |
| $\alpha$ -glucosidase                                                       | <b>22, 23</b>                     |                     |
| calcium receptor                                                            | <b>129</b>                        |                     |
| bradykinin (BK)                                                             | <b>47, 48</b>                     |                     |
| B <sub>1</sub> and B <sub>2</sub> receptors                                 |                                   |                     |
| trypanothione reductase                                                     | <b>108</b>                        | <b>49</b>           |
| plasmepsin II                                                               | <b>147, 148</b>                   |                     |
| cyclooxygenase                                                              | <b>129–131</b>                    |                     |
| Neurotoxic                                                                  | <b>1, 4, 19</b>                   |                     |
| Labour-stimulating                                                          | <b>39</b>                         |                     |
| Fungicidal                                                                  | <b>11, 12, 15</b>                 |                     |
| Cytotoxic                                                                   | <b>60, 129–132, 139–144</b>       |                     |

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<sup>b</sup> — *Chem. Nat. Compd. (Engl. Transl.)*

<sup>c</sup> — *Russ. J. Org. Chem. (Engl. Transl.)*



# The main aspects of the modern theory of the passive state of metals

Yu A Popov

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**Abstract.** The modern theoretical models of the active–passive transition and of the passive state of metals are surveyed. General regularities underlying the functioning mechanisms of passivating oxide layers as well as the adsorption and salt passivation are formulated. The bibliography includes 99 references.

## I. Introduction

Despite numerous studies of the passive state of metals conducted over the last few decades and extensive experimental data collected in this field, there is still no consensus on the mechanism of formation<sup>1–19</sup> and functioning<sup>20–25</sup> of passivating (oxide) layers (hereinafter, PL). Passivating systems are thermodynamically non-equilibrium, therefore it is the *in situ* techniques that are the most efficient in their studies. Probably, this is one of the reasons for the frequent succession violations of the theoretical concepts related to the passivity problem, *i.e.*, earlier prevailing concepts are rejected and replaced with new ones. This substantiates a thorough comparative analysis of different passivity models.

The current understanding of the mechanism of the formation of a PL has evolved through several steps. The original concept elaborated by representatives of the German school of electrochemists<sup>26–34</sup> postulated the existence of an equilibrium phase oxide (the so-called phase-film concept). This implied that the passivation is caused by the mechanical shielding of the metal surface (*S*) by a thermodynamically equilibrium oxide layer, the constant passive current being in this case due to the chemical dissolution of the oxide. Gradually, serious contradictions to experiments were found within this concept. In particular, it appeared that the critical potentials observed in polarisation curves, *i.e.*, the activation and passivation potentials, differed from the potentials of formation of the respective oxides. For instance, in the case of iron, the difference is as large as 0.63 V (relative to the standard hydrogen electrode).<sup>26</sup> The experimen-

tally established dependence of the passivation and activation potentials on the electrolyte composition, pretreatment of the metal surface and its properties also contradicted to the phase-film concept. The postulate on the constancy of the passive current, which is equivalent to the rate of the chemical dissolution of the passivating oxide, was disproved by the experimental results, which supported the electrochemical mechanism of transition of the passivated metal into a solution. However, despite the above contradictions, Vetter has proposed<sup>26</sup> an approach rationalising the stability and functioning of a PL. According to the experimental results,<sup>19, 25, 26</sup> the stability is due to the ion exchange between the PL and the electrolyte, which complies with the general conditions of the thermodynamical equilibrium between these two phases.

By the late 1970s, the self-contradictory, in general, phase-film model featured the correct idea that it is the oxide layer that plays a prominent role in the passivation mechanism. These concepts were further developed by other authors who considered the processes of ion transfer through the interfaces and the effects of ion vibrations in the nodes of a crystal lattice.<sup>35–46</sup> The processes of the cluster growth of oxide PL on iron, nickel, copper and other metals were investigated, and semiconducting properties of the PL and the mechanism of breakdown of the passive state were analysed. Popov and Sakha<sup>47</sup> formulated the following systematisation criteria for the models of the passive state.

1. Functioning of a passivating layer is stable provided that the equilibrium between the oxide and the electrolyte is achieved owing to the exchange of oxygen ions. Since the passivated metal undergoes anodic dissolution, the equilibrium with the electrolyte is incomplete and involves only the oxygen sublattice of the PL. Overall, the system oxide–electrolyte is non-equilibrium thermodynamically and thus it should be analysed taking into consideration kinetic factors.

2. The anion composition of a stationary PL remains constant; the anions drift gradually following the shift of the interface metal–oxide (M–O) due to the hopping diffusion. Meanwhile, the composition of the cation (metal) sublattice of the PL is continuously renewed due to transfer of the  $M_{ox}^{z+}$  ions into the electrolyte, which is accompanied by cleavage of their bonds with the  $O_{ox}^{2-}$  anions migrating in the bulk of the PL. A part of the  $M_{ox}^{z+}$  ions that diffuse through the PL from the interface M–O come into the electrolyte independently of the migration of the oxygen anions, which results in continuous disappearance of oxide cells within the PL.

**Yu A Popov** State Scientific Centre of the Russian Federation  
'L Ya Karpov Institute of Physical Chemistry', ul. Vorontsovo Pole 10,  
105064 Moscow, Russian Federation. Fax (7-095) 975 24 50,  
tel. (7-095) 129 62 53

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3. In a stationary mode, new oxide cells are continuously formed at the interface M–O, which compensates for their dissolution in the electrolyte. This provides the stability of the PL. The  $O_{ox}^{2-}$  anions are incorporated into the metal phase so that the compensating process of metal conversion into passivating oxide occurs. The volume of the latter typically exceeds the initial volume of the metal.

4. The metal conversion process gives rise to the spatial balance problem due to the difference in the volumes of the initial metal and the derived oxide. The balance is kept due to non-equilibrium cation vacancies at the interface oxide–electrolyte (O–E), which diffuse through the PL towards the interface M–O, where they convert into oxide anion vacancies.<sup>19, 25</sup> This is the first role played by the non-equilibrium vacancies.

5. The passivity region has a finite dimension (length), which means that a passivity theory should describe the transpassive transition.<sup>19, 23, 25</sup> This necessitates accounting for the diffusion in the PL, which gives rise to a dependence of the concentration of non-equilibrium vacancies (*i.e.*, point defectiveness of the PL), which affects the PL length, on the anode potential  $\varphi$ . At low defect concentrations in the PL (*e.g.*, in the cases of Al, Ti, Ta and Zr), the transition potential can be appreciably high. This is the second role played by the non-equilibrium vacancies.

6. A passivity theory should explain from a unified standpoint the mechanisms of the processes that proceed at both interfaces, O–E and M–O, and the ion transfer between them.

The behaviour of metals in electrolyte solutions is characterised by a dependence of the current density of the anode dissolution  $i_a$  on the interface potential drop. A polarisation curve typical of such metals as Fe, Ni and Cr is shown schematically in Fig. 1.

The state of a metal surface in an electrolyte is determined by the value of  $\varphi$ . Four major states of a surface are known, *viz.*, active dissolution, active-passive transition, passive state and transpassive transition, to which correspond the following four ranges of the potential values:  $\varphi < \varphi_0$ ,  $\varphi_0 < \varphi < \varphi_a$ ,  $\varphi_a < \varphi < \varphi_p$  and  $\varphi > \varphi_p$  in Fig. 1. The characteristic points  $\varphi_0$ ,  $\varphi_a$  and  $\varphi_p$  depend on the metal and electrolyte properties and on their interaction.

The present review describes the existing theories of the mechanism and kinetics of processes occurring in two most important and complex states, *viz.*, the active-passive transition and the passive state itself.

The multitude of corrosion phenomena cannot be covered within a single theory. The knowledge of the specificity of a system is a prerequisite of any study. For instance, one should determine the statistical scatter in the interatomic distances and bond directions within a PL to account for its incomplete structural ordering (*i.e.*, when it is amorphous). A microscopic-level mechanism of the metal–electrolyte interactions can also be highly specific to the system, *etc.*

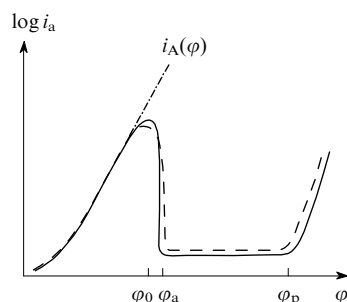


**Figure 1.** The experimental<sup>26</sup> (solid line) and theoretical<sup>19</sup> (dashed line) dependences of the current densities ( $i_a$ ) corresponding to dissolution of a metal in an electrolyte on the anode potential;  $i_A(\varphi)$  is the current density in the Tafel region,  $(\varphi_0 - \varphi_a)$  is the active-passive transition,  $(\varphi_a - \varphi_p)$  is the passivity region.

Meanwhile, shapes of the polarisation curves are essentially identical for many metals: they show the aforementioned regions of the active and passive dissolution as well as of the active-passive and transpassive transitions. This indicates that it is possible (and thus desirable) to develop a unified theoretical model to include maximally simplified processes that govern the shapes of the polarisation curves. These processes include migration of ions through the interfaces PL–metal and PL–electrolyte and within the PL structure itself, an increase in the defectiveness of a PL upon an increase in the potential and the PL crystallisation during the active-passive transition. The kinetics of these processes differ depending on the potential and therefore one process dominates at any specific potential value, which gives rise to the alteration of the four above regions with an increase in the potential. The unified elementary model serves as a base ('framework'), which can be extended or modified to take into account specific factors for consideration of real systems. The author believes that exactly this purpose is pursued by the theory described below, which is open for any extensions and modifications.

## II. Formation of a passivating oxide layer upon the active–passive transition ( $\varphi_0 < \varphi < \varphi_a$ )

According to numerous investigations, the compositions and structures of passivating layers on such metals as Fe, Cr, Ni, Mo and Cu correspond to those of metal oxides  $M_nO_m$  (*e.g.*,  $Fe_2O_3$  or  $Fe_3O_4$  in the case of iron). This is evident from both early studies of passivating layers using X-ray diffraction<sup>26</sup> and layer-by-layer etching and more recent methods of scanning tunnelling and optical microscopy.<sup>45, 46</sup> Ellipsometry is becoming increasingly popular in studies of PL.<sup>48–52</sup> Especially promising is the ellipsometric topography method,<sup>53, 54</sup> which exploits the dependence of the transmission coefficient of a PL on the radiation wavelength.

If an oxide PL possesses a disordered structure (*i.e.*, it is amorphous, as in the case of PL formed on Al, Ti, Ta, Zr and other metals), it can be described by statistical distributions of the interatomic distances and angular directions. However, the passive current density and other parameters can finally be expressed<sup>25</sup> through dispersions in the interatomic distances, angular directions and electric field strengths within the PL. The problem of the independent determination of these parameters is not solved as yet.

In agreement with the concepts formulated above and the general theory of heterogeneous nucleation,<sup>1–18</sup> it was suggested<sup>18–21</sup> that it is the two-dimensional nuclei of an oxide  $MO_{z/2}$  that are formed in the initial step of PL formation on the surface of anodically dissolving metal. The formation of nuclei starts at the point  $\varphi_0$  of the second region in the polarisation curve and is completed at  $\varphi_a$  in the end of this region (see Fig. 1).

In the steady-state mode, the probability  $I_e$  of nuclei generation (the number of nuclei per  $cm^2$  per s) is an increasing function of the anode potential  $\varphi$ . Respectively, the steady-state coverage  $\Theta_e$  of the surface  $S$  by nuclei also increases reaching the maximum value  $\Theta_e(\varphi_a) \sim 1$  at  $\varphi_a$ .

A further increase in the potential actuates the transition into the passive region in which the thickness of the passivating layer  $\delta(\varphi)$  increases with retention of the equilibrium between the oxide and the electrolyte. Indeed, an equilibrium potential  $\varphi_{pb}$  is settled in this range, whereas the surplus potential drop  $(\varphi - \varphi_{pb})$  is expended within the thickness  $\delta(\varphi)$  of the passivating layer.

This section considers modern models of the kinetics of formation of a PL, functional dependences of  $I_e$ ,  $\Theta_e$  and anodic current density  $i_a$  on the potential, the energy of the interparticle interactions, energetic heterogeneity of the metal surface and other parameters. These dependences reproduce a nearly vertical decrease (by 5–7 orders of magnitude) in the current upon the active-passive transition, *i.e.*, over a narrow range of potentials  $\varphi_0 < \varphi < \varphi_a$  with a width of only 50–70 mV.

### 1. Kinetics of crystallisation of a passivating layer

Simulations of crystallisation of passivating layers on metal surfaces are based on the molecular-kinetic theory of nucleation. This theory developed in the mid 1970s<sup>1–18</sup> retains its significance to date. According to this theory, nuclei of the passivating layer are generated due to the stepwise attachment of particles to faces of the existing two-dimensional crystals (*i.e.*, prenuclei).

The molecular-kinetic theory<sup>1–18</sup> differs from two other thermodynamical theories by Volmer and Gibbs, which consider generation of nuclei as a mere condensation process without any structure formation. In contrast, the molecular-kinetic theory describes the stepwise attachment of particles to a crystal taking into account its surface structure, influence of neighbours and possible ordering into a crystal lattice. The key steps of these processes can be established<sup>1–14</sup> using simple models that approximate a crystal structure with a lattice of points or array of cubes. These models are based on the nearest-neighbour-interaction approximation, which assumes that the interactions between the real particles rapidly attenuate with an increase in the interparticle distances.

Let the interatomic distance in the crystal be  $r_0$  and its size  $a = nr_0$  changes due to elementary processes of the type  $a \rightarrow a \pm r_0$ , *i.e.*, due to attachment or detachment of a peripheral atomic row, which gives rise to the transformation of the crystal with an edge  $a$  to that with an edge  $a \pm r_0$ . If  $P$  and  $V$  are, respectively, the probabilities and the rates of the following transitions

$$\begin{aligned} P_{a \rightarrow a \pm r_0}, \quad P_{a \pm r_0 \rightarrow a}, \\ V_{a \rightarrow a \pm r_0}, \quad V_{a \pm r_0 \rightarrow a} \end{aligned} \quad (1)$$

$n_a$  is the concentration of crystals with an edge  $a$ , then

$$\begin{aligned} V_{a \rightarrow a \pm r_0} &= n_a P_{a \rightarrow a \pm r_0}, \\ V_{a \pm r_0 \rightarrow a} &= n_{a \pm r_0} P_{a \pm r_0 \rightarrow a}. \end{aligned} \quad (2)$$

Provided that  $a \gg r_0$ , the following relations can be derived

$$\begin{aligned} P_{a+r_0 \rightarrow a} &\simeq P_{a \rightarrow a-r_0}, \\ P_{a \rightarrow a+r_0} &\simeq P_{a-r_0 \rightarrow a}. \end{aligned} \quad (3)$$

The resultant rates of the direct and reverse stationary transitions ( $I$ ) are given by

$$I = V_{a-r_0 \rightarrow a} - V_{a \rightarrow a-r_0} = V_{a \rightarrow a+r_0} - V_{a+r_0 \rightarrow a} \quad (4)$$

or further

$$\begin{aligned} I &= V_{a \rightarrow a+r_0} - V_{a+r_0 \rightarrow a} = \\ &= n_a (P_{a \rightarrow a+r_0} - P_{a \rightarrow a-r_0}) - P_{a \rightarrow a-r_0} (n_{a+r_0} - n_a). \end{aligned} \quad (5)$$

If  $a$  reaches the value  $a_2 = n_2 r_0$ , where  $n_2$  is the number of particles in the edge of the two-dimensional nucleus, then

$$P_{a_2 \rightarrow a_2+r_0} = P_{a_2 \rightarrow a_2-r_0}.$$

Furthermore, for sufficiently large  $a$

$$\begin{aligned} n_{a+r_0} - n_a &\simeq \left( \frac{dn_a}{da} \right) r_0, \\ a &\gg r_0. \end{aligned} \quad (6)$$

Taking into account the equation (5), we obtain

$$I_e = \left( P_{a \rightarrow a-r_0} \frac{dn_a}{da} \right)_{a=a_2}. \quad (7)$$

The first term in the right part of the equation can be expressed through the work of formation of the peripheral atomic row ( $W_{a_2}$ )

$$P_{a_2 \rightarrow a_2-r_0} = \text{const} \left[ a_2 \exp \left( -\frac{W_{a_2}}{kT} \right) \right]^2. \quad (8)$$

The exponent 2 means that a transition of a square nucleus with an edge  $a_2$  into that with an edge  $a_2 + r_0$  requires simultaneous attachment of two rows of particles to two adjoining edges;  $a_2^2$  is the area of the substrate where the nucleus is formed. The second term can be determined from (3) and (4) reformulated as

$$\begin{aligned} \frac{n_{a+r_0} - n_a}{n_a - n_{a-r_0}} &= \frac{P_{a \rightarrow a+r_0}}{P_{a \rightarrow a-r_0}}, \\ \frac{P_{a \rightarrow a+r_0}}{P_{a \rightarrow a-r_0}} &= \left[ \exp \left( -\frac{W_a - W_a^*}{kT} \right) \right]^2. \end{aligned} \quad (9)$$

Here,  $(W_a^* - W_a)$  is the difference between the energies of attachment and detachment of a peripheral row of particles.<sup>25</sup> The equations (6), (8) and (9) can be transformed into

$$\begin{aligned} \ln \left( \frac{dn_a}{da} \right)_{a+r_0} - \ln \left( \frac{dn_a}{da} \right)_a &= r_0 \frac{d}{da} \left( \ln \frac{dn_a}{da} \right), \\ r_0 \frac{d}{da} \left( \ln \frac{dn_a}{da} \right) &= \left[ \exp \left( -\frac{W_a - W_a^*}{kT} \right) \right]^2. \end{aligned} \quad (10)$$

This according to Stranski *et al.*<sup>2,5</sup> gives rise to

$$\left( \frac{dn_a}{da} \right)_{a=a_2} = \text{const} \exp \left( -\frac{W}{2kT} \right), \quad (11)$$

where  $a_2 = n_2 r_0$ ,  $W = 2n_2 \Psi$  ( $\Psi$  is the interaction energy of two particles arranged at a distance  $r_0$  from each other).

If  $n_2$  is the number of particles in the edge of a square two-dimensional nucleus and  $a_2 > a$ , then the work of its formation can be represented as a product of the perimeter ( $L$ ) and specific edge surface of the nucleus ( $\kappa$ )

$$W = L\kappa,$$

where  $L = 4a_2$ ,  $\kappa = \Psi/2r_0$ . With account of the equations (7), (8) and (11), this gives rise to

$$I_e = \text{const} \left[ a_2 \exp \left( -\frac{W_{a_2}}{kT} \right) \right]^2 \exp \left( -\frac{W}{2kT} \right), \quad (12)$$

$$a_2 = n_2 r_0,$$

$$W_{a_2} = \left( \Psi - \frac{\Psi}{n_2} \right),$$

$$W = 2n_2 \Psi.$$

The terms in the right part of the equation (12) account for structuring and condensation, respectively (through values of  $W_{a_2}$  and  $W$ ).

It has been shown<sup>19</sup> that the number of particles in the edge of a nucleus of passivating oxide upon formation of the PL on the surface of an anodically dissolving metal is expressed as

$$n_2(\varphi) = \frac{\Psi}{ze(\varphi - \varphi_{p1}) + \Psi_0 - \Psi},$$

where  $\varphi_{p1}$  is the potential of formation of the passivating oxide  $\text{MO}_{x/2}$ , and  $\Psi_0$  is the interaction energy of particles constituting the oxide nucleus with the metal substrate.

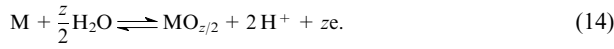
According to the equation (12), the rate of formation of the oxide is

$$I_e(\varphi) \simeq I_0 \exp \left[ -\frac{2\Psi^2/kT}{ze(\varphi - \varphi_{p1}) + \Psi_0 - \Psi} \right]. \quad (13)$$

This formula is in agreement with that derived by Pangarov.<sup>11</sup>

## 2. Coverage of the metal surface with a passivating oxide

The process of coverage of the metal surface with a passivating oxide has been investigated by several authors.<sup>19, 26</sup> The oxide nuclei are generated according to the reaction



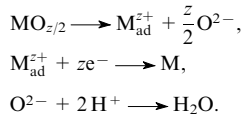
Two different phases, *viz.*, the metal  $M$  and an aqueous electrolyte, serve as sources of ions. This is a feature of the PL formation. At the active-passive transition, the nuclei of  $MO_{z/2}$  are in equilibrium only with the metal phase. To realise the complete equilibrium, the interphase potential at the interface with the electrolyte should have a specific value, which is not yet reached at  $\varphi < \varphi_a$ . Therefore, the nuclei dissolve after certain (mean) lifetime.

Indeed, upon the active-passive transition, the transfer of the  $M^{z+}$  cations from  $MO_{z/2}$  into the electrolyte (*i.e.*, dissolution) is continuously compensated for by their transport from the metal substrate. This means that the cationic sublattice of the nucleus remains in a stationary state. From this viewpoint, the critical nucleus of  $MO_{z/2}$ , as has been said above, is in equilibrium with the metal  $M$ , and its size  $a_2$  is determined by the standard equation

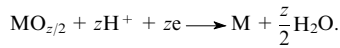
$$\sum_i \mu_i v_i = ze\varphi,$$

where  $\mu_i$  and  $v_i$  are the chemical potential and stoichiometric coefficient of the  $i$ th reactant in the equation (14), respectively.

The oxygen sublattice of the nucleus of  $MO_{z/2}$  is not in a stationary state, since the transfer of the  $O^{2-}$  anions into the electrolyte is not compensated for by other processes. This is accompanied by the following reactions



The overall process can be formulated as



The current density induced by oxygen removal is

$$\begin{aligned} I_O(\varphi_b) &= \\ &= i_{ex} \left\{ \exp \left[ \alpha_O \frac{z_O F}{RT} (\varphi_b - \varphi_{pb}) \right] - \exp \left[ -\beta_O \frac{z_O F}{RT} (\varphi_b - \varphi_{pb}) \right] \right\}, \end{aligned} \quad (15)$$

where  $i_{ex}$  is the exchange current;  $\alpha_O$  and  $\beta_O$  are the transfer coefficients ( $\alpha_O + \beta_O = 1$ ,  $z_O = 2$ );  $F$  is the Faraday number;  $\varphi_b$  is the interface potential;  $\varphi_{pb}$  is the potential of the partial oxygen equilibrium. The equilibrium of the oxide with the electrolyte with respect to oxide ions is achieved only in the end of the transition, *i.e.*, at the potential  $\varphi \sim \varphi_a$  (see Fig. 1), the equilibrium being characterised by

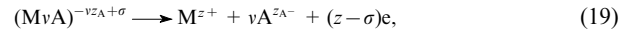
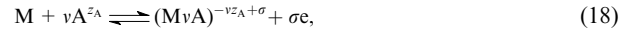
$$\begin{aligned} \varphi_b(\varphi) &= \varphi_{pb}, \\ \varphi &= \varphi_a, \end{aligned} \quad (16)$$

where  $\varphi_{pb}$  is defined by the condition

$$I_O(\varphi_{pb}) = 0. \quad (17)$$

Therefore, in the end of the active-passive transition, the dissolution of passivating nuclei gradually ceases, the first oxide monolayer becomes continuous, the coverage reaches the value of  $\Theta_e(\varphi_a) = 1$ , and gradual transition to the passive region occurs.<sup>19, 20</sup>

However, this is still an incomplete physical description of the active-passive transition since the reaction (14) competes with the process of active anodic dissolution, which proceeds according to the scheme



$A^{z_A-}$  are activating anions from the electrolyte and  $\sigma$  is the fraction of the electron charge involved in the chemisorption bonding. The metal surface is covered not only with two-dimensional nuclei [the degree of coverage is  $\Theta_e(\varphi)$ ], but with surface complexes  $(MvA)^{-vz_A+\sigma}$  [the degree of coverage is  $\Theta_a(\varphi)$ ] as well. The stationary equations for  $\Theta_e(\varphi)$  and  $\Theta_a(\varphi)$  can be written as

$$(1 - \Theta_a - \Theta_e)K_a(\varphi) = \Theta_a K_i(\varphi), \quad (20)$$

$$(1 - \Theta_a - \Theta_e)I_e = \Theta_e I_O(\varphi),$$

where  $K_a(\varphi)$ ,  $K_i(\varphi)$  are the rates of adsorption of activating anions  $A^{z_A-}$  and ionisation of the intermediate complexes  $(MvA)^{-vz_A+\sigma}$ , respectively,

$$K_a(\varphi) = k_a C_a^v \exp \left[ \frac{\alpha_a (z_A - \sigma) F \varphi}{RT} \right],$$

$$K_i(\varphi) = k_i \exp \left[ \frac{\alpha_i (z_M - \sigma) F \varphi}{RT} \right].$$

$k_a$ ,  $C_a^v$  and  $k_i$  are preexponential factors;  $\alpha_a$  and  $\alpha_i$  are the transfer coefficients of anions and ions of the intermediate complexes, respectively.

Therefore,

$$\Theta_e = \frac{I_e}{I_O + (1 + \Theta'_a)I_e} (1 - \Theta'_a), \quad (21)$$

$$\Theta_a = (1 - \Theta_e)\Theta'_a,$$

$$\Theta'_a = \frac{K_a(\varphi)}{K_a(\varphi) + K_i(\varphi)}. \quad (21a)$$

The anodic currents (rates)  $I_e(\varphi)$  and  $i_a(\varphi)$  corresponding to the processes (14) and (19) differently depend on the potential  $\varphi_0$ . At low  $\varphi$ , the reactions (19) dominate and the coverage  $\Theta_e(\varphi)$  is small. With an increase in  $\varphi$ , the rate  $I_e(\varphi)$  increases and  $I_e(\varphi_0) \sim i_a(\varphi_0)$  at  $\varphi = \varphi_0$  (see Fig. 1). Starting from this moment, two-dimensional nuclei are predominantly generated owing to the strong dependence of  $I_e$  on  $\varphi$ , and the current density of anodic dissolution decreases by several orders of magnitude with a change in  $\varphi$  in a narrow range of the order of tens of mV. The total current density  $j(\varphi)$  caused by the transfer of the  $M^{z+}$  ions into the electrolyte is described by the equation

$$j(\varphi) = \Theta_a(\varphi)K_i(\varphi) + [I_O(\varphi_b) + i_O(\varphi_b)]\Theta_e(\varphi), \quad (22)$$

where

$$i_O(\varphi_b) = i_0 \exp \left( \frac{\alpha z_M F}{RT} \varphi_b \right),$$

$i_0$  is the preexponential factor and  $\alpha$  is the particle transfer coefficient.

The formula (22) takes into account all mechanisms contributing to the value of  $j(\varphi)$ . The first term corresponds to the active dissolution; the second one is due to dissolution of the nuclei at a rate  $I_O(\varphi_b)$ , which results in flaking away of the  $M_{ox}^{z+}$  ions; the third term accounts for the metal ion transfer through the nuclei into the solution and their migration through the two-dimensional passivating oxide layer; it predominates for the passive region at  $\varphi > \varphi_a$ .

## 3. The energetic inhomogeneity of a metal surface

The concepts described above underlie the modern theory of the PL formation. A further step in this approximation consists of consideration of the energetic inhomogeneity of a surface, which implies that different areas of a surface  $\Delta S_i$  interact with the electrolyte with different strengths and generate different current densities of anodic dissolution. A variable energy  $\Psi_{0i}$  can be

attributed to every sufficiently small area and the overall surface will thus be characterised by a sum

$$S = \sum_i \Delta S_i(\Psi_{0i})$$

or integral

$$S = \int_{\varepsilon_{\min}}^{\varepsilon_{\max}} dS(\Psi_{0i}),$$

the integration limits  $\varepsilon_{\max}$  and  $\varepsilon_{\min}$  depend on the properties of the metal. The electrode processes can be described using the specially specified autonomous function  $f(\Psi_{0i})$  of statistical distribution of energies  $\Psi_{0i}$  over the surface, the local current density  $j(\varphi, \Psi_{0i})$  and the local coverage  $\Theta(\varphi, \Psi_{0i})$ . Their integral values are determined by the following equations

$$\begin{aligned} \int_{\varepsilon_{\min}}^{\varepsilon_{\max}} f(\Psi_{0i}) d\Psi_{0i} &= 1, \\ i_a(\varphi) &= \int_{\varepsilon_{\min}}^{\varepsilon_{\max}} d\Psi_{0i} f(\Psi_{0i}) j_i(\varphi, \Psi_{0i}), \\ \Theta_e(\varphi) &= \int_{\varepsilon_{\min}}^{\varepsilon_{\max}} d\Psi_{0i} f(\Psi_{0i}) \Theta_{ei}(\varphi, \Psi_{0i}). \end{aligned} \quad (23)$$

The energy of interaction of particles constituting a nucleus with the metal  $\Psi_{0i}$  is contained in the probability (13) and, consequently, in all other parameters. The local coverages and current densities can be expressed as follows:

$$\Theta_{ei}(\varphi, \Psi_{0i}) = \frac{I_{ei}(\varphi, \Psi_{0i})[1 - \Theta'_a(\varphi)]}{I_O(\varphi_b) + [1 - \Theta'_a(\varphi)]I_{ei}(\varphi, \Psi_{0i})}, \quad (24)$$

$$\Theta_{ai}(\varphi, \Psi_{0i}) = [1 - \Theta_{ei}(\varphi, \Psi_{0i})] \Theta'_a(\varphi),$$

$$I_{ei}(\varphi, \Psi_{0i}) = I_0 \exp \left[ -\frac{2\Psi^2/kT}{ze(\varphi - \varphi_0) + \Psi_{0i} - \Psi} \right],$$

$$j_i(\varphi, \Psi_{0i}) = \Theta_{ai}(\varphi, \Psi_{0i})K_i(\varphi) + [I_O(\varphi_b) + i_O(\varphi_b)]\Theta_{ei}(\varphi, \Psi_{0i}).$$

The formulas (23) and (24) together determine the total coverage  $\Theta_e(\varphi)$  of the surface  $S$  with the two-dimensional passivating oxide layer and the total anodic current density  $i_a(\varphi)$  within the region of the active–passive transition. The system of equations (23), (24) and (21a) gives rise to

$$\Theta_e(\varphi) = \int_{\varepsilon_{\min}}^{\varepsilon_{\max}} d\Psi_{0i} f(\Psi_{0i}) \Theta_{ei}(\varphi, \Psi_{0i}),$$

$$i_a(\varphi) = \int_{\varepsilon_{\min}}^{\varepsilon_{\max}} d\Psi_{0i} f(\Psi_{0i}) j_i(\varphi, \Psi_{0i}),$$

$$i_A(\varphi) = \frac{K_a(\varphi)K_i(\varphi)}{K_a(\varphi) + K_i(\varphi)},$$

$$i_a(\varphi) = i_A(\varphi)[1 - \Theta_e(\varphi)] + [I_O(\varphi_b) + i_O(\varphi_b)]\Theta_e(\varphi),$$

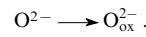
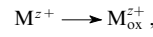
where  $i_A(\varphi)$  corresponds to the current density of the active dissolution of those parts of the metal surface, which are not covered by passivating two-dimensional nuclei.

The latter expression represents the general formula for the calculation of the dissolution current  $i_a(\varphi)$  over the whole range of the potential. The calculations using this formula (see the dashed line in Fig. 1) agree with the experimental data.<sup>26</sup>

The functions  $i_A(\varphi)$  and  $\Theta_e(\varphi)$  play the key role in the prepassive region  $\varphi < \varphi_0$ . According to calculations, it is the active dissolution that makes the dominant contribution to the total anodic current  $i_a(\varphi)$  before the maximum of the polarisation curve (*i.e.*, at  $\varphi < \varphi_0$ ) because  $\Theta_e(\varphi)$  is small and  $i_A(\varphi)$  becomes more important. After the maximum, *i.e.*, in the region of the active–passive transition, the coverage  $\Theta_e(\varphi)$  rapidly increases and the active dissolution is gradually replaced by the formation of two-dimensional nuclei. A continuous monolayer with  $\Theta_e \approx 1$  is completed at  $\varphi = \varphi_a$  and the passivity region itself starts afterwards ( $\varphi > \varphi_a$ ).

### III. Processes in a steady-state passivating oxide layer at $\varphi_a < \varphi < \varphi_p$

The processes proceeding in a passivating layer have been analysed in numerous studies.<sup>19, 22–25, 37–47, 55–59</sup> According to the concepts developed in these works, the structure of a PL consists of two interpenetrating ionic sublattices (metallic and oxygen). The ions electrodiffuse *via* vacancies in the respective sublattices. Overall, the composition of PL formed on hard metals (Fe, Ni, Cr, Cu, *etc.*), as has been mentioned above, corresponds to oxides  $M_nO_m$ . The ions constituting these oxides are marked with the subscript index ‘ox’, *i.e.*,



Positions of the PL and interfaces M–O and O–E are shown in Fig. 2. To provide stability of the PL, the interphase (crystal–electrolyte) equilibrium conditions should be met at the external interface O–E for both the cation and anion sublattices.<sup>19, 26, 27</sup> For a general case of an ionic crystal  $N_nP_m$ , these conditions are derived from the expressions for the ion current densities  $i_N$  and  $i_P$ .

$$i_N = \vec{k}_N \exp \left( \alpha_N \frac{z_N F}{RT} \varphi_b \right) - \overleftarrow{k}_N C_N \exp \left( -\beta_N \frac{z_N F}{RT} \varphi_b \right), \quad (25)$$

$$i_P = \vec{k}_P C_P \exp \left( \alpha_P \frac{z_P F}{RT} \varphi_b \right) - \overleftarrow{k}_P \exp \left( -\beta_P \frac{z_P F}{RT} \varphi_b \right),$$

$$\alpha_P + \beta_P = 1,$$

$$\alpha_N + \beta_N = 1,$$

where  $\vec{k}$  and  $\overleftarrow{k}$  are the rate constants of the direct and reverse reactions of the ion transfer into the electrolyte solution;  $\alpha$  and  $\beta$  are the transfer coefficients;  $C_N$ ,  $C_P$ ,  $z_N$  and  $z_P$  are the concentration and charge numbers, respectively, of ions  $N^{z_N+}$  and  $P^{z_P-}$  that constitute  $N_nP_m$  crystal;  $\varphi_b$  is the interface O–E potential.

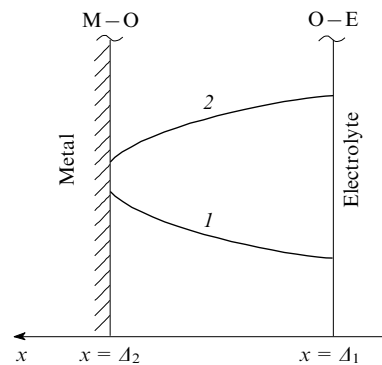


**Figure 2.** A scheme of ion concentration distributions  $N_M(x)$  (1) and  $N_O(x)$  (2) in a passivating layer.  $\delta(\varphi) = A_2 - A_1$ .

At the equilibrium, the currents  $i_N$  and  $i_P$  should be equal to zero, and the potential  $\varphi_b$  should have its equilibrium value  $\varphi_{pb}$ , *i.e.*,

$$\begin{aligned} i_N &= 0, \\ i_P &= 0, \\ \varphi_b &= \varphi_{pb}. \end{aligned}$$

This gives rise to the following two expressions for  $\varphi_{pb}$

$$\begin{aligned} \varphi_{pb} &= \frac{RT}{z_N F} \left( \ln \frac{\overleftarrow{k}_N C_N}{\overrightarrow{k}_N} \right), \\ \varphi_{pb} &= \frac{RT}{z_P F} \left( \ln \frac{\overleftarrow{k}_P}{\overrightarrow{k}_P C_P} \right). \end{aligned} \quad (26)$$

They are compatible provided that

$$\begin{aligned} C_N^n C_P^m &= \left( \frac{\overleftarrow{k}_N}{\overrightarrow{k}_N} \right)^n \left( \frac{\overleftarrow{k}_P}{\overrightarrow{k}_P} \right)^m, \\ z_N n &= z_P m. \end{aligned} \quad (27)$$

If these conditions are not met, no equilibrium is possible between the electrolyte and the ionic crystal and the latter disintegrates.

The situation is more complicated in the case of a PL. Indeed, since the anodic current is non-zero in the passivity region  $\varphi_a \leq \varphi \leq \varphi_p$ , which means that the passivated metal dissolves at a low rate, the metal sublattice of the PL appears non-equilibrium with respect to the electrode.

Notwithstanding, according to experiments, passivating layers are stable, and the anodic current does not depend on the potential in the range  $\varphi_a \leq \varphi \leq \varphi_p$  (see Fig. 1).

These experimentally established facts are only possible provided that two conditions are met. First, the oxygen sublattice should be in equilibrium with the electrolyte in a steady-state mode, *i.e.*, a partial equilibrium PL–electrolyte should be realised, which means that

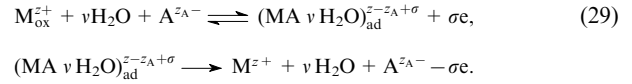
$$\begin{aligned} i_O &= 0, \\ i_M &\equiv i_a \neq 0, \end{aligned} \quad (28)$$

where  $i_O$  and  $i_M$  are the current densities of the  $O_{ox}^{2-}$  and  $M_{ox}^{z+}$  ions, respectively. Second, the transfer of the  $M_{ox}^{z+}$  ions from the PL to the electrolyte should be compensated for by their continuous supply from the bulk of the PL to its border (that is the interface O–E). The interface M–O serves as a source of the  $M_{ox}^{z+}$  ions.

Therefore, all the processes proceeding at the interfaces and in the bulk of the PL are self-consistent. Three components can be distinguished in the mechanism of a PL functioning, *viz.*, the interaction of the interface O–E with the electrolyte, which initiates detachment of the  $M_{ox}^{z+}$  ions from the PL lattice and their transfer into the electrolyte; the ion transfer through the bulk of PL described above; the processes at the interface M–O where the  $O_{ox}^{2-}$  ions diffuse into the metal and form new cells  $M_n O_m$ . These three components and the self-consistency between them have been considered elsewhere.<sup>19, 23–25</sup>

### 1. The interaction between metal and electrolyte at the interface oxide–electrolyte

Activating anions  $A^{zA-}$  and water molecules are adsorbed at the metal surface  $S$  and form molecular complexes  $(MA \cdot v H_2O)^{z-zA+\sigma}$  with the  $M_{ox}^{z+}$  ions. This is accompanied by weakening of binding of the surface sites  $M_{ox}^{z+}$  with the surface itself, *i.e.*, the energy barrier to their transfer into the electrolyte is decreased. The molecular complexes are characterised by a mean lifetime  $\tau$  on the metal surface; the  $M^{z+}$  ions constituting the complexes detach from the surface and pass into the electrolyte. The mechanism of the surface disintegration (anodic dissolution) can be represented with a two-step scheme



The  $A^{zA-}$  species and  $H_2O$  molecules manifest catalytic activity, and the resultant current density  $i_a$  of the  $M^{z+}$  ions in the steps (29) (that is the number of the elementary acts of the particle detachment per s per  $cm^2$ , *i.e.*,  $i_a \sim 1/\tau$ ) is given by

$$i_a \simeq k N_M [A^{zA-}] \exp \left[ - \frac{\varepsilon - \alpha(z - \sigma) F \varphi_b}{RT} \right], \quad (30)$$

where  $k$  is the rate constant of the second step of the reaction (29);  $N_M \simeq 10^{16} \text{ cm}^{-2}$  is the concentration of the  $M_{ox}^{z+}$  ions on the surface  $S$ ;  $\varepsilon$  is the binding energy of the complexes, which depends on the existence of  $A^{zA-}$ ;  $\alpha$  is the transfer coefficient describing the asymmetry of the potential drop ( $\alpha < 1$ ). The involvement of the  $A^{zA-}$  anions from the electrolyte in the elementary acts of the anodic dissolution has been established experimentally.

The equilibrium exchange of the oxide ions between the PL and the electrolyte, which provides the stability of the PL, is the second stationary process proceeding on the metal surface<sup>26</sup>



This exchange realises a partial equilibrium between the electrolyte and the PL. It determines the equilibrium potential  $\varphi_{pb} = \varphi_b$  of the passive region, and, consequently, independence of the current corresponding to the anodic dissolution of the passivated metal of the anode potential. Water molecules dissociating upon adsorption on the metal surface serve as a source of ions in the process (31). A more detailed scheme of the oxide ion exchange is given below:



the overall process can be represented as



The current density corresponding to the reaction (33) is described by the equation

$$i_O = \overrightarrow{k} [H_2O] N_M \exp \left( \frac{\alpha_O z_O F \varphi_b}{RT} \right) - \overleftarrow{k} N_O [H^+]^2 \exp \left( - \frac{\beta_O z_O F \varphi_b}{RT} \right),$$

where  $N_M$  and  $N_O$  are the surface concentrations of the  $M_{ox}^{z+}$  and  $O_{ox}^{2-}$  ions, respectively, on the metal surface,  $\alpha_O + \beta_O = 1$ ,  $z_O = 2$ . If the equilibrium (33) is reached, then

$$\begin{aligned} i_O &= 0, \\ \varphi_b &= \varphi_{pb}. \end{aligned} \quad (34)$$

This gives rise to

$$\varphi_{pb} = \frac{RT}{z_O F} \ln \left( \frac{\overleftarrow{k}}{\overrightarrow{k}} \frac{N_O}{N_M} \frac{[H^+]^2}{[H_2O]} \right). \quad (35)$$

The value of  $\varphi_{pb}$  can be estimated using the following relations:<sup>19</sup>

$$\begin{aligned} \varphi &= \varphi_{pb} + \Delta\varphi, \\ \Delta\varphi &= E\delta(\varphi), \\ E &= \frac{\varphi_p - \varphi_{pb}}{\delta_p}, \end{aligned} \quad (35a)$$

where  $\Delta\varphi$  and  $E$  are the potential drop and decrease in the electric field strength within the PL;  $\delta_p$  is the thickness of the PL at  $\varphi = \varphi_p$  (see Fig. 1).

The equation (35a) gives rise to

$$\varphi_{pb} = \frac{\varphi_a \delta_p - \varphi_p \delta_a}{\delta_p - \delta_a}, \quad (35b)$$

where  $\delta_a$  is the thickness of the PL in the beginning of the passive region.

Since the equilibrium interphase potential (35) is constant in the passive region  $\varphi_a \leq \varphi \leq \varphi_p$ , the thickness of the PL depends on  $\varphi$ . It can be determined using the Güntersulz formula for the current density of the  $M^{z+}$  ions through the interface M–O,

$$i_b = i_{b0} \exp(\beta E), \quad (36)$$

where

$$E = \frac{\varphi - \varphi_{pb}}{\delta(\varphi)},$$

$$\beta = \alpha_b a_M \frac{zF}{RT},$$

$\alpha_b$  is the transfer coefficient at the interface PL–metal, and  $a_M$  is the sublattice constant of the PL. In a steady-state mode, flows of the metal ions through the interfaces M–O and O–E are the same, *i.e.*,

$$i_a = i_b. \quad (37)$$

The equations (30), (36) and (37) give rise to

$$\delta(\varphi) = \beta \frac{\varphi - \varphi_{pb}}{\ln(i_a/i_{b0})}. \quad (38)$$

A surplus potential drop  $\Delta\varphi = \varphi - \varphi_{pb}$  is realised on a thickness  $\delta(\varphi)$ .

## 2. Ion transfer in the bulk of the passivating layer

When an  $M_{ox}^{z+}$  metal ion passes from the PL lattice to the electrolyte, its original bonds to the neighbouring  $O_{ox}^{2-}$  counterions are broken, and thus the oxide unit cell is destroyed. This gives rise to a gradual drift of the interface O–E towards metal in a steady-state mode. Simultaneously, the dynamical equilibrium (31) is realised and consequently the anion composition of the PL remains constant.

At the inner interface M–O, the  $O_{ox}^{2-}$  ions constantly diffuse into the metal structure forming new PL cells and compensating for their disappearance from the outer interface O–E. The diffusion rate is determined by the formula for the current density  $i_b$  of the  $M^{z+}$  ions [see formula (36)]. The emerging oxide cells replace the metal M, which means that the metal is converted layer-by-layer into oxide. A part of the  $M^{z+}$  metal ions located near the interface M–O are transferred through it to the PL and converted into the  $M_{ox}^{z+}$  ions, which further migrate *via* vacancies of the metal sublattice towards the electrolyte. As a result, the near-interface area of the metal is enriched with vacancies, which are required for diffusion of the  $O_{ox}^{2-}$  ions into the metal lattice.

These processes result in a drift of the interface M–O towards the metal. If a metal layer with a thickness of  $\Delta x$  disappears for a time  $\Delta t$ , the interface M–O also drifts by  $\Delta x$  at a velocity of

$$v = \frac{\Delta x}{\Delta t} = \frac{i_b}{z_M F} \frac{\mu}{\rho_0}, \quad (39)$$

where  $\mu$  and  $\rho_0$  are the amount (in moles) and density of the metal, respectively. The whole anionic composition of the PL, *i.e.*, its oxygen sublattice, drifts together with the interface.

Thus the  $M_{ox}^{z+}$  and  $O_{ox}^{2-}$  ions move in the bulk of the PL in the opposite directions. This provides self-consistency in the kinetic and structural interrelations between the interfaces O–E and M–O.<sup>37–43</sup> The ratio of the electrodiffusion flows of these ions is determined by the strengths of their interactions with the electrolyte and the metal.

Thus, the mutually compensating processes of the PL formation and disintegration proceed at the interfaces O–E and M–O in the steady-state mode. The thickness of the PL remains constant at a level sufficient to make a surplus potential drop

$\Delta\varphi = \varphi - \varphi_{pb}$ , where  $\varphi_{pb}$  is the potential of the interface O–E, which remains constant over the whole passive region. As a result, the current density  $i_a$  corresponding to the transfer of the  $M_{ox}^{z+}$  ions into the electrolyte is independent of the anode potential. The ion transfer through the bulk of the PL proceeds by the mechanism of electrodiffusion in a strong electric field (in strong electric fields, the Ohm law is violated), this results in a specific concentration distribution of the  $M_{ox}^{z+}$  and  $O_{ox}^{2-}$  ions and non-equilibrium vacancies over the PL lattice. The ions move *via* vacancies of their own sublattices, their occurrence in foreign sublattices can be considered as fluctuations, since the own sublattices provide sufficient amount of free sites. In this context, the anion and cation sublattices can be regarded as closed subsystems.

### a. Electric field in the passivating layer

Let us introduce the following notations  $N_M(x)$ ,  $N_O(x)$ ,  $N_{Mv}(x)$  and  $N_{Ov}(x)$  for the concentrations of the  $M_{ox}^{z+}$  and  $O_{ox}^{2-}$  ions and the non-equilibrium vacancies of the metal  $V_M(x)$  and oxygen  $V_O(x)$  in the respective sublattices of the PL, respectively, *i.e.*,

$$N_M = [M_{ox}^{z+}], \quad (40)$$

$$N_O = [O_{ox}^{2-}],$$

$$C_M(x) = \frac{N_{Mv}}{N_{Mg}}, \quad (40a)$$

$$C_O(x) = \frac{N_{Ov}}{N_{Og}},$$

where  $N_{Mg}$  and  $N_{Og}$  are the densities of the total number of sites in the cation and anion sublattices

$$N_{Mg} = N_M(x) + N_{Mv}(x), \quad (41)$$

$$N_{Og} = N_O(x) + N_{Ov}(x).$$

The bulk charge density  $\rho(x)$  in the PL can be represented as a sum of the ion and electron terms<sup>55–57</sup>

$$\rho(x) = \rho_i(x) + \rho_e(x),$$

where

$$\rho_i(x) = e[z_M N_M(x) - z_O N_O(x)],$$

$$\rho_e(x) = -e C_e(x),$$

$C_e(x)$  is the electron concentration in the PL. The electric field potential in a layer  $\varphi_1(x)$  is given by the Poisson equation

$$\frac{d^2 \varphi_1(x)}{dx^2} = -\frac{4\pi}{\varepsilon_1} \rho(x),$$

$$\varphi_1(A_1) = \varphi_{pb},$$

$$\varphi_1(A_2) = \varphi,$$

$$A_1 \leq x \leq A_2(\varphi),$$

$\varepsilon_1$  is the dielectric constant of the PL,  $A_1$  and  $A_2$  are coordinates of the interfaces O–E and M–O, respectively (see Fig. 2). A solution of the Poisson equation can be written as

$$\varphi_1(Z) = \varphi_{pb} + (\varphi - \varphi_{pb})Z + \Phi_0 Q_0(Z), \quad (41a)$$

where

$$Z = \frac{x - A_1}{\delta(\varphi)},$$

$$\delta(\varphi) = A_2(\varphi) - A_1,$$

$$0 \leq Z \leq 1,$$

$$\Phi_0 = \frac{4\pi F z_M}{\varepsilon_1} \left( \frac{N_{Mg}}{N_A} \right) \delta^2(\varphi),$$

( $N_A$  is the Avogadro number),

$$Q_0(Z) = \int_0^Z d\eta \int_0^\eta d\xi \bar{\rho}(\xi) - Z \int_0^1 d\eta \int_0^\eta d\xi \bar{\rho}(\xi), \quad (41b)$$

$$\bar{\rho}(Z) = n_M(Z) - n_O(Z) - n_e(Z),$$

$$n_M(Z) = \frac{N_M(Z)}{N_{Mg}},$$

$$n_O(Z) = \frac{N_O(Z)}{N_{Og}},$$

$$n_e(Z) = \frac{C_e(Z)}{z_M N_{Mg}}.$$

The parameter  $\Phi_0 \sim \delta^2(\varphi)$  is small and thus the last term in the equation (41a) can be neglected. In the physical sense, this is due to the fact that the field of the bulk charge in the PL is small as compared to the field induced by the interphase potential drop. Taking this into account, the electric field strength in the PL can be rewritten as

$$\vec{E} = -k_0 \left[ -\frac{\partial \varphi_1(Z)}{\partial x} \right],$$

and

$$\frac{\partial \varphi_1(Z)}{\partial x} \simeq \frac{\varphi - \varphi_{pb}}{\delta(\varphi)},$$

which is in agreement with the expressions (36) and (38).

#### b. Electrodiffusion of ions of the passivating layer in a strong electric field

The ion transfer in a PL is determined<sup>37, 55–59</sup> by the kinetics of the  $M_{ox}^{+}$  ions transfer into the electrolyte and diffusion of the  $O_{ox}^{2-}$  ions into the metal. Owing to the transfer, specific concentration distributions of the  $N_M(x, t)$  and  $N_O(x, t)$  ions (see Fig. 2) and  $N_{Mv}(x, t)$  and  $N_{Ov}(x, t)$  vacancies are settled, which depend on the anode potential  $\varphi$ . They characterise the concentration of point defects in the PL, i.e.,  $C_M$  and  $C_O$  [see relations (40a)].

The defectiveness determines the stability of the PL structure. If the critical value  $C_c$  is exceeded, the structure disintegrates. This is achieved at a potential  $\varphi_p$ , which corresponds to the transpassive transition (see Fig. 1). Theoretical estimation of the values of  $\varphi_p$  and  $\varphi_a$  is one of the most important problems.<sup>60–72</sup>

The expressions for the electrodiffusion flows  $j_M$  and  $j_O$  of the  $M_{ox}^{+}$  and  $O_{ox}^{2-}$  ions through the PL lattice assume a strong electric field  $E$ . The ions move *via* vacancies of their own sublattices. The sum of flows of ions  $j_M(x)$  and  $j_O(x)$  and non-equilibrium vacancies  $j_{Mv}(x)$  and  $j_{Ov}(x)$  is equal to zero

$$j_M(x) + j_{Mv}(x) = 0, \quad (42)$$

$$j_O(x) + j_{Ov}(x) = 0.$$

A microscopic-level scheme of ion hopping between the neighbouring atomic planes separated by interatomic distances  $a_M$  and  $a_O$  can be applied<sup>19, 37</sup> to determine  $j_M(x)$  and  $j_O(x)$ . Typically, three consecutive atomic planes I, II and III with coordinates  $x$  and  $x \pm a$  (Fig. 3) are considered within a PL lattice. The probabilities of direct and reverse ion jumps between them are proportional to the concentrations  $N_M(x)$  or  $N_O(x)$ , to the number of unoccupied sites in the respective planes [i.e., concentrations  $C_M(x)$  and  $C_O(x)$ ] and to the activation energy of the jumps  $W_0$ . An electric field  $E$  decreases the activation energy  $W_0$  by  $\pm azFaeE$  (or, on the contrary, increases, if an ion moves against the field direction).<sup>37</sup> Taking this into account, the required flows of cations  $j_M(x)$  and anions  $j_O(x)$  can be represented as sums of the flows corresponding to direct and reverse jumps

$$j_M(x) = j_{II \rightarrow III}^M - j_{III \rightarrow II}^M, \quad (43)$$

$$j_O(x) = j_{I \rightarrow II}^O - j_{II \rightarrow I}^O.$$

The equations for  $j_M$  and  $j_O$  can be rewritten explicitly

$$j_M = a_M v \left[ N_M(x) C_M(x + a_M) \exp\left(-\frac{W_{M0} + \Delta W_M}{kT}\right) - N_M(x + a_M) C_M(x) \exp\left(-\frac{W_{M0} - \Delta W_M}{kT}\right) \right], \quad (44)$$

$$j_O = a_O v \left[ N_O(x - a_O) C_O(x) \exp\left(-\frac{W_{O0} + \Delta W_O}{kT}\right) - N_O(x) C_O(x - a_O) \exp\left(-\frac{W_{O0} - \Delta W_O}{kT}\right) \right], \quad (44a)$$

where  $v$  is the number of vibrational periods of ions in occupied sites;  $\Delta W_M$  and  $\Delta W_O$  are the changes in the energy barriers for ion hopping between the planes I–III (see Fig. 3) when the electric field with a strength  $E$  is applied.

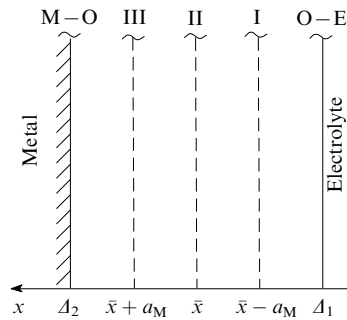


**Figure 3.** An arrangement of the atomic planes I–III in a passivating layer;

$a_M$  is the interatomic distance within the metallic sublattice ( $a_O$  is the respective distance within the oxygen sublattice).

By expanding the functions  $N_M(x \pm a_M)$ ,  $C_M(x \pm a_M)$ ,  $N_O(x \pm a_O)$  and  $C_O(x \pm a_O)$  into series and taking only linear terms, the following final expressions for  $j_M$ ,  $j_O$ , diffusion coefficients ( $D_M$  and  $D_O$ ),  $\Delta W_M$  and  $\Delta W_O$  can be obtained

$$j_M \simeq -\frac{D_M}{a_M} C_M N_M - D_M C_M \frac{\partial N_M}{\partial x}, \quad \frac{\partial N_M}{\partial x} > 0, \quad (45)$$

$$j_O \simeq \frac{D_O}{a_O} C_O N_{MO} - D_O C_O \frac{\partial N_O}{\partial x}, \quad \frac{\partial N_O}{\partial x} < 0, \quad (45a)$$

$$D_M = a_M^2 v \exp\left(-\frac{W_{M0} - \Delta W_M}{kT}\right),$$

$$D_O = a_O^2 v \exp\left(-\frac{W_{O0} - \Delta W_O}{kT}\right),$$

$$\Delta W_M = \alpha_M z_M a_M e E,$$

$$\Delta W_O = \alpha_O z_O a_O e E,$$

$$z_O = 2.$$

The flows of non-equilibrium vacancies can be determined using these equations together with the condition (42).

The concentrations  $N_M(x, t)$  and  $N_O(x, t)$  of the  $M_{ox}^{+}$  and  $O_{ox}^{2-}$  ions contained in the formulas (45) are determined by equations of their hopping migration

$$\frac{\partial N_M}{\partial t} = -\frac{\partial j_M}{\partial x}, \quad (46)$$



$$\frac{\partial N_O}{\partial t} = -\frac{\partial j_O}{\partial x},$$

$$\Delta_1(t) \leq x \leq \Delta_2(t),$$

$$\Delta_2(t, \varphi) - \Delta_1(t) = \delta(t, \varphi).$$

The concentrations of the  $M_{ox}^{z+}$  and  $O_{ox}^{2-}$  ions at the interfaces M–O and O–E are equal to  $N_{M2} \equiv N_M(\delta)$  and  $N_{O1} \equiv N_O(0)$ , respectively, whereas the concentrations of their vacancies  $N_{Mv2}$  and  $N_{Ov1}$  at the same interfaces are interrelated through the following expressions

$$N_{M2} = N_{M0} - N_{Mv2},$$

$$N_{O1} = N_{O0} - N_{Ov1}.$$

The interface M–O serves as a source of the  $M_{ox}^{z+}$  ions and a sink of the cation vacancies. Similarly, the interface O–E serves as a source of the  $O_{ox}^{2-}$  ions and a sink of the anion vacancies. Therefore,

$$N_{Mv2} \ll N_{M2} \simeq N_{M0},$$

$$N_{Ov1} \ll N_{O1} \simeq N_{O0}.$$

For a steady-state mode, the system of equations (44)–(46) can be reduced to two equations for concentrations of non-equilibrium cation and anion vacancies  $C_M(x)$  and  $C_O(x)$  within the respective sublattices of the PL [ $0 \leq x \leq \delta(\varphi)$ ]<sup>19</sup>

$$\frac{D_M}{a_M} C_M(1 - C_M) - D_M C_M \frac{dC_M}{dx} + v(1 - C_M) = v \frac{N_{met}}{N_{M0}}, \quad (47)$$

$$-\frac{D_O}{a_O} C_O(1 - C_O) - D_O C_O \frac{dC_O}{dx} + v(1 - C_O) = 0,$$

$$C_M(0) \equiv C_{M1}, \quad C_M(\delta) \equiv C_{M2} \sim 0,$$

$$C_O(0) \equiv C_{O1} \simeq 0, \quad C_O(\delta) \equiv C_{O2},$$

where  $v$  is the velocity of the interface M–O drift,  $N_{met}$  is the concentration of occupied sites in the metal lattice.

These vacancies induce an electrical charge and strains in the PL structure and determine its point defectiveness, which in turn determines the dimension of the passive region, *i.e.*, the value of the anode potential  $\varphi = \varphi_p$ .

Actually, the point defectiveness of a PL cannot exceed a certain threshold depending on the strength of the PL ionic structure. Thus, there is a critical, *i.e.*, the maximum possible value  $C_c = (C_M)_{max}$  of the concentration  $C_M(x)$ . When the critical concentration is exceeded, the dependence of the thickness of the passivating layer on the anode potential [see equation (38)] is violated, which actuates the transpassive transition (transpassivation) observed at  $\varphi = \varphi_p$ . The theoretical prediction of  $\varphi_p$  as a function of the characteristic parameters of a passivating system is a key challenge to a passivation theory.

The critical defectiveness is reached at  $\varphi = \varphi_p$  at the interface O–E since it serves as a source of vacancies of the cation sublattice. In order to find  $\varphi_p$ , one can determine the functions  $C_M(x)$  and  $C_O(x)$  from the equation (47) and then set  $C_{M1} = C_M(0)$ . Additionally, it should be taken into account that  $C_M(x) \ll 1$ ,  $C_O(x) \ll 1$ . In this case,

$$\int_0^\delta C_M(x) dx + \frac{a_M}{2} C_{M1}^2 \simeq v \frac{a_M \delta}{D_M} \left( \frac{N_{met}}{N_{M0}} - 1 \right), \quad (48)$$

$$\int_0^\delta C_O(x) dx + \frac{a_O}{2} C_{O2}^2 \simeq v \frac{a_O \delta}{D_O}.$$

An approximate solution of the first equation gives

$$2 C_{M1} + C_{M1}^2 - 2q\delta = 0,$$

where

$$q = \frac{v}{D_M} \left( \frac{N_{met}}{N_{M0}} - 1 \right).$$

For instance, in the case of a system Fe in 1 M  $H_2SO_4$  (see Refs 73 and 74), which is characterised by the following parameters  $D_M \simeq 0.5 \times 10^{-16} \text{ cm}^2 \text{ s}^{-1}$ ,  $z_M \simeq 3$ ,  $\alpha_M \simeq 0.5$ ,  $i_b \simeq 10^{-6} \text{ A cm}^{-2} \text{ s}^{-1}$ ,  $\delta \sim 10^{-7} \text{ cm}$ , the equation is transformed into

$$C_{M1} = q\delta(\varphi). \quad (49)$$

### c. Transpassive transition

The equation (49) implies that the maximum possible defectiveness  $C_c$  corresponds to the ultimate thickness of the passivating layer  $\delta_p$  exactly at the potential of the transpassive transition  $\varphi_p$

$$\delta_p = \frac{C_c}{q}. \quad (50)$$

A study of the stability of a lattice with respect to its point defectiveness for the case of a cubic packing of black and white balls has established that  $C_c \simeq 0.2$ , since the long-range order disappears at  $C > 0.2$ .<sup>75</sup>

An expression for the required  $\varphi_p$  can be obtained from the equations (50), (36) and (38). Indeed, the value of the anode potential corresponding to the oxygen equilibrium  $\varphi_{pb}$ , which is contained in the equation (38), can be estimated using the equation (35b). This gives rise to

$$\varphi_p = \varphi_{pb} + \frac{\delta_p}{\beta} \ln \left( \frac{i_a}{i_{b0}} \right), \quad (51)$$

$$\beta = \alpha_b a_M \frac{zF}{RT},$$

$\delta_a$  is the thickness of the PL in the beginning of the passive region ( $\varphi = \varphi_a$ ), where the PL can be regarded as a monolayer.

Thus, the equations (51), (35b) and (50) comprise a system of three equations with three unknowns, *viz.*,  $\varphi_p$ ,  $\varphi_{pb}$  and  $\delta_p$ . Solving this system, for instance, for M = Fe, yields:  $\varphi_{pb} \simeq 0.4 \text{ V}$ ,  $\varphi_p \simeq 1.6 \text{ V}$ ,  $\delta_p \simeq 2 \times 10^{-7} \text{ cm}$ , which is in agreement with the experimental data.<sup>26</sup>

## 3. The interface metal–oxide

### a. Interphase reactions

As has been shown above, the incorporation of near-boundary  $O_{ox}^{2-}$  ions belonging to the anion sublattice of the PL into the metal is the main process proceeding at the interface M–O. The anions react with the  $M^{z+}$  cations forming new unit cells of the passivating oxide  $M_n O_m$  and giving rise to a drift of the interface M–O at a velocity  $v$  [see equation (39)].

To form a new cell, an  $O_{ox}^{2-}$  ion should pass an interatomic distance  $a_O$  typical of the anion sublattice structure and cross the interface M–O, so that a potential drop  $\Delta\varphi = a_O E$  is overcome. The electric field  $E$  decreases the transition barrier by  $\Delta U = \alpha_O z_O a_O e E$ .

The probability of oxygen incorporation is proportional to the number of unoccupied sites in the near-boundary layer of the metal  $\Delta M$ , which is equivalent to the concentration  $C_{met}$  of vacancies in the lattice  $\Delta M$ . The respective current density of incorporation  $i_{b0}$  is ( $m/n = z/2$ )

$$i_{b0} = i_{b0}^0 C_{met}^{z/2} \frac{N_{O2}}{N_{Og}} f(U) \exp(\beta_O E), \quad (52)$$

$$\beta_O = \alpha_O z_O a_O \frac{F}{RT},$$

$$E = \frac{\varphi - \varphi_{pb}}{\delta(\varphi)},$$

$$C_{\text{met}} = \frac{N_{\text{vmet}}}{N_{\text{g}}},$$

$$N_{\text{g}} = N_{\text{met}} + N_{\text{vmet}},$$

where, as before,  $N_{\text{O}_2^-}$  is the concentration of the  $\text{O}_{\text{ox}}^{2-}$  ions at the interface M–O;  $N_{\text{met}}$ ,  $N_{\text{vmet}}$  and  $N_{\text{g}}$  are the concentrations of metal atoms and vacant sites in the metal lattice and their sum, respectively. The transfer coefficient  $\alpha_{\text{O}}$  characterises the asymmetry of the energy barrier  $\Delta U$ ;  $f(U)$  is the term describing the ordering process within  $\Delta M$ .

Due to conversion of the metal into the oxide, an oxide layer with a thickness  $\Delta_{\text{ox}}$  and a number of the  $\text{M}_{\text{ox}}^{z+}$  cations  $\Delta N_1$  appears in place of the starting boundary layer  $\Delta M$  with a number of metal atoms  $\Delta N$ . In general, thicknesses of the layers  $\Delta M$  and  $\Delta_{\text{ox}}$  are different. As has been mentioned above, the spatial balance is kept due to the subsystem of vacancies.<sup>19</sup>

Evidently,  $\Delta N_1 < \Delta N$ . Consequently, only a part of ions from  $\Delta N$  is involved in the formation of oxide in the layer  $\Delta_{\text{ox}}$ . The remaining part  $\Delta N_2 = \Delta N - \Delta N_1$  is surplus and should move away through the interface M–O into the PL and further to the electrolyte. This is the only way to keep the spatial balance in the layer  $\Delta M$ . Meanwhile, the continuous transfer of the  $\text{M}_{\text{ox}}^{z+}$  ions should proceed in the PL by the mechanism of hopping migration in a strong electric field, as discussed above.

Consequently, the total current  $i_{\text{b}}$  of the metal disintegration (or anode dissolution) specified in the formula (36) can be subdivided into the current of the  $\text{M}_{\text{ox}}^{z+}$  ion transfer through the PL  $i_{\text{bM}}$  and the current  $i_{\omega}$  corresponding to the formation of oxide cells within the layer  $\Delta M$ . The latter is determined by the number of bonds between the  $\text{M}^{z+}$  ions and incorporated oxide ions formed per second in the layer  $\Delta M$ , which generate  $\omega$  new cells in each unit volume, *i.e.*,

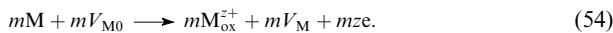
$$\Delta N_1 + \Delta N_2 = \Delta N, \quad (53)$$

$$i_{\text{bM}} + i_{\omega} = i_{\text{b}},$$

for meaning of  $i_{\text{b}}$ , see the formula (36).

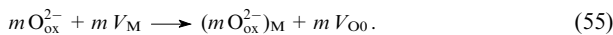
The formation mechanism of new cells  $\text{M}_n\text{O}_m$  based on the vacancy model of the interphase processes has been considered elsewhere.<sup>19,37</sup> To form a cell,  $m \text{O}_{\text{ox}}^{2-}$  ions should diffuse from the PL to the layer  $\Delta M$  leaving  $m$  anion vacancies in the PL layer. This requires availability of  $m$  vacant sites  $V_{\text{M}}$  within the lattice  $\Delta M$ , which can be generated only as a result of preceding transition of  $m$  out of  $\Delta N_2$  ions  $\text{M}^{z+}$  into the PL. These incoming ions occupy  $m$  cation vacancies within the cation sublattice of the PL (which are in turn transferred from the interface O–E by the flow of vacancies) and move towards the electrolyte. The flows of vacancies  $j_{\text{Mv}}$  and  $j_{\text{Ov}}$  are generated due to the hopping migration of the  $\text{M}_{\text{ox}}^{z+}$  and  $\text{O}_{\text{ox}}^{2-}$  ions in the opposite directions within the PL.

Thus, the formation of an oxide cell  $\text{M}_n\text{O}_m$  is described by a scheme involving several steps. In the first step,  $m \text{M}^{z+}$  ions pass from the metal lattice to the PL being converted into  $\text{M}_{\text{ox}}^{z+}$  ions and leaving  $m$  vacancies  $V_{\text{M}}$  in originally occupied sites, which can be written as



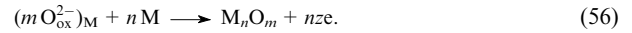
The vacancies  $V_{\text{M0}}$  appear at the interface M–O owing to their hopping migration from the source, *viz.*, the external interface O–E. New  $\text{M}_{\text{ox}}^{z+}$  ions migrate in the opposite directions, *i.e.*, towards the interface O–E, which serves as their sink.

In the second step,  $m \text{O}_{\text{ox}}^{2-}$  ions are incorporated into the metal, occupy vacancies  $V_{\text{M}}$  and are converted into the  $(\text{O}_{\text{ox}}^{2-})_{\text{M}}$  ions of the transition layer  $\Delta M$ , which can be represented as

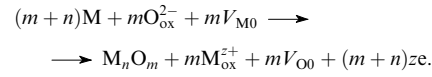


Vacancies  $V_{\text{O0}}$  are generated in the formerly occupied sites and then migrate towards the interface O–E.

In the third step, the ions within  $\Delta M$  undergo structural ordering, which results in the formation of an oxide cell  $\text{M}_n\text{O}_m$ , *i.e.*,



This process is quantified by the term  $f(U)$  in the equation (52). The overall process including the steps (54) and (56) can be written as



The above scheme implies that the conversion of vacancies and of their flows occurs at the interface M–O (Fig. 4), *viz.*,

$$V_{\text{M0}} \longrightarrow V_{\text{M}} \longrightarrow V_{\text{O0}},$$

$$j_{\text{Mv}} \longrightarrow j_{\text{Ov}},$$

so that the vacancies  $V_{\text{M}}$  act as mediators combining the processes (54) and (56).

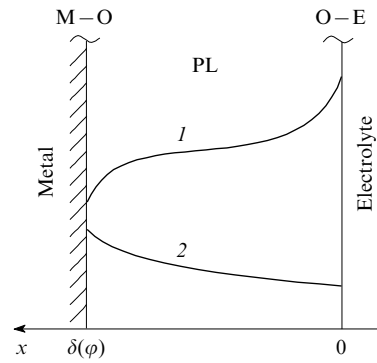


**Figure 4.** A scheme of concentration distributions of non-equilibrium vacancies in the cationic (1) and anionic (2) sublattices of a passivating layer.

## b. Current densities

According to the equation (52), the total current density of the metal anode dissolution can be represented as a sum of two terms. The first term is the current density  $i_{\text{bM}}$  corresponding to the transition of the  $\text{M}^{z+}$  ions from  $\Delta M$  to the PL, which gives rise to the generation of vacancies  $V_{\text{M}}$  within the layer  $\Delta M$  with the concentration  $C_{\text{met}}$ . The second term is the current density  $i_{\omega}$  corresponding to the formation of cells of  $\text{M}_n\text{O}_m$  in the layer  $\Delta M$  owing to the incorporation of the  $\text{O}_{\text{ox}}^{2-}$  ions at a velocity  $i_{\text{bO}}$ .

The parameters  $i_{\text{b}}$ ,  $i_{\text{bM}}$ ,  $i_{\text{bO}}$  and  $i_{\omega}$  are linked through a self-consistent relation<sup>19–25</sup> imposed by the reactions (54) and (55). Indeed, currents of these reactions are equal, since they represent currents of the formation of the vacancies  $V_{\text{M}}$  and simultaneously of their filling with the  $\text{O}_{\text{ox}}^{2-}$  ions, therefore, in a steady-state mode,

$$i_{\text{bM}} = i_{\text{bO}}. \quad (57)$$

If  $\omega$  oxide cells  $\text{M}_n\text{O}_m$  are formed in the unit volume of  $\Delta M$  per second, this consumes  $n\omega \text{M}^{z+}$  and  $m\omega \text{O}_{\text{ox}}^{2-}$  ions, which means that

$$i_{\omega} = n\omega ze, \quad (58)$$

$$z \equiv z_{\text{M}},$$

$$i_{\text{bO}} = m\omega 2e.$$

The required relation can now be derived from the equations (53), (57) and (58)

$$\begin{aligned}
i_w &= \frac{n}{\gamma m} i_{bO}, \\
i_{bO} &= i_{bM}, \\
i_b &= i_w + i_{bM} = \left( \frac{\gamma m + n}{\gamma m} \right) i_{bO}, \\
\gamma &= \frac{2}{z}, \\
i_{bO} &= i_{bO}^0 C_{\text{met}}^{z/2} \frac{N_{O_2}}{N_{O_0}} f(U) \exp(\beta_O E), \\
C_{\text{met}} &= \left\{ \frac{i_{bO} \exp[(\beta - \beta_O)E]}{i_{bO}^0 [(\gamma m + n)/\gamma m] (N_{O_2}/N_{O_0}) f(U)} \right\}^{2/z}.
\end{aligned}$$

This makes it possible to calculate the number of oxide cells  $M_nO_m$  appearing per second per  $\text{cm}^2$  of the interface  $M-O$

$$\omega = \frac{i_w}{n z e} = \frac{i_b}{(n + \gamma m) z e}.$$

For an oxide  $M_2O_3$ ,  $n = 2$  and  $m = 3$ .

The above mathematical approach is applicable to such metals as Fe, Ni, Cr, Mo, Cu, *etc.* Passivating layers on their surfaces are crystalline. In the case of the so-called valve metals (Ta, Ti, Al, Sn, Sb, *etc.*), the PL are characterised by amorphous structures. To allow for this, a statistical scatter in the interatomic distances and angular directions has to be taken into consideration. In such a case, coefficients in the transfer equations will be random quantities and the equations themselves will be stochastic.

The ion transfer also referred to as electrodiffusion, or hopping migration, plays an important role in the functioning mechanism of an oxide PL. It can be formulated as follows.

1. Ion flows provide kinetic and structural interrelations between the interfaces and enable occurrence of electrochemical reactions on them. This retains the ionic sublattices of the PL and ensures its stability.

2. Ion flows govern the growth of the layer  $\delta(\varphi)$  thickness. At any potential  $\varphi$ , a specific surplus potential  $\varphi - \varphi_{pb}$  is consumed so that the partial interphase equilibrium metal–electrolyte is maintained.

3. The concentration of vacancies increases with an increase in the thickness  $\delta(\varphi)$  and reaches its critical value  $C_c$  inducing the transpassive transition at  $\varphi = \varphi_p$ . Therefore, the ion transfer determines the extension of the passive region.

4. Ion transfer generates a subsystem of non-equilibrium vacancies, which maintains the spatial balance at the interface  $M-O$ .

In the case of metal alloys, which are the main engineering materials, the passivation process is more complicated. First, a border layer of the alloy appears, which is characterised by modified physical properties. Second, passivating oxide layer formed on the alloy surface contains at least three (in the case of a simple binary A–B alloy) rather than two components. An attempt to develop a theory for such a system has been undertaken<sup>19</sup> but the goal is still far from reach.

Unfortunately, outdated concepts are still employed in the studies devoted to the mechanisms of the electrode processes. The electrode surface is represented as an array of distributed microelectrodes forming galvanic pairs anode–cathode. Within this approach, fictitious electric circuits composed of a small group of atoms are considered and characterised with parameters applicable to macrocircuits, such as resistivity, current and so on.

#### IV. Other models of the passive state of metals

The mathematical model of passivating layers outlined above is based on the general thermodynamical principle stating that a stable passive state of a metal surface is only possible provided

that conditions of the interphase equilibrium between the passivating layer and the electrolyte are met. According to extensive investigations accomplished by the electrochemists of the German school,<sup>26–34</sup> this equilibrium is established due to the reaction



*i.e.*, due to the exchange of the oxide ions (that are formed upon dissociative adsorption of water) between water and the oxide sublattice of the PL. Transfer of the  $M_{ox}^{z+}$  ions from the metal sublattice is continuously compensated for by their supply from the metal substrate. The self-consistency of all the processes is determined by the value of the equilibrium interphase potential  $\varphi_{pb}$ . The following two equations

$$\begin{aligned}
\vec{k} [H_2O] \exp\left(\alpha_O z_{rmo} F \frac{\varphi_{pb}}{kT}\right) - \overleftarrow{k} [H^+]^2 \exp\left(-\beta_O z_O F \frac{\varphi_{pb}}{kT}\right) &= 0, \\
\alpha_O + \beta_O &= 1
\end{aligned}$$

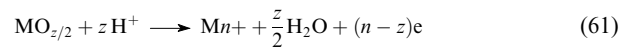
express the equality of the total numbers of the direct and reverse reaction events (59) occurring at a unit surface for 1 s. The self-consistency of the processes can be explained by the stability of anodically dissolvable (*i.e.*, thermodynamically non-equilibrium, in overall) oxide.

Attempts have been undertaken<sup>60–67</sup> to rationalise functioning of a PL in a different way assuming no interphase equilibrium. A few of them are briefly considered below. A mathematical model referred to as ‘self-adjusting dissolution of a passivated metal’<sup>63</sup> assumes simultaneous consistent changes in the anode potential  $\varphi$ , dissolution current density  $i$  and thickness of the passivating layer  $\delta(\varphi)$ .

The model is supposed to explain the independence of the stationary current density of the anode potential. It postulates that a PL and a double electrical layer (DEL) can be considered as series capacitors. In that case, the potential drops in the layer and DEL are inversely proportional to their capacities  $C_f$  and  $C_d$ , respectively,

$$\frac{\varphi - \varphi_b - \varphi_{12}}{\varphi_b} = \frac{C_d}{C_f}. \quad (60)$$

Here,  $\varphi_b$  is the DEL potential and  $\varphi_{12}$  is a suggested potential drop at the interface with the metal. The postulated inverse proportionality substitutes the condition of Vetter’s partial oxygen equilibrium (59). Another assumption is that the PL is dissolved according to the equation



and is formed at the opposite interface

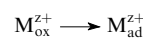
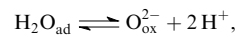


The rates of these reactions are described by the following expressions

$$i_1 = K_1 \exp\left[\frac{\alpha_1(n - z)F}{RT} \varphi_b\right], \quad (63)$$

$$i_2 = K_2 \exp\left(\frac{\alpha_O z_O F}{RT} aE\right),$$

where subscripts 1 and 2 denote the interfaces PL–electrolyte and PL–metal, respectively;  $a$  is the interatomic distance. It is also assumed that the reactions



are compatible provided that the exchange current of the first reaction exceeds substantially that of the second one.

This condition can be considered as unrealisable since the corrosion potential of a passivated metal sometimes manifests

sensitivity to the currents at levels comparable to the rate of corrosion and it is the equilibrium that adjusts itself to the potential  $\phi_b$  rather than *vice versa*.<sup>63</sup> It is also presumed that

$$C_f = \frac{\varepsilon_f}{\delta(\phi)},$$

$$C_d = \frac{\varepsilon_d}{\delta_d},$$

where  $\varepsilon_f$ ,  $\varepsilon_d$ ,  $\delta(\phi)$  and  $\delta_d$  are dielectric constants and thicknesses of the PL and DEL, respectively. Taking into account the above assumptions, the equation (60) is transformed into

$$\frac{\phi - \phi_b - \phi_{12}}{\phi_b} = \frac{\varepsilon_f}{\varepsilon_d} \frac{\delta(\phi)}{\delta_d}, \quad (64)$$

and the following equation is postulated for the film thickness

$$\delta(\phi) = \frac{\phi - \phi_{12} - \phi_b}{E}.$$

The system composed of the last two equations contains three unknowns, *viz.*,  $\delta(\phi)$ ,  $E$  and  $\phi_b$  at a fixed  $\phi_{12}$ . The equality of the steady-state rates of dissolution [see equation (63)] and formation of the passivating layer [see (61) and (62)] can be used as the third equation, *i.e.*,

$$i_1 = K_1 \exp\left[\frac{\alpha_1(n-z)F}{RT} \phi_b\right] = K_2 \exp\left(\frac{\alpha_O z_O F}{RT} aE\right) = i_2.$$

This gives rise to

$$\phi_b = \frac{RT}{\alpha_1(n-z)F} \ln\left(\frac{K_2}{K_1}\right) + \frac{\alpha_O z_O}{\alpha_1(n-z)} aE. \quad (65)$$

The system (60)–(65) is now closed with respect to the unknowns  $\phi_b$ ,  $E$  and  $\delta(\phi)$  provided that the value of  $\phi_{12}$  is known. After a few simplifying assumptions, these equations can be transformed into

$$\phi_b = \frac{RT}{F\alpha_O z_O} \ln\left(\frac{K_2}{K_1}\right) \left[ \frac{\varepsilon_d a}{\varepsilon_f \delta_d} - \frac{\alpha_2(n-z)}{\alpha_O z_O} \right]^{-1},$$

$$E = \frac{RT}{F\alpha_O z_O} \ln\left(\frac{K_2}{K_1}\right) \left\{ \frac{\varepsilon_d}{\varepsilon_f} \delta_d \left[ \frac{\varepsilon_d a}{\varepsilon_f \delta_d} - \frac{\alpha_2(n-z)}{\alpha_O z_O} \right]^{-1} \right\}.$$

The last two formulas are final since they are no more dependent on the potential drop  $\phi_{12}$ . Also note that the following expressions can be written instead of the equation (64)

$$\frac{\phi_p}{\phi_d} = \frac{Q_s}{Q_d} \frac{c_d}{c_p},$$

$$Q_s \neq Q_d,$$

$$Q_s + Q_d + Q_M = 0,$$

where  $\phi_d$  is the DEL potential,  $Q_s$  is the solution charge,  $Q_d$  is the DEL charge,  $c_d$  is the DEL capacity,  $c_p$  is the PL capacity,  $Q_M$  is the metal charge.

Other models do not require fulfilment of the condition of the interphase equilibrium between the passivated metal and water molecules of a solvent as regards oxygen ions. In the model proposed by Alekseev and Kolotykin,<sup>66</sup> no diffusion is considered and the current is assumed to be due to the migration of ions in a constant electric field. Respectively, the concentrations of ionic components in sublattices of the PL are independent of coordinates and identical at both interfaces. The neglect of diffusion decreases the order of the ion transfer equations; interfaces and the transpassive transition are described by the integration limits.

The above considerations support Vetter's suggestion<sup>26</sup> that the stability of a passivating layer is caused by the equilibrium exchange of oxygen ions between the PL anionic sublattice and the electrolyte. The existence of the metal sublattice of the PL is provided by a steady-state supply of the  $M^{z+}$  ions from the metal through the PL to the interface with the electrolyte. This compensates for continuous transfer of the  $M^{z+}$  ions into the electrolyte. Thus, the cation composition of a PL is continuously renewed, whereas the anion composition remains constant but constantly drifts following the dissolving metal surface. The oxygen equilibrium according to Vetter (32) coincides with the condition of the thermodynamical phase equilibrium.<sup>70–72</sup>

Admitting the fundamental character of studies performed by representatives of the German school of electrochemists, it however was noted that their suggestions on the chemical mechanism of dissolution of a passivated metal are erroneous. Actually, the mechanism is electrochemical in character, as has been demonstrated by Novakovsky and Likachev.<sup>68,69</sup> Therefore, it might be concluded that the experimental fundamentals of the passivity theory are laid by the combination of the two works cited above.<sup>26,68</sup>

## V. The adsorption and phase-film theories of passivity

The current understanding of the passive state of metals has been evolving over the entire time of its investigation. Originally, the adsorption and phase-film theories of passivity were widely adopted. Their experimental backgrounds have been summarised elsewhere.<sup>73–76</sup> The major postulates of the theories can be formulated as follows.

A general assumption that the passivation is caused by the interaction of the surface metal atoms with the oxygen of the adsorbed water molecules underlies the adsorption theory. This is based on the experimental data from polarisation measurements combined with dedicated studies of adsorption phenomena. It has been established that the current density of the anodic dissolution decreases manyfold when a small amount of oxygen ions forming only a fraction of an oxygen submonolayer is adsorbed.

The following adsorption schemes were considered in order to rationalise this experimental fact

$$(1 - \Theta)K_{ad} = \Theta K_i, \quad (66)$$

where

$$K_{ad} \sim \exp(\alpha_a \sigma \varepsilon),$$

$$K_i \sim [\beta_i(z_M - \sigma)\varepsilon],$$

$$\varepsilon = \frac{F\phi}{RT},$$

$$i_a = \Theta K_i,$$

$\Theta$  is the coverage of the metal surface with adsorption complexes formed as a result of the interaction between the surface metal atoms and the oxygen atoms of water molecules;  $K_{ad}$  is the rate of formation of these complexes;  $K_i$  is the rate of transfer of the complexes to the solution;  $\varepsilon$  is a dimensionless potential;  $\sigma$  is the fraction of partially transferred charge;  $i_a$  is the transition current density. The equation (66) gives rise to

$$i_a = \frac{K_{ad} K_i}{K_{ad} + K_i}. \quad (67)$$

This equation clearly shows that the equation (66) cannot reproduce the shape of the polarisation curve shown in Fig. 1 for any possible combination of  $K_{ad}$  and  $K_i$ . Indeed, only three cases are possible.

1.  $K_{ad} \sim K_i$ ; the rates of formation and dissolution of the complexes are similar; consequently,  $i_a \approx K_i$  or  $i_a \approx K_{ad}$ ; the dissolution current increases exponentially with an increase in

the potential so that no active – passive and passive transitions can be identified in the polarisation curve.

2.  $K_{ad} \gg K_i$ ; the dissolution step is rate-limiting. In this case, the dependence of the dissolution current on the potential is the same as above.

3.  $K_{ad} \ll K_i$ ; the adsorption step is rate-limiting and  $i_a \sim K_{ad}$ ; the situation remains the same: no passivity region can be identified.

The conclusion on the impossibility of identification of an extended passivity region in the polarisation curve based on the equation (66) directly follows from the equation (67). Since the passivity region is characterised by  $i_a = \text{const}$ , the equation (67) can be represented in an algebraic form with respect to the potential  $\varphi$

$$\frac{K_{ad}(\varphi)K_i(\varphi)}{K_{ad}(\varphi) + K_i(\varphi)} = \text{const}, \quad (68)$$

the equality condition is met only for one or a few values of  $\varphi$ , which correspond to the roots of the equation. In other words, no extended passivity region is possible.

Sukhotin suggested<sup>76</sup> a modification of the passivity theory by complicating the adsorption scheme through inclusion of several interaction steps of metal atoms with water molecules. Each step gives rise to its own coverage  $\Theta_k$  of the surface with oxygen-containing complexes, such as  $[\text{MOH}]_{ad}$ ,  $[\text{M}(\text{OH})_2]_{ad}$ ,  $[\text{M}(\text{OH})_3]_{ad}$  and  $[\text{MO}]_{ad}$ . Consequently, the partial currents corresponding to individual steps are  $i_k = \Theta_k K_{i,k}$ , the total coverage  $\Theta$  and the total dissolution current  $i_a$  can be represented as

$$\Theta = \sum_k \Theta_k,$$

$$i_a = \sum_k \Theta_k K_{i,k}.$$

The kinetics of each  $k$ th steps is determined by its parameters  $\alpha_k$ ,  $\beta_k$ ,  $K_{ad,k}$  and  $K_{i,k}$ . The total number of such steps is large. The theoretical results are to be reconciled with the experimental data by a proper selection of the steps. Nevertheless, despite the use of numerous free variables, discrepancies remain significant,<sup>76</sup> which indicates inadequacy of the adsorption model of passivity. Probably, the substantial deceleration of anodic dissolution by a small amount of preadsorbed oxygen relates to the repulsive interactions between the adsorbed ions. Their mutual influence impedes adsorption on the adjacent neighbouring sites giving rise to a specific dead zone around each adsorbed ion. Taking this into account,<sup>19</sup>

$$K_{ad} \sim \exp(-f_a \Theta) \exp(\alpha_a \sigma \varepsilon),$$

$$K_i \sim \exp(f_i \Theta) \exp[\beta_i (z_M - \sigma) \varepsilon],$$

where  $f_a$  and  $f_i$  are constants. These expressions also describe blockage of the active sites on an energetically heterogeneous metal surface, which is a reason for deceleration of the anodic dissolution.

No doubt, the adsorption from solution always represents the first step of formation of a passivating oxygen layer on a metal surface. However, as has been mentioned above, the presence of an oxygen ad-layer is not sufficient to explain all the regions observed in polarisation curves (in particular, the transpassive transition and a finite dimension of the passive region, which is characterised by the independence of the current of a passivated metal dissolution on the potential). Therefore, additional steps of the mechanism of formation of a passivating system have to be considered. The fact of formation of oxide layers with finite thicknesses, which corresponds to the equilibrium oxide – electrolyte, also support the above requirement.

The evolution of concepts concerning oxygen-induced passivation has resulted in the emergence of a phase-film theory of oxide passivity. This theory postulates<sup>26,76</sup> the existence of a

thermodynamically stable oxide layer (unlike that described above) on the surface of hard metals, which is observed at anode potentials  $\varphi > \varphi_a$ . This layer is referred to as a ‘film’. Its structure corresponds to stoichiometry  $M_nO_m$ . In the case of valve metals, the film is structurally disordered and can be substantially thicker. Within this theory, the passivation is explained by a mechanical shielding of the metal surface by the phase oxide. The independence of the passive current of the anode potential seems to be attributed to the chemical dissolution of the oxide layer. The potential corresponding to the beginning of the passive region  $\varphi_a$  (see Fig. 1) is interpreted as a potential of formation of the equilibrium oxide.

The postulate on the chemical mechanism of dissolution of the passivating oxide adopted in the phase-film theory is not supported by experimental data.<sup>68</sup> Typically, the potential of the beginning of the passive region  $\varphi_a$  differs from the potential of formation of the equilibrium oxide. For instance, this discrepancy is as large as 0.63 V in the case of iron.<sup>26,76</sup> Neither the experimentally observed dependences of  $\varphi_a$  on the surface properties of the metal (e.g., its cleanliness<sup>70</sup>), nor the solution composition and other factors can be explained within this theory.

The passivity theories that were developed later still relied on the assumption that the passivation was achieved due to the interaction of the metal surface with oxygen produced by dissociation of adsorbed water molecules. Presumably, the  $\text{O}^{2-}$  ions interact with the surface metal atoms forming the topmost ordered monolayer of oxide  $M_nO_m$ . This assumption is in agreement with the general theory of heterogeneous formation of a crystal phase through the generation of its two-dimensional nuclei or their stacks. Evidently, kinetics of such a process differs from that of a simple adsorption. In particular, the probability of generation of a two-dimensional nucleus manifests a stronger dependence on the interphase potential drop [see formula (13)].

In the course of growth, further oxide layers are formed atop the first structured monolayer. The increase in the thickness of the layer is caused, first, by too high an electrodiffusion current of the metal ions through the oxide layer to the interface O – E and, second, by too low a surplus potential expended for the current passage through the interface

$$\Delta\varphi = \varphi - \varphi_b.$$

Therefore, the dissociation of water molecules (the donor of the  $\text{O}^{2-}$  ions) is too intense. Due to an excess of the reactants, i.e.,  $\text{O}^{2-}$  and  $\text{M}^{z+}$  ions, new oxide cells are formed, the thickness of the layer increases and, respectively, the potential  $\varphi_b$  decreases.

This process ceases when the potential  $\varphi_b$  decreases to the level corresponding to the equilibrium between the PL and the electrolyte due to thickening of the PL. This means that a steady-state mode of the anodic dissolution of passivated metal is settled. Since then, new cells of oxide  $M_nO_m$  are formed only on the inner interface, where the oxide ions are incorporated into the metal. This process compensates for the disappearance of cells at the interface O – E. Only anionic sublattice of oxide  $M_nO_m$  is in equilibrium with the electrolyte. Between the two interfaces, oppositely directed electrodiffusion flows of the metal and oxide ions are established. Therefore, a stationary passivating layer, overall, is non-equilibrium. The interphase potential drop is

$$\Delta\varphi = \varphi - \varphi_{pb},$$

$$\varphi_b = \varphi_{pb},$$

$$\delta = \delta(\varphi),$$

where  $\varphi_{pb}$  corresponds to the Vetter potential<sup>26,27</sup> and  $\delta(\varphi)$  is the stationary thickness of the PL dependent on  $\varphi$ . Due to changes in  $\delta(\varphi)$ , the structure of the PL and processes proceeding in it adjust themselves to conditions of the thermodynamical equilibrium with the electrolyte at every value of  $\varphi$ . In contrast to this, the adsorption theory of oxygen passivation assumes that the oxide coverage remains monolayer at all values of  $\varphi$  and only the dependence of  $\varphi$  on the adsorption coverage of the metal surface

with oxide ions is considered. In other words, growth of the passivating layer is admitted only along this surface.

The oxygen-adsorption and phase-film theories can be considered as particular cases of the formation and functioning of an passivating oxide system (see Sections II and III of the present review).

It is known that a metal can be protected by inhibition of its surface with certain chemicals. The initial stage of this process also includes adsorption from solution, which plays the major role in the mechanism of formation of inhibiting coatings.<sup>77–79</sup> Several authors suggested<sup>80–84</sup> that the inhibition mechanism relates to a change in the rate of the electrode reactions involving organic compounds. This can be due to redistribution of charges over the double electric layer.

The development of mixtures of adsorption inhibitors that provide more efficient protection than any of their components becomes increasingly important. The non-additive action of such mixtures was attributed<sup>85–88</sup> to a change in the charge of the DEL due to the adsorption of anions, which adds a partial negative charge to the intrinsically positive metal surface. An analysis of possible reasons for the non-additive protective action of inhibitor mixtures and, particularly, their mutual intensification (*i.e.*, synergism) has been performed by Kuznetsov *et al.*<sup>89,90</sup>

Finally, it should be noted that not only the initial stage but further steps as well can be of significance in explaining the inhibition mechanism. These steps can either have the adsorption character (*i.e.*, polymolecular adsorption) or the mechanism involved is similar to that of salt passivation considered below.

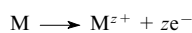
## VI. The salt passivation theory

At a potential  $\varphi < \varphi_a$  preceeding the oxide passivation, salt layers (SL) also possessing protective properties can appear on a metal surface.<sup>76</sup> The formation of such layers is referred to as salt passivation (SP) (sometimes, primary salt passivation).

The SP is observed in aqueous solutions of  $H_2SO_4$ ,  $HClO_4$ ,  $HNO_3$  and other acids in the presence of metal ions capable of forming poorly soluble salts with the respective  $A^{n-}$  anions. Two different mechanisms of the SL formation can be envisaged, depending on the solution composition and the nature of the ions.

The first mechanism is realised if salt-forming metal ions are the components of the acidic solution and the SL emerges due to salt precipitation on the metal surface. The formation of an SL according to this mechanism is determined by the saturation of the solution with reactants, the surface solubility product and general regularities of the heterogeneous nucleation.

The second mechanism is realised if the salt-forming  $M^{z+}$  metal ions are not present in the starting solution but are produced due to the interaction of the metal surface with the  $A^{n-}$  anions yielding salt molecules, *i.e.*, the SP is accompanied by the metal ionisation



and the anions are involved in the elementary events of the anodic process.

In this mechanism, the strength of the interparticle binding between the SP molecules and between an SP molecule and the metal substrate are of primary importance. This strength depends on the metal nature and solution composition. On the other hand, it determines the coverage of the surface with the salt layer and the rate of SL dissolution in the electrolyte. There are two possible mechanisms of the formation of an SL structure involving the  $A^{n-}$  anions and  $M^{z+}$  surface ions in the elementary acts.

According to the first variant, the bonds are sufficiently strong and thus the entire metal surface is covered with the SL, which means that  $\Theta = 1$ . Thus, a continuous salt layer with a thickness  $\delta(\varphi)$  is formed as a result. Its protective properties are determined by the strength of the bonds at the interface with the electrolyte, which prevents transfer of the  $M^{z+}$  ions to the electrolyte. Such an SL can possess a crystalline or amorphous structure. An amor-

phous structure within this approach to the SP problem can be regarded as a lattice that is characterised by a statistical scatter in the interatomic distances and angular directions.

A continuous SL is analogous in properties to a passivating oxide layer with the only difference that both the interparticle  $M-O$  bonds in the oxide and binding of the oxide to the metal substrate are stronger. Therefore, the protective properties of an oxide PL surpass those of an SL by several orders of magnitude. This was the first possible mechanism of formation of an SL corresponding to the complete coverage of the metal with salt. The theory of its emergence is fully analogous to the theory of oxide PL outlined in Sections II and III.

The second variant implies that the bonds formed between the SL and the metal are less strong (probably, due to the influence of the energetical inhomogeneity of the metal surface, which gives rise to continuous variations in the activity of different surface areas in the course of dissolution). For this reason, only a part of the surface appears covered, *i.e.*,  $\Theta < 1$ , and the SL cannot be continuous. The value of  $\Theta$  is determined by a balance of the direct and reverse processes of surface coverage. This mechanism of functioning of an SL has been considered by Sidorenko *et al.*<sup>91,93,95</sup> and by Popov *et al.*<sup>92,94–96</sup>. Its basic aspects can be formulated as follows.

The structure of an SL cannot be static since it is discontinuous and contains the  $M^{z+}$  ions of a metal that is dissolved. This follows from the general regularities of nucleation (of the SL, in this case), which starts with the adsorption step and generation of two-dimensional salt nuclei on the metal surface (at a coordinate  $x = 0$ ). The process further continues to the region  $x > 0$ , where the nuclei grow on the related, *i.e.*, their own, substrate. This should lead to the formation of a system of pores filled with the electrolyte within the salt structure. The pores constitute a connected space  $\Omega$  with an interface  $\Sigma$ . The existence of pores is necessitated by the fact that metal undergoes anodic dissolution only from uncovered parts of its surface put in contact with the electrolyte that is a mandatory participant of elementary events. Furthermore, the electrolyte solution is an ion-conducting medium, which is required for the withdrawal of the dissolved  $M^{z+}$  ions.

Popov *et al.*<sup>95,96</sup> demonstrated that a solution cannot be either oversaturated or unsaturated or simply saturated in all pores simultaneously. In other words, none of the three following relations

$$C_M^n C_a^m > C_H,$$

$$C_M^n C_a^m < C_H,$$

$$C_M^n C_a^m = C_H,$$

where  $C_M = [M^{z+}]$  and  $C_a = [A^{n-}]$  are the concentrations of the  $M^{z+}$  cations and  $A^{n-}$  counteranions, respectively, and  $C_H$  is the solubility product of the passivating salt  $M_nA_m$ , can be valid for all pores simultaneously. Indeed, in the first case, the pores would disappear owing to constant precipitation (crystallisation) of the salt on the pore walls so that the surface  $S$  would appear completely shielded and the metal dissolution would stop. In the second case, the pore walls would dissolve and the SL would disappear. In the third case, the concentration gradients of ionic components would become zero. This means that all pores at any moment  $t$  can be subdivided into two classes. In the first type of pores, the solution is oversaturated and the salt crystallises on the pore walls filling them. In the second type of pores, the solution is unsaturated and the salt is dissolved. The pores are continuously redistributed over the two classes. In other words, any elementary volume of an SL at any moment  $t$  represents either a solution-filled pore or solid phase. The steady-state porosity  $g(x)$ , which provides stable functioning of the SL, depends on the mean ratio of times, for which an elementary volume exists in these two states. The interface  $\Sigma$  does not remain static but rather continuously fluctuates. The porosity  $g(x)$  is a function of coordinate due to the

non-zero concentration gradients  $c_M(x)$  and  $c_A(x)$ . The reported data<sup>91–96</sup> are fully consistent with the experimental results.<sup>26,97</sup> Froment *et al.*<sup>97</sup> filmed an SL *in situ* using an accelerated-motion camera at a high magnification ( $\sim 3500$  times) and discovered a phenomenon referred to as ‘crystal swarming’, which is consistent with the above theory.<sup>91–96</sup> The apparent current density of the metal dissolution passing through an SL is given by the formula

$$i = g_s f(\varphi),$$

$$g_s = g(x)|_{x=0} = 0,$$

$$f(\varphi) = zF \frac{K_{ad}(\varphi)}{1 + \beta},$$

$$\beta = \frac{K_{ad}(\varphi)}{K_i(\varphi)},$$

where  $f(\varphi)$  is the actual current density at an uncovered part of the metal surface;  $K_{ad}(\varphi)$  and  $K_i(\varphi)$  are the rates of anion adsorption and metal ionisation in the elementary events of anodic dissolution (transfer of the  $M^{z+}$  ions into the electrolyte), respectively. The ion transfer processes proceeding in the pore space of an SL including reactions at the pore walls (*i.e.*, precipitation of the salt on them or dissolution) have been considered elsewhere.<sup>25,96,98,99</sup>

## VII. Conclusion

The investigations into the regularities of the interphase phenomena in non-equilibrium systems metal–electrolyte and into the passivation mechanism, in particular, are interdisciplinary in their nature combining physics of metals, solutions and electrolytes and interface processes. Such studies should take into account numerous factors and parameters, which affect the corrosion kinetics and determine the complex shape of polarisation curves (see Fig. 1). With this respect, the present review capitalises on the unified model principle, which assumes that all the phenomena proceeding on the surface of a dissolving metal as well as a sequence of the surface states are governed by a few key processes. The kinetics of these processes differs depending on the anode potential  $\varphi$  and therefore one process dominates at any specific potential value, which gives rise to the alteration of the surface states (with an increase in the potential  $\varphi$ ) corresponding to kinks of the polarisation curve and characteristic potentials  $\varphi_0$ ,  $\varphi_a$  and  $\varphi_p$ . The dissolution mechanism is changed at these points.

Adherence to the above principle imposes restrictions upon arbitrary assumptions in theoretical speculations with plentiful unknown parameters. The validity of this approach is also justified by the fact that the shapes of polarisation curves are virtually identical for the majority of metals (*e.g.*, Fe, Cr, Ni, Mo, *etc.*).

In the case of an anodically dissolvable metal, the unified model only includes such processes as the  $M^{z+}$ ,  $M_{ox}^{z+}$  and  $O_{ox}^{2-}$  ion transfer through the interfaces  $M-O$  and  $O-E$ ; hopping migration of the ions within the PL lattice; PL crystallisation by the mechanism of two-dimensional nucleation. This model is sufficient to reproduce the entire polarisation curve.

Specific features of real systems can be addressed by including respective supplementary factors. The problems of the electrochemical metal passivation under applied voltage and of the elementary event of the anodic dissolution are of special interest. They also can be treated within the approach described.

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<sup>a</sup> — *Protect. Met. (Engl. Transl.)*

<sup>b</sup> — *Russ. J. Phys. Chem. (Engl. Transl.)*

<sup>c</sup> — *Russ. J. Electrochem. (Engl. Transl.)*



# Chemical vapour deposition of thin-film dielectrics

V Yu Vasilev, S M Repinsky

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**Abstract.** Data on the chemical vapour deposition of thin-film dielectrics based on silicon nitride, silicon oxynitride and silicon dioxide and on phosphorus- and boron-containing silicate glasses are generalised. The equipment and layer deposition procedures are described. Attention is focussed on the analysis and discussion of the deposition kinetics and on the kinetic models for film growth. The film growth processes are characterised and data on the key physicochemical properties of thin-film covalent dielectric materials are given. The bibliography includes 139 references.

## I. Introduction

Layered semiconductor, dielectric and metallic composite materials are used in high-precision technologies. Such structures are the basis of modern electronics (in particular, solid-state integrated circuits are fabricated from single-crystalline silicon on semiconductor wafers).

Fabrication and use of multilayer structures became possible after solving the complicated problems of semiconductor materials science concerned with the synthesis of defect-free dielectric films (*e.g.*, silicon dioxide, silicon nitride, boron nitride and tin, titanium, aluminum, *etc.*, oxide films). At present, such films are fabricated using various versions of the chemical vapour deposition (CVD) technique.<sup>1</sup>

CVD methods have been used to fabricate ‘wafer – thin film’ structures since the mid-1960s.<sup>2,3</sup> The growth of a thin film, in the course of a CVD process, on the surface of a wafer heated to the desired temperature is the result of irreversible reactions of initially gaseous compounds. Dielectric films are synthesised using both research and industrial CVD flow reactors operating at atmospheric, reduced and low pressures. Vapour-phase mixtures of the precursors, oxidants or ammonia, in the presence of various carrier gases, are supplied to the reactor by a pressure drop in the carrier gas stream or as a result of the evacuation of the

system with a vacuum pump. One of the most important features of CVD processes is the possibility to grow films of variable thickness (from a few hundredths of a micrometre to a few micrometres) at relatively low temperatures. For instance, silicon dioxide films can be CVD grown at temperatures below 373 K, whereas silicon monoxide is formed at a noticeable rate by the oxidation of monocrystalline silicon with O<sub>2</sub> at temperatures above 1173 K. The film synthesis temperature can also be reduced by an additional (non-thermal) activation of the vapour phase using a high-frequency discharge, photochemically or by using laser irradiation.

Wide use of CVD methods in basic research and large-scale production is due to the fact that they require relatively simple equipment, are safe and manufacturable and provide high quality thin-film coatings fabricated under the optimum synthesis conditions. At present, thin-film CVD processes are basic technological processes in electronics<sup>4–6</sup> and their proportion in the overall device fabrication cycle is continuously increasing as the devices and methods of fabrication of multilayer structures become more and more complicated.

Both research practice and applied use of CVD methods face the problem of describing the film growth processes, which involves the establishment of some functional dependences.

First, it is necessary to obtain quantitative relations between the film growth rate and the parameters of the CVD process, *e.g.*, temperature (*T*), pressure (*P*), linear rate of gas stream (*v*) and the ratio of the component concentrations in the vapour phase (taking into account the geometry of the CVD reactor), features of the spatial arrangement of wafers in the reactor and the thermal and gas-dynamic effects in the reactor. Usually, these are the key factors for the optimization of the film deposition process, which eventually involves achievement of a maximum film growth rate at a minimum possible film thickness mismatch (desired values lie within limits of a few percent) across the entire wafer surface.

There are a number of good examples of solving optimization problems in film growth processes for different reactor types and various dielectric materials. One of them is modelling the operation of a low-pressure flow tube reactor under isothermal conditions.<sup>7</sup> The authors<sup>7</sup> succeeded in determining the parameters and spatial arrangement of wafers corresponding to a minimum film thickness mismatch at maximum reactor charge (several tens or even hundreds of semiconductor wafers). This is, in particular, due to the fact that no detailed information on the chemical stages of the growth process was required; the model

V Yu Vasilev, S M Repinsky Institute of Semiconductor Physics, Siberian Branch of the Russian Academy of Sciences, prosp. Acad. Lavrent'eva 13, 630090 Novosibirsk, Russian Federation. Fax (7-3832) 33 27 71, tel. (7-3832) 30 85 91, e-mail: vladislav\_v\_2000@yahoo.com (V Yu Vasilev), repinsky@land.ru (S M Repinsky)

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included only the rate constants for the reactions on the wafer surface or in the vapour-phase and the vapour-phase diffusion coefficients. However, in spite of the paramount importance of this solution, it is only a particular case for modelling of CVD process.

The second necessary functional dependence is a relation between the chemical composition and microcomposition of the film and the input parameters of the CVD process. For instance, the composition of silicon nitride films grown by ammonolysis of monosilane is usually described by the formula  $\text{Si}_3\text{N}_4$ . However, the microcomposition of such films should be described in terms of concentrations of the NH and SiH groups,<sup>8</sup> because the overall concentration of hydrogen in the silicon nitride films can vary between 4 at.% and 20 at.%, depending on the CVD method employed in each particular case. For many practical applications in electronics, the microcomposition plays the key role; therefore, this level of modelling of the CVD process requires knowledge of all stages of the growth process.

The third group of functional dependences includes correlations between the properties of the deposited films and the CVD conditions. It should be noted that most studies of the properties of dielectric materials were carried out using a particular deposition technique and a narrow range of parameters for the CVD processes.

Finally, searching for correlations between the electrophysical properties of deposited materials and the CVD parameters, including the reactor type, starting compounds, deposition conditions, *etc.*, is also an important task.

The considerable interest in the CVD processes is reflected in a continuous stream of publications, most of which describe the operation regimes, reactors and the properties of the films obtained. The properties of the films have been studied to different extents. Silicon-based films widely used in electronics have been best studied. The results of the investigations of silicon nitride films obtained up to 1980 have been comprehensively treated in a monograph.<sup>8</sup> Data on the deposition of silicon dioxide films, and especially binary and ternary silicate glass films, have almost not been summarised earlier. More complex thin-film materials, *e.g.*, silicate glasses, synthesised in four- and five-component chemical systems, have been poorly studied. This leads to an inadequate understanding of the physicochemical processes used in electronics. This conclusion can be drawn after close examination of the available monographs.<sup>2-6</sup> For instance, at present, the epitaxy, diffusion and thermal oxidation processes have been studied in detail and theoretically substantiated, whereas chemical vapour deposition of dielectric thin films is still descriptive in character.

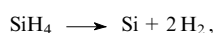
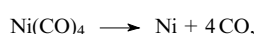
This review is concerned with the analysis of the problems of CVD of dielectric thin films. We discuss the methodological problems of CVD and the fundamentals of the molecular theory of dielectric film growth. The key characteristics responsible for the growth processes and main physicochemical properties of thin-film covalent dielectric materials are also considered.

## II. Chemical vapour deposition of thin-film dielectric materials: general

### 1. Reactions

Basic to CVD processes are the following chemical reactions of carbon and silicon compounds: pyrolysis (cracking process), reduction, oxidation, hydrolysis, ammonolysis and dehydrogenation. Given below are some examples of these reactions.

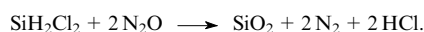
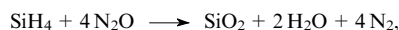
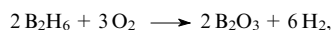
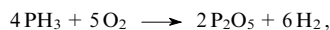
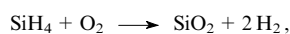
#### *Pyrolysis*



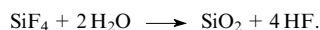
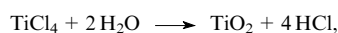
#### *Reduction*



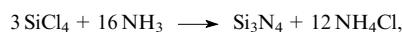
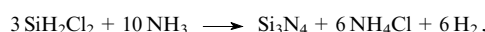
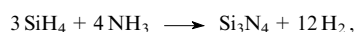
#### *Oxidation*



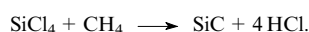
#### *Hydrolysis*



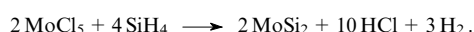
#### *Ammonolysis*



#### *Interaction with methane*



#### *Interaction with monosilane*



Among these, the hydrolysis and oxidation reactions are the fastest. A special position is occupied by the oxidation of silane, which proceeds as a branched-chain process; therefore,  $\text{SiO}_2$  films can be fabricated at low temperatures ( $\sim 343$  K). Note that in the case of CVD processes, the reaction schemes presented above can be used for descriptive purposes only, because the composition of the by-products depends on the particular conditions. For instance, the oxidation of hydrides under CVD conditions can result in both hydrogen and water.

Studies on the deposition of silicon nitride films in the course of the interaction between  $\text{SiCl}_4$  and  $\text{NH}_3$ , and of nickel films during pyrolysis of nickel carbonyls, were carried out more than four decades ago. Since then, some concepts of the character of these processes have been proposed and accepted.<sup>8,9</sup> The CVD approach can be employed to obtain (i) dielectric materials ( $\text{SiO}_2$ , binary and ternary glasses  $\text{SiO}_2\text{--B}_2\text{O}_3$ ,  $\text{SiO}_2\text{--P}_2\text{O}_5$ ,  $\text{SiO}_2\text{--B}_2\text{O}_3\text{--P}_2\text{O}_5$ ,  $\text{Si}_3\text{N}_4$ , silicon oxynitride  $\text{Si}_3\text{N}_4\text{--SiO}_2$  and  $\text{Al}_2\text{O}_3$ ,  $\text{AlN}$ ,  $\text{Ge}_3\text{N}_4$ ,  $\text{TiO}_2$ ,  $\text{TiC}$ ,  $\text{TiN}$ ), which are used as screening films, protective coatings, mirrors and waveguides; (ii) polycrystalline and amorphous semiconductor films (silicon,  $\text{SiC}$  and compounds of the types  $\text{A}^{\text{III}}\text{B}^{\text{V}}$  and  $\text{A}^{\text{II}}\text{B}^{\text{VI}}$ ) used for fabrication of transistor structures; (iii) metals and alloys ( $\text{Ni}$ ,  $\text{Al}$ ,  $\text{W}$ ,  $\text{Ta}$  and  $\text{Mo}$  and nickel, manganese, iron, titanium, cobalt, chromium, tungsten, tantalum, molybdenum, platinum and aluminum silicides) for production of conductors; (iv) superconductors  $\text{Nb}_3\text{Sn}$ ,  $\text{Nb}_3\text{Ge}$ ,  $\text{YBa}_2\text{Cu}_3\text{O}_{7-x}$ ,  $\text{Bi}_2\text{Sr}_2\text{Ca}_{n-1}\text{Cu}_n\text{O}_x$  ( $n = 1-3$ ); (v) ferroelectrics  $\text{Pb}(\text{Zr,Ti})\text{O}_3$  and  $(\text{Ba,Sr})\text{TiO}_3$ ; (vi) transparent conductors  $\text{SnO}_2(\text{In}_2\text{O}_3)$ , *etc.*

Thin film-wafer composites have found a variety of technological applications in electronics, mechanical engineering, power engineering, medicine, *etc.* The CVD method differs from other known thin film fabrication techniques (thermal, plasma or ion deposition) in the size of the deposited particles, which is of the order of a few tenths of a nanometre (*cf.* tens of nanometres for other methods). Molecular dispersion of the deposited particles makes possible the deposition of compact coatings on surfaces

with complex reliefs, with good adhesion and high mechanical properties for the coatings.

## 2. Thermodynamic aspects of CVD

The problem of growth of a dielectric film is part of the known problem with solid phase formation from particles present in gas or vapour phases. The thermodynamic aspect of this problem was first considered by Volmer.<sup>10</sup> The cases for complex multicomponent systems used for epitaxial crystal growth were generalised by Schäfer<sup>11</sup> and Kuznetsov *et al.*<sup>12</sup> However, it is impossible to analyse the film growth rate using thermodynamic description of chemical systems, because the vast majority of dielectric film fabrication processes proceed under conditions that are far from the thermodynamic equilibrium.

Concerning the possibility of using the crystal-growth theory methods to describe the growth of dielectric thin films, we can say the following.

The modern crystal-growth theory concerns three main problems:

- the mechanism of a new phase nucleation on the surface of a crystal or in the medium surrounding the growing crystal (*e.g.*, the gas or vapour phase);

- the nature of the processes that govern the nucleation kinetics (according to the layer-by-layer growth theory, these are the surface diffusion processes);

- the problem of retention of the growing plane in the crystal; solutions to this problem are best demonstrated in the Kossel model for an ideal crystal and in the model by Frank, Burton and Cabrera<sup>13</sup> for a real crystal (motion of the front of a screw dislocation).

In the theory of gas-phase nucleation, the critical radius,  $r_c$ , of a spherical nucleus is expressed through the surface energy  $\sigma$ ; the molecular volume,  $v_m$ , of the nucleus; the vapour pressure  $P_v$ ; and the equilibrium pressure  $P_e$  at the temperature  $T$

$$r_c = \frac{2\sigma v_m}{RT \ln(P_v/P_e)}. \quad (1)$$

Consider, as an example, formation of silicon dioxide films by the oxidation of monosilane with  $O_2$ , assuming that the gas–solid system is in thermodynamic equilibrium. Using the following dependence,<sup>†</sup>

$$P_e = 4.11 \times 10^{13} \exp\left(-\frac{336.4}{RT}\right)$$

we obtain  $P_e = 4 \times 10^{-8}$  Pa for  $T = 573$  K. Then, using the published data<sup>14,15</sup> for  $P_e = 133.3$  Pa ( $v_m = 22$  cm<sup>3</sup> and  $\sigma = 2 \times 10^{-5}$  J cm<sup>-2</sup>), we get  $r_c = 0.03$  nm. This means that the formation of silicon dioxide film does not begin with a homogeneous nucleation step. However, it is known that (i) reactions of monosilane with oxygen-containing oxidants ( $O_2$ ,  $N_2O$ ,  $CO$ ) result in  $SiO_2$  as the solid product and (ii) silicon dioxide molecules transferred to the vapour phase upon evaporation of this compound are present only above molten  $SiO_2$  (at  $T \sim 2273$  K).<sup>14</sup> Therefore, chemical vapour deposition of silicon dioxide films proceeds under conditions that are far from the thermodynamic equilibrium. Similar analysis of the growth of silicon nitride films in the course of monosilane ammonolysis leads to the same conclusion.

The analysis given above excludes the possibility of forming three-dimensional nuclei in the vapour phase; however, we can assume the appearance of a two-dimensional nucleus on the surface and consider the unique kinetic features of its growth. The melting temperatures,  $T_m$  (in K), of silicon and silicon compounds and the temperature intervals ( $\Delta T$ ) corresponding to typical conditions of synthesis for these compounds are listed below.

| Material        | $T_m$ | $(2/3)T_m$ | $\Delta T$ |
|-----------------|-------|------------|------------|
| Silicon         | 1693  | 1128       | 870–910    |
| Silicon dioxide | 1773  | 1182       | 470–970    |
| Silicon nitride | 2173  | 1448       | 970–1120   |

It is known that atom transfer processes, such as diffusion, viscous flow, recrystallisation, *etc.*, can be considered fast if they proceed at temperatures exceeding a value of  $(2/3)T_m$ . The data listed above show that in all cases silicon dioxide and silicon nitride films are formed at temperatures that are several hundreds of degrees lower than the corresponding  $(2/3)T_m$  value. This means that the mobility of the atoms of the growing film is hindered in the course of synthesis and the surface self-diffusion cannot be as intense as is assumed in layer-by-layer crystal growth theory.

Quantitative information about surface diffusion can be extracted from the results of experiments on the sintering of finely dispersed  $SiO_2$  powders obtained by hydrolysis of organosilicon compounds. The activation energy for the sintering of powders is known to be nearly 711 kJ mol<sup>-1</sup>; this process only proceeds at a measurable rate at 1273 K.<sup>16</sup>

Thus, thin-film dielectric materials are formed under CVD conditions as a result of complex heterogeneous chemical reactions involving vapour-phase processes and transformations on the growing surface of the dielectric material.

## 3. Kinetic aspects of CVD. Multipath and multistage film growth processes

Thin-film dielectric materials can be fabricated by deposition from vapour phases containing at least two reactive components using three main types of reactions. These are pyrolysis (thermal decomposition of organoelement compounds), oxidation and ammonolysis. For instance,  $SiO_2$  films can be obtained under CVD conditions and by pyrolysis, while  $Si_3N_4$  films can be prepared by ammonolysis of silicon compounds.

Let us illustrate specific features of the kinetics of the CVD reaction by taking silicon nitride films obtained in two reactions, (1)  $SiCl_4 + NH_3$  and (2)  $SiH_4 + NH_3$ , as examples. For the reaction involving  $SiCl_4$ , the formation of a product of direct interaction,  $Cl_3SiNH_2^+$ , in the vapour phase was detected by mass spectrometry,<sup>17</sup> the concentration of  $Cl_3SiNH_2^+$  being about 20% of the starting concentration of the  $SiCl_4^+$  ion. Considerable amounts of products of secondary collisions, containing one or two silicon atoms and  $NH_2$  groups were also detected; besides, these products always contain HCl. These results show that the first intermediate product of the vapour-phase reaction is  $Cl_3SiNH_2$  and further reactions result in the formation of  $Si(NH_2)_2Cl_2$  and  $Si_2NHCl_6$  particles. Detailed analysis of these reaction schemes and information on the rate constants for the different stages can be found in the literature (see, *e.g.*, Refs 8, 18, 19). Figure 1 presents a scheme of possible transformations of the starting reagents in the formation of  $Si_3N_4$  films.

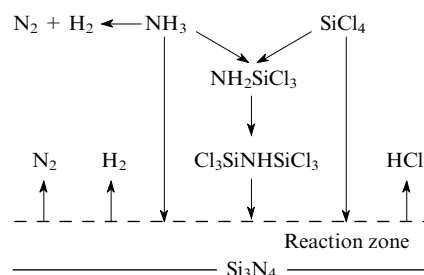
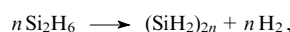
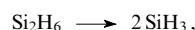
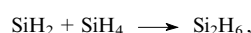
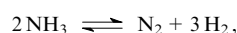


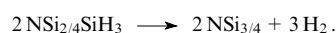
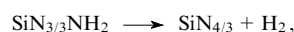
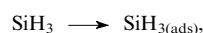
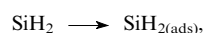
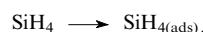
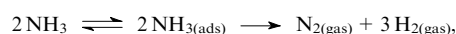
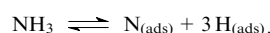
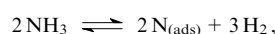
**Figure 1.** A scheme illustrating the sequence of stages and routes of chemical transformations during the formation of silicon nitride layers in the  $SiCl_4$ – $NH_3$  system.<sup>18</sup>

<sup>†</sup> From this point on the activation energy is given in kJ mol<sup>-1</sup>.

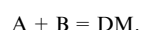
In the  $\text{SiH}_4 + \text{NH}_3$  system, the sequence of reactions, resulting in the formation of silicon nitride films, can involve both pure vapour-phase reactions:



and surface reactions:



These reaction schemes serve as the basis for a generalised kinetic model of a complex CVD reaction, determining the growth of a film. For instance, the overall reaction of the precursors A and B (Fig. 2) results in the formation of structural units of a thin-film dielectric material (DM)



This reaction is generally a multistage and multipath process. Consider three main paths. Route I is the interaction between A and B in the adsorption layer by the Langmuir–Hinshelwood or by the Eley–Rideal mechanisms. Route II is the interaction between the intermediate product, I, and the surface, S, of the growing film, resulting in the formation of an intermediate product, F, which is eventually transformed in the reaction zone into structural units of the DM and thus causes regeneration of an element of the pristine surface. Route III is characterised by the formation of the intermediate product, I, in the vapour phase and the subsequent formation of a by-product (end product C).

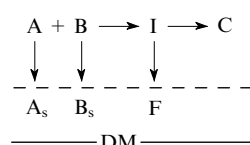


**Figure 2.** Generalised kinetic scheme of formation of a dielectric layer during the CVD process.<sup>18</sup>

A and B are the starting reagents;  $\text{A}_s$  and  $\text{B}_s$  are the reagents in the adsorption stage; I and F are intermediate products in the vapour phase and in the adsorption layer, respectively; C is a side product (gas or powder); and DM is the end product (thin layer of dielectric material).

The aforementioned can be represented as the matrix of stoichiometric coefficients of CVD stages (Table 1). In this representation, the growth process is described as a complex reaction following three concurrent routes, each of them being a multistage process. In particular, route I involves stages 2, 3, 4 and 6; route II involves stages 1, 5 and 6 and route III involves stages 1 and 7. Thus, the growth of a dielectric thin film can be considered as a multipath and multistage chemical reaction. To describe the kinetics of this reaction, one must have a complete set of rate constants for each of the individual stages. This is an intricate experimental task, which importantly can be solved using the

**Table 1.** Matrix of stoichiometric coefficients of different stages of the CVD process.<sup>18</sup>

| No. | Stage                                | Route |    |     |
|-----|--------------------------------------|-------|----|-----|
|     |                                      | I     | II | III |
| 1   | A + B = I                            | 0     | 1  | 1   |
| 2   | A + S = $\text{A}_s$                 | 1     | 0  | 0   |
| 3   | B + S = $\text{B}_s$                 | 1     | 0  | 0   |
| 4   | $\text{A}_s + \text{B}_s = \text{F}$ | 1     | 0  | 0   |
| 5   | I + S = F                            | 0     | 1  | 0   |
| 6   | F = DM                               | 1     | 1  | 0   |
| 7   | I = C                                | 0     | 0  | 1   |

formal approaches developed in the theory of the kinetics of heterogeneous catalysis.

#### 4. Structural aspect of thin film synthesis under CVD conditions

Formation of thin-film dielectric materials under CVD conditions proceeds as a heterogeneous chemical reaction, *i.e.*, a sequence of elementary acts involving the embedding of structural units into the matrix of the growing film. An important feature of this class of compounds is the absence of long-range order in their structures. Short-range order in covalent dielectric materials can be described using the concept of structural units proposed by Myuller.<sup>20</sup> A structural unit is the smallest possible atomic group in the nearest coordination sphere of a given atom, which reflects its coordination and the unique features of its embedding into the matrix material. Examples of the main structural units are provided by  $\text{SiO}_{4/2}$  for silicon dioxide,  $\text{BO}_{3/2}$  and  $\text{BO}_{4/2}$  for boron oxide,  $\text{O}-\text{P}^+\text{O}_{3/2}$  for phosphorus oxide,  $\text{GeO}_{4/2}$  for germanium oxide and  $\text{SiN}_{4/3}$  for silicon nitride. The properties of a layer can strongly depend, not only on the main unit, but also on other structural units. For instance,  $\text{SiO}_2$  layers can contain inclusions with  $\equiv\text{Si}-\text{OH}$  or  $\equiv\text{Si}-\text{H}$  bonds, *i.e.*, structural units  $\text{SiO}_{3/2}\text{OH}$ ,  $\text{SiO}_{2/2}(\text{OH})_2$  or  $\text{HSiO}_{3/2}$ ,  $\text{H}_2\text{SiO}_{2/2}$ . This means that the layer compositions should be described as sets of structural units responsible for the short-range order in the layer of dielectric material. Another important feature is connected with the character of a given combination of structural units, which governs the nature of the medium-range order in the layer. It is known that the  $\text{SiO}_{4/2}$  tetrahedra in  $\text{SiO}_2$  layers can be combined in such a fashion that formations of four-, five-, six- and eight-membered rings, comprised of the  $\text{Si}-\text{O}-\text{Si}$  bridges, become possible. This results in the appearance of micropores and mesopores in the matrix.

Structural features of synthesised films are also related to the character of the long-range order in the structure. When synthesising semiconductor films, it is usually possible to obtain single-crystalline films. Metal films are, as a rule, polycrystalline, while the synthesis of dielectric materials leads to formation of glassy or amorphous films. Interrelations between these structures are illustrated in Fig. 3, which shows variations in the structure of a  $\text{SiO}_2$  film of various degrees of disorder.<sup>21</sup>

The key role in the formation of a film structure is played by the temperature of the wafer, but generally one must also take into account other starting parameters of the CVD processes. Note that the properties of the surface of a dielectric material are determined by the set of the surface structural units characterised by the different heats of adsorption of the reagents. In this connection, one can assume a non-uniform energy distribution across the surface of the growing dielectric material. In contrast to the crystal model by Kossel, in which non-uniform energy distribution is determined by structural features, the model of a growing dielectric film is governed by the discrete set of structural units with different chemical compositions. This can be exemplified by considering the data on the surface chemistry of silica gels and quartz glass.

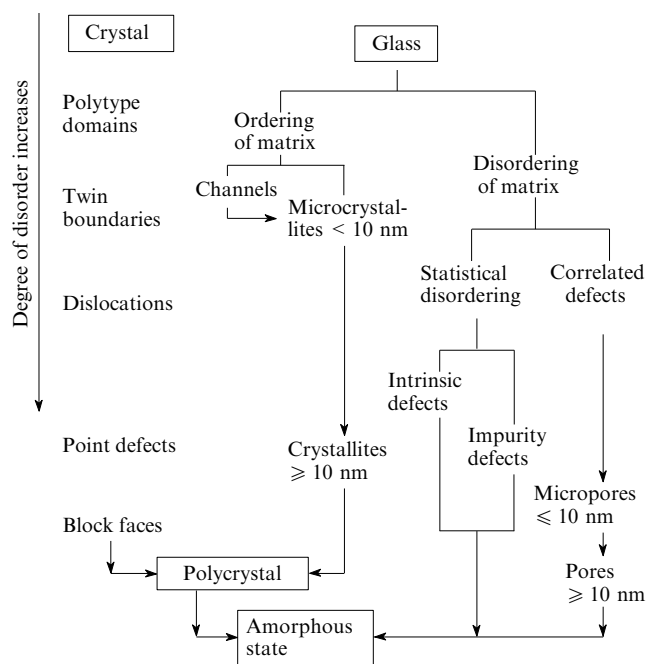


**Figure 3.** Scheme illustrating interrelations between defects in the crystalline, glassy and amorphous silicon dioxide.<sup>21</sup>

A study of the surface of a cleaved  $\text{SiO}_2$  face revealed the presence of  $\text{O}_2\text{SiO}_{3/2}$  and  $\text{OSiO}_{3/2}$  sites (see Ref. 22). Investigations of the adsorption characteristics of silica gels<sup>23,24</sup> established the presence of the  $(\text{O}_{3/2}\text{Si})_2\text{O}$ ,  $\text{HOSiO}_{3/2}$  and  $(\text{HO})_2\text{SiO}_{2/2}$  surface sites. The results of studies of the growth of polycrystalline silicon films and the data on hydrogen adsorption on the surface of this material indicates the formation of the  $\text{HSiSi}_{3/4}$  and  $\text{H}_2\text{SiSi}_{2/4}$  surface sites. Thus, generally, the surface energy of the growing dielectric material can be different at different points of the surface, owing to the chemical inhomogeneity of the adsorption sites. However, it should be noted that this can manifest itself only at low coverages of the adsorption layer. If the growth occurs as a monolayer or ultrahigh coverage, the kinetics of the process should be described with allowance for uniform energy distribution across the surface.

In the theory of layer-by-layer crystal growth, an important role is played by screw dislocations, whose outcrops provide a kind of constant sink for adatoms to the monatomic step. A distinctive feature of the glassy state of a compound is the absence of regular dislocation-type defects. This means that structurally, a dielectric film has a highly ordered surface. Some problems can be due to crystallisation of films, *viz.*, if it does occur, structural defects appear on the surface of the dielectric film.

It is possible to analyse various growth processes of thin-film dielectric materials from a unified point of view by using the concept of a reaction zone (a concept traditionally used in solid state chemistry when considering topochemical reactions). In certain simple cases, the reaction zone can be as thin as the monolayer coating. Generally, the thickness of the reaction zone is in the order of a few atomic sizes.

### III. Characteristics of film growth processes

#### 1. CVD equipment and reagents

A number of simplified schemes of flow reactors most widely used for the deposition of dielectric films are shown in Fig. 4. In these reactors, wafers can be arranged on heated pedestals or inside a quartz tube with isothermal heating. In the former case, the temperature of the reactor walls is lower than the wafer temperature; these reactors being called 'cold-wall' reactors. In the latter

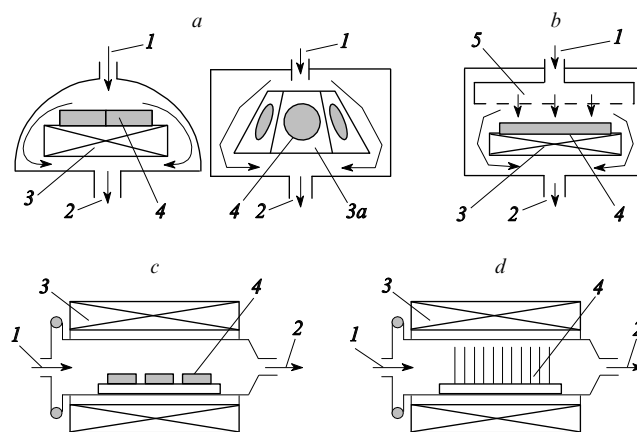


**Figure 4.** Main types of reactors (simplified schemes): atmospheric pressure reactor (a), reduced pressure reactor (b), low pressure reactor (c) and low pressure reactor with cross-vertical coaxial arrangement of wafers (d).

Gas inlet (1), exhaustion of used gas mixture or evacuation (2), heater (3), pyramidal heater (3a), wafer (4), gas distributor system (including the system with high-frequency power) (5).

case, wafers and reactor walls have the same temperature; these reactors being called 'hot-wall' reactors. The spatial arrangement of wafers in 'hot-wall' reactors can vary, namely, along or normal to the gas stream (see Fig. 4 c,d); respectively, one deals with flow and flow-diffusion reactors.

Depending on the reagent pressure, CVD reactors are conditionally divided into the atmospheric pressure reactors ( $P \geq 1 \times 10^5$  Pa), reduced pressure reactors ( $P < 1 \times 10^5$  Pa) and low pressure reactors ( $P \sim 10 - 2000$  Pa). The abbreviations of the corresponding CVD processes, derived from the reactor names, are APCVD, RPCVD and LPCVD, respectively. As the pressure under CVD conditions decreases, the reagent diffusion coefficients increase and the process is shifted to such an operation regime for which the mass transfer conditions become insignificant. This makes it possible to vary the spatial orientation of wafers, and hence improve the performance of CVD processes in the flow-diffusion LPCVD reactors (see Fig. 4 d).

The gas flow rate in the course of deposition can vary from a few (LPCVD reactors) to several hundreds (APCVD reactors) of  $\text{cm}^3 \text{ s}^{-1}$ , which approximately corresponds to a range of linear rates for the gas stream from a few  $\text{cm s}^{-1}$  (APCVD reactors) to tens of  $\text{m s}^{-1}$  (LPCVD reactors). Evacuation of LPCVD reactors is achieved using high-pressure vacuum pumps. If necessary, so-called Roots pumps are also used; their performance can be as high as several hundreds of  $\text{dm}^3 \text{ s}^{-1}$ , at pressures ranging between a few tens to hundreds of Pa.

A significant drawback of all flow reactors is their low performance due to incomplete consumption (often, less than 10%) of the starting reagents, which often does not meet environmental safety conditions. Studies on the possibility of using reactors with a closed gas cycle for the synthesis of thin films led to unsatisfactory results, owing to intense formation of by-products (microparticles) in the cold regions of reactors. However, it was found that silicon nitride films can be synthesised from  $\text{SiCl}_4$  and  $\text{NH}_3$  using a LPCVD reactor with a quasi-closed cycle. After evacuation of the reactor, the flow rates of the starting reagents, in the ratios corresponding to the stoichiometric equation, are specified. A stable low pressure in the reactor is self-maintained during the course of the growth process, because all products of this reaction are isolated as solids deposited on the cold walls of the reaction chamber.

Thin film deposition itself occurs when the vapour-gas mixture of a specified composition is supplied for a necessary

time interval into the reactor containing no atmospheric gases (this is achieved by blowing-in an inert gas or by evacuation); the wafer temperature must be pre-stabilised. Equipment and methods for the deposition of thin-film dielectric materials have been well documented (see, e.g., Refs 25–27).

Numerous combinations of various compounds were used in the studies of the CVD synthesis of dielectric films carried out over a long period of time. For instance, silicon dielectric films were deposited using monosilane, disilane, dichlorosilane, silicon tetrachloride, tetraethylorthosilicate (TEOS), dimethyldichlorosilane, hexamethyldisilazane and hexamethyldisiloxane. Nowadays, the starting combinations of silicon compounds for industrial use in electronics are well established.

Silicon nitride films are mainly synthesised by ammonolysis of dichlorosilane in LPCVD reactors and much more rarely by ammonolysis of silicon tetrachloride. The ammonolysis of monosilane is mainly used in the case of plasma-enhanced deposition.

Silicon dioxide films, as well as boron-containing and phosphorus-containing glass films are fabricated using two versions of the CVD method:

— hydride technique involving monosilane (if necessary, phosphine and diborane are also used) and oxygen in all types of reactors at a low temperature ( $\sim 673$  K); in some cases, boron trichloride and organic esters of boric, phosphorous or phosphoric acids are used instead of diborane and phosphine;

— pyrolysis of tetraethylorthosilicate at temperatures above 923 K or oxidation of mixtures of this compound with organic esters in all types of reactors at a low temperature ( $\sim 673$  K); here, possible oxidants are oxygen or oxygen–ozone mixtures (with ozone concentration of up to 13 mass%).

## 2. Characteristics of film deposition regimes in flow reactors

Gas flows under CVD conditions are characterised by the Reynolds number

$$Re = \frac{\rho_g v d}{\eta_g}$$

( $\rho_g$  is the density of the gas,  $\eta_g$  is the viscosity of the gas,  $v$  is the linear flow rate of the gas stream and  $d$  is the characteristic linear size of the reactor), which varies between 10 and 100. At such Re values, turbulence effects are insignificant. Depending on the total pressure in the reactor, the Knudsen numbers (ratio of the mean free path of molecules to the linear size of the reactor) vary from 1 (in RPCVD reactors) to  $10^{-4}$  (in APCVD reactors). If a process is carried out at a pressure in the range 133–1333 Pa, the diffusion coefficients of reagents increase by 1.9–2.9 orders of magnitude compared to their values under normal conditions. Because of this, the process becomes kinetically controlled. A quantitative characteristic of this regime is the ratio of the reaction rate to the diffusion rate — the Thiele criterion, which, for a first-order reaction, has the form

$$\Phi = \frac{k d}{D},$$

where  $k$  is the rate constant for the reaction and  $D$  is the diffusion coefficient. At  $\Phi \leq 0.1$ , the process is determined by the rate of the heterogeneous reaction, becoming diffusion controlled at  $\Phi \geq 1$ .

## 3. Experimental determination of film growth rate constants

Methodologically correct determination of the growth rate constants is of crucial importance for the qualitative description of film growth processes under CVD conditions. The growth rate depends on specific features of the heat and mass transfer processes, viz., the reactor and wafer heating mode, reactor geometry, shape of wafer pedestals, reactant gas supply technique, total pressure and linear flow rates of gas mixtures. In some particular cases, it is possible to perform quantitative heat and mass transfer calculations and determine the growth rate constants. These parameters can also be determined experimentally.

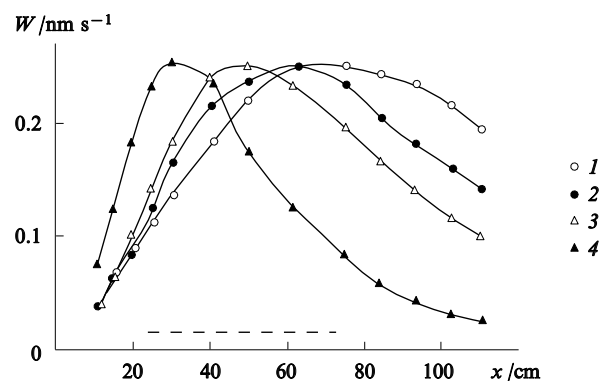


**Figure 5.** Growth rate distribution of silicon nitride layers along the axis of a horizontal isothermal reactor with isothermal zone 1123 K (shown by dashed line).<sup>8</sup>

Linear rate  $/\text{cm s}^{-1}$ : 494 (1), 395 (2), 328 (3) and 197 (4);  $P = 1995$  Pa,  $[\text{SiH}_4] = 2.76 \times 10^{-7}$  mol litre $^{-1}$ ,  $[\text{NH}_3]/[\text{SiH}_4] = 90$ .

Isothermal horizontal tube reactors of internal radius  $r_r = 20$ –60 mm (see Fig. 4 c,d) with a sufficiently extended isothermal zone in the central part of the reactor appear to be most convenient for carrying out such experiments. The length of the isothermal zone is usually at least one third of the total length of the reactor. The thickness of the film deposited on wafers (wafer radius,  $r_w$ , usually lies between 20 and 50 mm) varies along the length of the reactor, namely, it increases at the beginning of the isothermal zone, reaches a maximum value and decreases near the end of the isothermal zone. This is illustrated in Fig. 5. In the initial portions of curves, the deposition rate ( $W$ ) increases to its maximum value ( $W_{\text{max}}$ ), corresponding to the instant when the gas stream is heated in the whole volume. Subsequent decrease in the deposition rate is due to depletion of monosilane. Let a gas stream move along the reactor at the linear rate  $v$  and the gas mixture arrives at point  $x$  at time

$$\tau = \frac{x}{v},$$

which is called the residence time of the gas mixture in the reactor. Using this ratio, the dependence of the rate of the process on the coordinate (along the reactor) can be re-calculated to the corresponding dependence on  $\tau$ .

After this treatment, the family of dependences shown in Fig. 5, plotted in the new coordinates, looks as a single kinetic curve, passing through a maximum ( $\tau_{\text{max}}$ ). In this case, the process can be described by the model of a plug reactor, which is based on two assumptions: (1) constant reagent concentrations at a given reactor section and (2) the rate of convective transfer of a reagent is higher than the diffusion rate along the reactor axis. Analysis of the curves plotted in Fig. 6 a revealed yet another salient feature, namely, depletion of the gas mixture decreases exponentially (this is clearly seen in Fig. 6 b).

The rate of conversion of the  $i$ th component, of initial concentration  $c_{0i}$ , in the course of a first-order chemical reaction is expressed as follows:

$$-\frac{dc_i}{dt} = kc_i, \quad c_i = c_{0i} \exp(-kt).$$

From here, the rate constant for the reaction is given by:

$$k = \frac{\Delta \ln(c_i/c_{0i})}{\Delta t}.$$

The rate constant for the reaction can be determined by plotting the film growth rates,  $W_{\text{max}}$ , corresponding to maxima on the  $W(x)$  curves (see Fig. 5) vs. concentration  $c_{0i}$ :

$$W_{\max} = kc_{0i}^n.$$

In this case, it is possible to determine both the rate constant  $k$  and the reaction order  $n$ . Determination of the initial concentration  $c_{0i}$  can appear to be difficult. In the case in point, the stage described by the raising portion of the  $W(\tau)$  curve (see Fig. 6a) is characterised by partial depletion of the gas mixture from the  $i$ th component, and the  $c_{0i}$  value does not correspond to the real initial concentration. The depletion value,  $\Delta c_i$ , must be calculated by integrating the total mass of the layer formed on the reactor walls from the point corresponding to the beginning of registration of the film growth to the point  $x_{\max}$  (maximum position):

$$\Delta c_i = \xi \frac{\rho_f 2\pi r_f}{v_T M} \int_0^{x_{\max}} W_x dx.$$

Here  $\xi$  is the stoichiometric number, which shows how many moles of the  $i$ th reagent should be consumed in order to form 1 mole of product,  $\rho_f$  is the film density,  $v_T$  is the gas flow rate at the temperature  $T$  and  $M$  is the molecular mass of the film material. This expression for  $\Delta c_i$  is valid for a cylindrical reactor with horizontally arranged small wafers (see Fig. 4c). In other cases (e.g., vertically arranged wafers), calculations are more complicated.

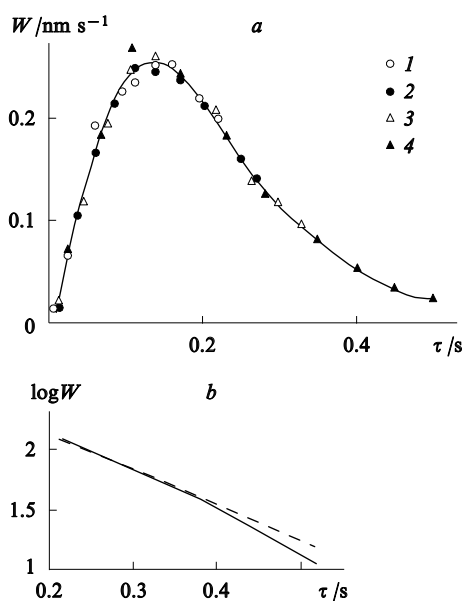


**Figure 6.** Dependences presented in Fig. 5 plotted in the 'growth rate–residence time of the gas mixture in the reactor' coordinates (a) and in semilogarithmic coordinates (b).<sup>8</sup>

For notation (1–4), see the caption to Fig. 5.

If the change,  $\Delta h$ , in the thickness of the deposited film after time  $\Delta t$  in a flow reactor of the surface area  $S$  equals the deposition rate  $W_s$ , one can find the number,  $\Delta m$ , of moles of reaction product formed:

$$\Delta m = \frac{S\rho_f}{M} \frac{\Delta h}{\Delta t} \Delta t = \frac{S\rho_f}{M} W_s \Delta t.$$

For a static system or under plug reactor conditions one has

$$\Delta m = -\xi V \frac{\Delta c}{\Delta t} \Delta t = -\xi V W_v \Delta t,$$

where  $V$  is the volume of the reactor,  $c$  is the molar concentration of the reagent and  $W_v$  is the rate of the vapour-phase reaction. For a one-path process, one gets a simple relation between these rates:

$$\frac{dh}{dt} = \xi \frac{VM}{S\rho_f} \frac{dc}{dt}.$$

Generally (the case of multipath reactions),  $W_v > W_s$  and the ratio of these rates determines the contribution of a given path. When the reaction kinetics is studied experimentally, one must determine how the ratio of the surface area,  $S$ , of the reactor to its volume,  $V$ , affects the reaction rate. This criterion allows us to answer the question of which (gas-phase or heterogeneous) stage is the rate-determining step of the reaction. Assuming that a certain reaction is characterised by the dependence  $W = kc$ , if the overall rate is determined by the slow surface reaction, i.e.,

$$W_s = \frac{dh}{dt} = k_s c,$$

where  $k_s$  is the rate constant for the surface reaction, the rate of the reagent conversion is given by

$$-\frac{dc}{dt} = \frac{S\rho_f}{M\xi V} \frac{dh}{dt}$$

and

$$\frac{dc}{c} = \frac{S\rho_f}{M\xi V} k_s dt.$$

From here it is seen that:

$$W_s = k_s c_0 \exp\left(-\frac{S}{V} \frac{\rho_f}{M\xi} k_s t\right).$$

Having determined the rate constant at  $t = 0$  (this corresponds to the position in the plot shown in Fig. 6a), we obtain the  $k_s$  value, which is independent of the reactor geometry. Using the experimental data in the  $\ln W - t$  coordinates, one can find the effective rate constant

$$k = \frac{S}{V} \frac{\rho_f}{M\xi} k_s,$$

which depends on the  $S/V$  ratio. In particular, for cylindrical reactors one has  $S/V = 2/r_r$ . In this case it is convenient to compare the reaction development times  $\tau_1$  and  $\tau_2$ , corresponding to the same degree of reagent conversion in reactors of different cross-sectional areas (radii  $r_{r1}$  and  $r_{r2}$ ). As can be seen,  $\tau_1/\tau_2 = r_{r1}/r_{r2}$ . This can be illustrated by Fig. 7, where the growth rate of silicon nitride films in the reaction of monosilane with ammonia in different cylindrical reactors is plotted against time. Both cases are characterised by the same maximum rate, although the linear gas flow rates differ by nearly a factor of four. Assuming that the reactions are complete at, e.g., 70% conversion, one can obtain  $\tau_1 = 0.26$  and  $\tau_2 = 0.10$  s, the  $\tau_1/\tau_2$  ratio being in good agreement with the ratio  $r_{r1}/r_{r2} = 38/16 = 2.4$ .

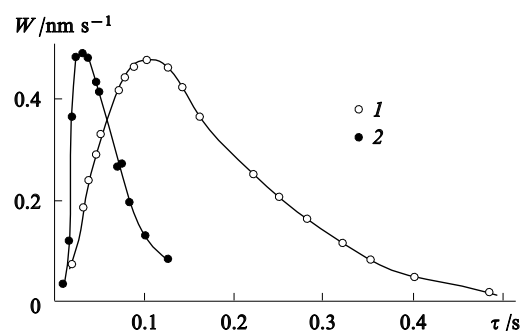


**Figure 7.** Growth rate of silicon nitride layer plotted vs. the residence time of gas mixture in reactors of radii 38 (1) and 16 mm (2).<sup>8</sup>  $T = 1123$  K,  $P = 2000$  Pa,  $[\text{SiH}_4] = 3.64 \times 10^{-7}$  mol litre<sup>-1</sup>, gas flow rate  $70 \text{ cm}^3 \text{ s}^{-1}$  under normal conditions,  $[\text{NH}_3]/[\text{SiH}_4] = 90$ .

Let us consider a volume gas-phase reaction. Assuming that passage of the gas containing an active reagent with the concentration  $c$  along the reactor at the rate  $v_T$  results in the formation of a film of thickness  $\Delta h$  after time  $\Delta t$ :

$$\Delta h = \frac{M}{S\rho_F} v_T c \Delta t.$$

The rate constant for the deposition reaction is given by:

$$k = \frac{M\xi}{S\rho_F} v_T.$$

From here we get:

$$W = \frac{M}{S\rho_F} v_T c_0 \exp\left(-\frac{Mxi}{S\rho_F} v_T t\right).$$

This equation shows that, firstly, the deposition rate at  $t = 0$  is proportional to the linear gas flow rates. Secondly, a decrease in the reaction rate with time, in reactors of different cross-sections and experiments with constant linear gas flow rate, is independent of the reactor cross-section and inversely proportional to the reactor surface area (for a cylinder, to  $\sim r_r^{-1}$ ) at constant gas flow rate.

Mention may also be made that the rate constants for growth can be most reliably determined when using the dependences that follow the process to high degrees of reagent conversion. Usually, the progression of the reaction is accompanied by significant changes in the kinetics of the process and, as a consequence, by changes in the properties of the growing film. Processes in LPCVD reactors are conducted to low degrees of reagent conversion (usually, 5%–10%); therefore, such reactions are of limited use for determining rate constants.

#### 4. Comparative characteristics of industrial CVD processes

Practical implementation of CVD in high-precision technologies often involves the use of various reactors and various combinations of reagents (and hence chemical reactions) with significantly different deposition conditions. In addition, different CVD processes are described to different extents. In particular, the approach to the determination of the rate constants (see above) has only been practically implemented for silicon nitride. Numerous studies on the subject report mainly on the dependences of the deposition rates on some parameters of the CVD processes for particular types of reactors, while the geometric parameters of reactors are often not reported.

However, long-term investigations in the field of the synthesis of silicon-based dielectric materials showed that different film deposition processes can be compared, in order to determine the most efficient technology, by using simplified approaches that are consistent with the general method of analysis of the rate constants (see above). The good reasons are as follows.

Firstly, the kinetic dependences shown in Fig. 5, as an example, appeared to be valid for all dielectric thin film deposition processes involving two or more components. The dependences only differed in the positions of the maxima of curves (the exceptions are pyrolysis of monosilane and oxidative pyrolysis of TEOS). In addition, the reactors studied met the ideal displacement conditions.

Secondly, almost all dielectric film deposition processes studied are first order with respect to the silicon-containing compound and pseudo zero order with respect to oxidants or ammonia. Acceleration or retardation of the oxidation processes in the presence of phosphorus or boron compounds manifested themselves in corresponding changes in the film growth rates.

Thirdly, industrial CVD processes proceed under conditions of maximum reaction yield, which correspond to regions of maxima in the kinetic curves.

Fourthly, modern deposition processes are performed at similar  $S/V$  ratios because high-quality film deposition in reactors

requires elimination of the 'extra' volumes in which undesired gas-phase processes can proceed. For instance, the spacing between wafers in the most widely used industrial CVD reactors (see Fig. 4*b,d*) is  $\sim 5$  mm.

Fifthly, using the film growth laws, industrial CVD processes can be characterised by a simplified approach to multipath and multistage reactions. In the framework of the kinetic model discussed above, we chose a simplified model for a CVD process, which involves three possible paths: a heterogeneous route (I), a two-stage route involving stages of homogeneous formation and heterogeneous consumption of the intermediate product (II) or formation of side aerosol products (III).

To perform a generalised characterisation of CVD processes, the main parameter chosen was the so-called effective rate constant,  $k_{\text{ef}}$ , for the process, *i.e.*, the ratio of the deposition rate, corresponding to the maximum value ( $W_{\text{max}}$ ) in the  $W = f(\tau)$  curve, to the concentration of the silicon component [Si] in the vapour phase

$$k_{\text{ef}} = \chi \frac{W_{\text{max}}}{[\text{Si}]}, \quad (2)$$

where  $\chi$  is the coefficient of proportionality. Substantiation of this approach to the description of CVD processes and the determination of  $k_{\text{ef}}$  is available in the literature (see, *e.g.*, Refs 28–31). A comparison of different processes for the synthesis of polycrystalline silicon, silicon nitride and silicon dioxide thin films and glasses showed that the experimental  $k_{\text{ef}}$  value lies in the range  $\sim 0.3$ – $10$  cm s $^{-1}$ .

Based on the results obtained, a classification of CVD processes for silicon thin films was proposed,<sup>29–31</sup> which allows for the specific features of the thin film synthesis in various chemical systems (Table 2).

#### 5. Growth of thin film dielectrics on relief surfaces

Fabrication of high-precision microelectronic devices involves a transformation of an initially planar wafer surface into a relief surface. The width of gaps separating adjacent elements of devices and the relief height can vary from fractions of a micrometre to a few micrometres. Film deposition on relief surfaces occurs at different rates. This fact is allowed for by so-called layer conformity,<sup>4–6</sup> *i.e.*, the ratio of the film thickness on the lateral face of the step to the film thickness on the top of the step  $h_2/h_1$  (Fig. 8). It was established<sup>29,32,33</sup> that layer conformity (in %) in the dielectric silicon film deposition processes depends on the rate constant  $k_{\text{ef}}$ ; the approximate empirical relation being as follows:

$$\frac{h_2}{h_1} \approx 45.4 k_{\text{ef}}^{-0.51}.$$

Some experimentally determined conformity values and intervals for the deposition on relief steps of rectangular cross-section are listed in Table 2.

Thin film deposition on the relief steps of microelectronic devices comprising ultra-small gaps between elements faces the

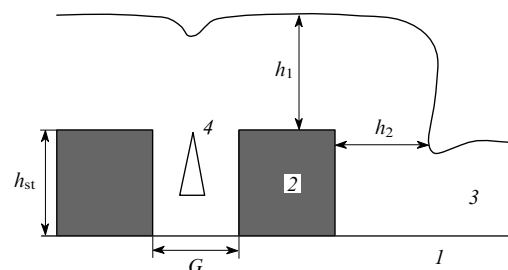


**Figure 8.** Cross-section of steps with deposited layer and corresponding main parameters.<sup>33</sup> Wafer (1), relief step (2), deposited layer (3) and unfilled void (4).



**Table 2.** Classification of CVD processes of silicon-containing thin films.<sup>30–32</sup>

| Process characteristics                                                                               | Type of CVD process |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                  |                                   |                                                                                                                                                                                                                                            |                                                                                                                                                      |
|-------------------------------------------------------------------------------------------------------|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                       | A                   | B                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | C                                                | D                                 | E                                                                                                                                                                                                                                          | F                                                                                                                                                    |
| Chemical system                                                                                       |                     | $\text{SiH}_4$ (pyrolysis) $\longrightarrow$ $\text{SiH}_4 - \text{PH}_3$ ; $\text{SiH}_4 - \text{NH}_3$ ;<br>$\text{SiH}_4 - \text{O}_2 (-\text{PH}_3)$<br>$\text{SiH}_4 - \text{N}_2\text{O} (< 950 \text{ K}) \longrightarrow \text{SiH}_4 - \text{N}_2\text{O} (> 950 \text{ K})$<br>$(\text{CH}_3)_2\text{SiCl}_2 - \text{O}_2 \longrightarrow (\text{CH}_3)_2\text{SiCl}_2 - \text{O}_2 - \text{PCl}_3$<br>$\text{SiH}_2\text{Cl}_2 - \text{NH}_3$ ; $\text{SiCl}_4 - \text{NH}_3$ ;<br>$\text{SiH}_2\text{Cl}_2 - \text{N}_2\text{O}$ |                                                  |                                   |                                                                                                                                                                                                                                            | fast non-optimised oxidation and ammonolysis reactions involving $\text{SiH}_4$ including PE-CVD <sup>a</sup> of silicon nitride and silicon dioxide |
|                                                                                                       |                     | $(\text{C}_2\text{H}_5\text{O})_4\text{Si}$ (pyrolysis) $\longrightarrow (\text{C}_2\text{H}_5\text{O})_4\text{Si} - \text{O}_2 - \text{B}(\text{OC}_3\text{H}_7)_3$<br>$(\text{C}_2\text{H}_5\text{O})_4\text{Si} - \text{O}_3/\text{O}_2 \longrightarrow (\text{C}_2\text{H}_5\text{O})_4\text{Si} - \text{O}_3/\text{O}_2 - \text{B}(\text{OC}_2\text{H}_5)_3$                                                                                                                                                                            |                                                  |                                   | $(\text{C}_2\text{H}_5\text{O})_4\text{Si} - \text{O}_2 - \text{PH}_3$<br>$(\text{C}_2\text{H}_5\text{O})_4\text{Si} - \text{O}_3/\text{O}_2 - \text{PO}(\text{OCH}_3)_3$ ,<br>and optimised PE-CVD of silicon nitride and silicon dioxide |                                                                                                                                                      |
| $k_{\text{ef}}/\text{cm s}^{-1}$                                                                      | 0.1–0.2             | $< 2.7^b$<br>$\sim 0.38^c$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 0.05–0.28                                        | 0.12–1.0                          | $\sim 0.37^d$<br>$1 - 2.6^e$                                                                                                                                                                                                               | $> 2$                                                                                                                                                |
| Factors responsible for constant film thickness                                                       | CVD conditions      | CVD conditions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | CVD conditions                                   | CVD conditions and reactor design | reactor design                                                                                                                                                                                                                             | —                                                                                                                                                    |
| Minimum film thickness non-uniformity (%)                                                             | $< 2$               | $< 2$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | $< 2$                                            | $< 5$                             | $< 10$                                                                                                                                                                                                                                     | $> 10$                                                                                                                                               |
| Aerosol formation                                                                                     | no                  | no                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | no                                               | no                                | no                                                                                                                                                                                                                                         | yes                                                                                                                                                  |
| Layer conformality (%)                                                                                | $\sim 130$          | $\sim 100$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 90–100                                           | 70–90                             | 40–70                                                                                                                                                                                                                                      | 0–20                                                                                                                                                 |
| Reaction route, possible limiting stage                                                               | I                   | I                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | II, consumption of intermediate product on wafer | II                                | II, formation of intermediate product in the vapour phase                                                                                                                                                                                  | II and III, formation of intermediate product in the vapour phase                                                                                    |
| Performance of CVD process for cylindrical LPCVD (see Fig. 4 d), number of wafers used in the process |                     | 250                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 200                                              | 80                                | 50                                                                                                                                                                                                                                         | —                                                                                                                                                    |

**Note.** Arrows denote which types correspond to a particular initial CVD process (groups A, B C) characterised by retardation or acceleration of the deposition reaction upon variation of temperature, addition of the second reagent (in pyrolysis) and addition of boron and phosphorus compounds (in oxidation processes). Analysis was performed based on the  $k_{\text{ef}}$  values taking into account (i) dependences of the film thickness non-uniformity on the parameters of the CVD process and on the reactor design, (ii) data on non-uniform thin-film deposition on the relief surfaces (see below), *etc.* The averaged values of the maximum performance of CVD processes (at the minimum film thickness non-uniformity values listed in this Table) for the most widely used cylindrical low-pressure flow CVD reactors are given in the bottom line.

<sup>a</sup> PE-CVD is Plasma-Enhanced CVD. <sup>b</sup> For pyrolysis of  $\text{SiH}_4$ . <sup>c</sup> For pyrolysis of  $(\text{C}_2\text{H}_5\text{O})_4\text{Si}$ . <sup>d</sup> For the joint pyrolysis of  $\text{SiH}_4$  and  $\text{PH}_3$ . <sup>e</sup> For the oxidation and ammonolysis reactions.

problem of high-quality (continuous) filling of the gaps with deposited film containing voids (see Fig. 8). This problem is known in the literature as the ‘Gap fill’ problem. A possible criterion for the filling of a certain gap is the parameter  $h_{st}/G^2$  (Refs 32 and 33). The quality of gap filling using CVD methods can be assessed using the approximate relationship:

$$\frac{h_{st}}{G^2} \approx 3.03k_{ef}^{-1.47}$$

( $h_{st}/G^2$  in  $\mu\text{m}^{-1}$ ).

## 6. Modern approaches to the optimisation of industrial CVD processes

The modern high-precision technologies used in microelectronics were designed to be implemented in so-called group production, *i.e.*, treatment of a particular number of wafers during one technological process. This approach implies a very high level (>95%) of reproducibility of the properties of the material and the sizes of device elements within the same semiconductor wafer, and for all wafers within the same group. This requires (i) determination of the most important parameters of the CVD processes under study, which can influence the device characteristics, and (ii) plotting their distributions schematically, shown in, *e.g.*, Fig. 9a. The desired reproducibility of the parameters of high-precision devices is achieved as a result of the optimisation of technological processes, which implies a search for an optimum ‘parameter window’ for the CVD process (see Fig. 9b), which can be realised in a reactor by using a particular combination of starting reagents. In the case of CVD processes, the number of such parameters is rather large, *viz.*, the temperature, reagent concentrations, pressure, reagent feed rate, *etc.*

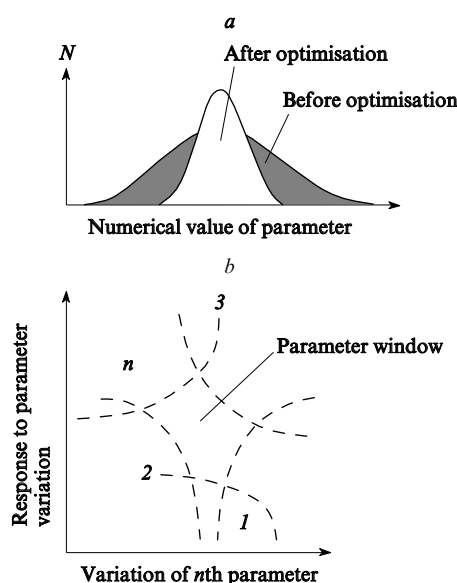


**Figure 9.** Conditional CVD parameter distribution before and after optimisation of the deposition process (a) and the parameter window (b). Dashed lines correspond to parameters 1–n.

Optimisation leads to a narrowing of the parameter distribution (see Fig. 9a). A CVD process reproducibility in the chosen parameter window is confirmed by running the ‘marathon’ test (check of the equipment and technological processes for continuous operation, or the mean-time-between-failure evaluation). When running such tests, the total number of wafers treated in a 24 h day can be as high as a few thousands, all film parameters being checked for, *e.g.*, on every 25th wafer. The reproducibility control of the CVD process, and maintenance of the parameter

distribution within the specified intervals and within the limits of necessary deviations, is achieved using methods of mathematical statistics. Combining this approach with full automation of the film deposition equipment allows one to obtain reproducible film thickness parameters and the physicochemical and electrophysical properties of the films deposited.

## IV. Deposition of silicon nitride films

Silicon nitride and boron nitride thin film fabrication technology is based on the ammonolysis reactions at elevated temperatures in the vapour phase. Silicon nitride deposition reactions are conducted using silicon hydrides, silicon halides, ammonia and hydrazine.<sup>8</sup>

The results of kinetic studies of  $\text{SiH}_4$  and  $\text{SiCl}_4$  ammonolysis have been summarised.<sup>8,34</sup> Only a few publications concerned with the kinetics of dichlorosilane ammonolysis are available, and these data have not been reviewed so far. Below we present the most important data on the kinetics and growth mechanisms of the systems involving  $\text{SiH}_4$ ,  $\text{SiCl}_4$ ,  $\text{SiH}_2\text{Cl}_2$  and  $\text{NH}_3$ .

### 1. System $\text{SiH}_4$ – $\text{NH}_3$

The main kinetic characteristics of the process of silicon nitride film deposition in the temperature range 873–1123 K were determined using an isothermal reactor, operating in the ideal-displacement regime at linear gas flow rates ranging between 4 and 20  $\text{cm s}^{-1}$ . These characteristics depend on the monosilane concentration (in the range from  $1 \times 10^{-5}$  to  $7 \times 10^{-5}$   $\text{mol litre}^{-1}$ ) and ammonia concentration (in the range from  $2 \times 10^{-5}$  to  $2.5 \times 10^{-2}$   $\text{mol litre}^{-1}$ ). The film growth rate increases in proportion to the increase in the monosilane concentration; the activation energy for this reaction, equal to 160.6  $\text{kJ mol}^{-1}$ , was determined from the temperature dependence of the rate constant. The reaction rate is independent of the ammonia concentration in the range from  $1 \times 10^{-5}$  to  $1 \times 10^{-3}$   $\text{mol litre}^{-1}$  and then monotonically increases. Taken altogether, the kinetic data obtained were described by the following empirical equation:<sup>8</sup>

$$W = k_1[\text{SiH}_4] \left[ \frac{k_2[\text{NH}_3]}{1 + k_2[\text{NH}_3]} + (1.80 \pm 0.05) \right] \frac{1}{1 + k_3[\text{H}_2]}. \quad (3)$$

The coefficients of this equation are listed in Table 3. The  $k_1$  constants of the processes carried out at reduced pressures are five to ten times higher than those carried out at atmospheric pressure. The difference is more pronounced when comparing the data for processes performed at higher temperatures. One can assume that the more accurate  $k_1$  values were determined in the experiments at a reduced pressure. This permits the most accurate determination of the rates at low degrees of monosilane conversion (here, the content of such a reaction product as, *e.g.*, hydrogen in the vapour phase, can be neglected).

To analyse the reaction of monosilane with ammonia, let us return to Fig. 5, which presents the silicon nitride growth rate distribution along the isothermal zone of the reactor. The decrease in the monosilane concentration during the reaction corresponds

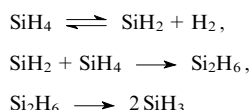
**Table 3.** Parameters of empirical equation (3) obtained for the low and atmospheric pressure CVD reactors ( $\text{\AA litre mol}^{-1} \text{ min}^{-1}$ ).<sup>8</sup>

| T / K | $k_1$                        | $k_2$              | $k_3$              |
|-------|------------------------------|--------------------|--------------------|
|       | LPCVD                        | APCVD              |                    |
| 873   | —                            | $0.58 \times 10^6$ | —                  |
| 973   | $(10.6 \pm 1.6) \times 10^7$ | $0.81 \times 10^7$ | $0.26 \times 10^4$ |
| 1023  | $(4.9 \pm 0.6) \times 10^8$  | —                  | —                  |
| 1073  | $(6.7 \pm 0.7) \times 10^8$  | $0.33 \times 10^8$ | $0.11 \times 10^4$ |
| 1123  | $(10.6 \pm 0.2) \times 10^8$ | —                  | —                  |

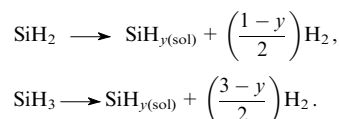
to 30%–50% monosilane conversion. At these degrees of conversion, the monosilane decomposition rate is given by:<sup>35</sup>

$$\frac{d[\text{H}_2]}{dt} = 10^{13.2} \exp\left(-\frac{214.0}{RT}\right) [\text{SiH}_4].$$

Unfortunately, this equation is valid for a relatively narrow temperature range. But the assumption of its validity at  $T = 973$  K is such that, if the overall reaction is limited by the rate of the homogeneous reaction, these degrees of conversion will be attained at a distance of a few millimetres from the beginning of the isothermal zone. These estimations suggest that thermal decomposition of monosilane, considered as a stage of the synthesis of silicon nitride, is a fast reaction. The reactions



result in the formation of the vapour-phase species  $\text{SiH}_2$  and  $\text{SiH}_3$ , involved in the interaction with the solid surface:



The composition of the particles forming the solid phase varies depending on the degree of monosilane conversion. Tetravalent silicon in  $\text{SiH}_{y(\text{sol})}$  is involved in Si–H bonding and in the bonds with the atoms of the solid phase (Si–Si or Si–N). At  $y = 2$ , the surface  $\text{SiH}_2$  group is not an adsorption site, but at  $y < 2$  it can form a chemisorption bond. Hydrogen desorption from silicon surfaces has been well studied<sup>36,37</sup> and it was shown that hydrogen atoms are strongly adsorbed on the silicon surface and that an exposure of 0.3 Langmuir leads to the formation of coatings similar to monolayers. Two adsorption forms can be clearly seen in the thermodesorption spectra. It is assumed that the first form corresponds to the surface complex  $\equiv\text{SiH}$ , characterised by a desorption energy of  $2.5 \pm 0.1$  eV; the second form being the structure  $=\text{SiH}_2$ , with a desorption energy of  $1.9 \pm 0.3$  eV.

Thermal decomposition of ammonia in the vapour phase at low pressures is proportional to the ammonia and inert gas concentrations, the rate constant (in  $\text{s}^{-1}$ ) being given by:<sup>38</sup>

$$k = 10^{14.4} \exp\left(-\frac{275.8}{RT}\right).$$

In studies of the thermal decomposition of ammonia in ammonia–argon mixtures at Ar concentrations in the range  $6 \times 10^{-4}$ – $3 \times 10^{-3}$  mol  $\text{cm}^{-3}$ , the first order rate constant (in  $\text{s}^{-1}$ ) is found from the equation:

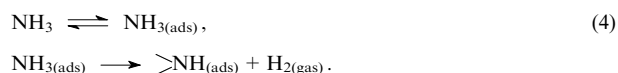
$$k = 10^{12.82 \pm 0.54} \exp\left(-\frac{409.6 \pm 20.9}{RT}\right).$$

The reaction proceeding under these conditions involves breaking of the N–H bond, characterised by a dissociation energy of 427.3 kJ  $\text{mol}^{-1}$ .

Vapour-phase synthesis produces no stable intermediates ( $\text{SiH}_4$  and  $\text{NH}_3$ ). A laser IR heating study<sup>39</sup> of the pyrolysis of monosilane–ammonia mixtures revealed (i) almost no decrease in the ammonia concentration under conditions of fast monosilane decomposition and (ii) the absence of stable products of the reaction between monosilane and ammonia, in the vapour phase. However, in the presence of ammonia the activation energy for monosilane pyrolysis decreases from  $250.4 \pm 8.4$  to  $154.2 \pm 8.4$  kJ  $\text{mol}^{-1}$ . No simple explanation for this effect has been proposed as yet. One can assume that the reaction between ammonia and monosilane results in unstable products, which favours generation of radicals. One such product can be silylamine

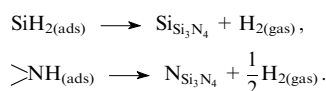
$\text{H}_2\text{NSiH}_3$ . In contrast to similar phosphorus and arsenic compounds,  $\text{H}_2\text{PSiH}_3$  and  $\text{H}_2\text{AsSiH}_3$ , silylamine is unstable; attempts at detecting it in the vapour phase having failed.

Thus, vapour-phase decomposition of ammonia can occur only at temperatures that are much higher than the temperature interval under study, 873–1073 K. Therefore, the decomposition of ammonia mainly proceeds by a heterogeneous mechanism, described by the following reactions:



As can be seen, the surface of the growing silicon nitride film meets the conditions necessary for establishment of an adsorption equilibrium. For instance, conventional film growth rates lie in the range  $10^{-2}$ – $10^{-1}$  nm  $\text{s}^{-1}$  (*i.e.*,  $\sim 5 \times 10^{14}$  molecule  $\text{cm}^{-2}$   $\text{s}^{-1}$ ). The collision frequency of  $\text{NH}_3$  molecules with the surface is  $3 \times 10^{16}$  molecule  $\text{cm}^{-2}$   $\text{s}^{-1}$  at a partial pressure of 1330 Pa, being a few orders of magnitude higher than the growth rate. Therefore, reaction (4) results in the establishment of an equilibrium, which is followed by a concentration dependence of the process, according to the Langmuir equation. The effective heat of adsorption of ammonia on the silicon nitride surface is 95.3 kJ  $\text{mol}^{-1}$ .

Decomposition of monosilane and ammonia leads to the formation of groups containing Si–H or N–H bonds on the film surface. The presence of chemisorbed hydrogen atoms on the surface hampers further adsorption; because of this, reactions producing active sites (hydrogen desorption reactions) are needed:



The retarding effect of hydrogen in the temperature range 973–1073 K at  $[\text{SiH}_4] = 3.0 \times 10^{-5}$  and  $[\text{NH}_3] = 6.4 \times 10^{-3}$  mol litre $^{-1}$  manifests itself as a dramatic decrease in the deposition rate<sup>40</sup> upon changing the hydrogen concentration from 0 to  $3.5 \times 10^2$  mol litre $^{-1}$ . The effective heat of hydrogen adsorption on the silicon nitride surface, determined from the temperature dependence of the adsorption constant, is 67.3 kJ  $\text{mol}^{-1}$ . Yet another reason for the retardation of the synthesis of silicon nitride in the presence of hydrogen can be the reversibility of the vapour-phase reaction, *e.g.*,



In this case

$$[\text{SiH}_2] = \frac{[\text{SiH}_4]}{[\text{H}_2]} K,$$

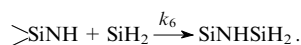
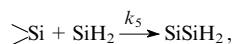
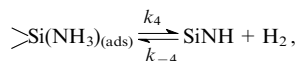
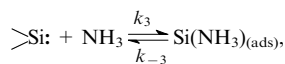
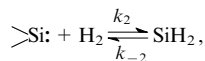
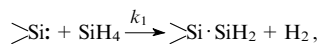
where  $K$  is the equilibrium constant.

Based on the natural assumption that the reaction rate is proportional to the concentration of  $\text{SiH}_2$  particles, we summarise that the temperature dependence of the reaction rate must have the form  $\exp[-(E_a + \Delta H)/RT]$ , where  $E_a$  is the activation energy for the reaction proceeding in the absence of hydrogen in the vapour phase, and  $\Delta H$  is the enthalpy of the reaction of  $\text{SiH}_2$  production from monosilane. The enthalpies of formation of monosilane and silylene are 34.6 and 247.9 kJ  $\text{mol}^{-1}$ , respectively;<sup>41</sup> therefore, the effective activation energy for the reaction must increase by 213.3 kJ  $\text{mol}^{-1}$  in the presence of hydrogen. It was experimentally found that the activation energy for the deposition of silicon nitride films in the presence of hydrogen is 234 kJ  $\text{mol}^{-1}$ , *i.e.*, increases by  $\sim 66$ –75 kJ  $\text{mol}^{-1}$ . Hence, our assumption of shift of the equilibrium in a certain vapour-phase reaction in the presence of hydrogen contradicts the experimental data.

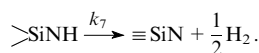
Thus, the growth rate of silicon nitride films in the reaction of monosilane with ammonia is determined by a transformation in the adsorption layer, hydrogen desorption being the slowest stage. The results of our qualitative considerations permit the derivation of an expression for the growth rate of dielectric films. Let us

assume that four types of adsorption site can be present on the surface of a growing silicon nitride film. These types are as follows: **I** —  $\text{>Si}$ , **II** —  $\text{>SiH}_2$ , **III** —  $\text{>Si(NH}_3\text{)}_{(\text{ads})}$  and **IV** —  $\text{>SiNH}$ .

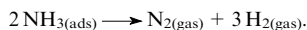
Assume also that only one reaction, *e.g.*, reaction (5), can proceed in the vapour phase. Consider the following reactions involving the adsorption sites on the surface of the growing film:



The reaction proceeding in the interior of the growing film is:



In addition to the stages considered above, a side reaction of ammonia decomposition can probably proceed on the surface of the growing film:



As the gas stream moves along the axis of the isothermal reactor, this reaction provides an increasing concentration of hydrogen in the mixture, which results in a decrease in the silicon nitride growth rate.

Taking into account the scheme of consecutive and concurrent reactions taking place on the surface of the growing film (see above), the equation for the growth rate of the dielectric film can be written in the form:

$$W = k_1[\text{I}][\text{SiH}_4] + k_4[\text{III}] + k_5[\text{II}][\text{SiH}_2] + k_6[\text{IV}][\text{SiH}_2].$$

Note that in this expression, the growth rate of structural units containing Si–N bonds is determined by the terms containing the  $k_4$  and  $k_6$  constants. The terms containing the  $k_1$  and  $k_5$  constants are responsible for the growth rate of structural units containing Si–Si bonds. This means that the stoichiometry of the films synthesised will change, depending on the reaction conditions. The rates of the stages governed by the  $k_5$  and  $k_6$  constants explicitly depend on the concentrations of the intermediate products of monosilane decomposition in the vapour phase ( $\text{SiH}_2$  and  $\text{SiH}_3$ ); therefore, specific features of the vapour-phase reactions will manifest themselves in the kinetics of silicon nitride film growth.

## 2. System $\text{SiCl}_4$ – $\text{NH}_3$

Experimental data on silicon nitride deposition in the  $\text{SiCl}_4$ – $\text{NH}_3$  system have been summarised.<sup>8,18,34</sup> The silicon nitride film growth rate distribution profile along the length of the isothermal zone of a flow tube isothermal LPCVD reactor, in the temperature range 1023–1173 K, at  $\text{SiCl}_4$  and  $\text{NH}_3$  concentrations lying in the ranges  $1 \times 10^{-5}$ – $1 \times 10^{-4}$  and  $1 \times 10^{-4}$ – $2 \times 10^{-3}$  mol litre<sup>-1</sup>, respectively, has a characteristic curve shape with a maximum, similar to the curves shown in Fig. 5. An increase in the linear flow rate of the gas mixture leads to a shift of the maximum into the interior of the reactor. These data suggest that the criterion for plug reactors is met in this case.<sup>42</sup> The dependence of the maximum reaction rate on the ammonia concentration at various  $\text{SiCl}_4$  concentrations, and on the  $\text{SiCl}_4$  concentration at a constant  $\text{NH}_3$  concentration, show that initially the reaction rate is proportional to the  $\text{NH}_3$  and  $\text{SiCl}_4$  concentrations. At specified  $\text{SiCl}_4$  concentrations, the region of zero order reaction with respect to

$\text{NH}_3$  is clearly seen, starting from a certain concentration of  $\text{SiCl}_4$ . A change in the  $\text{SiCl}_4$  concentration at a specified  $\text{NH}_3$  concentration initially leads to a linear increase in the reaction rate, which is then replaced by a region corresponding to zero order with respect to  $\text{SiCl}_4$ . In mixtures with a large excess of ammonia, the reaction rate increases with the  $\text{SiCl}_4$  concentration, faster than does a linear function.

Taking into account the characteristic dependences of the silicon nitride film growth rate on the ammonia concentration, it was assumed that the growth mechanism corresponds to a heterogeneous reaction, similar to the Langmuir–Hinshelwood reaction. This means that the process is treated as a reaction in the adsorption layer, with the reaction rate governed by the coverage of the surface of the growing film by the adsorbed  $\text{SiCl}_4$  and  $\text{NH}_3$  molecules. However, the aforementioned observations show that this assumption can only be valid for a particular set of reaction parameters. For instance, if wafers are vertically arranged in the isothermal LPCVD reactor (see Fig. 4d), the deposition rate depends on the spacing between wafers.<sup>43</sup> Analysis of the results obtained show that these features correspond to retardation at the stage of surface transformation, with allowance for diffusion supply of reagents from the vapour phase.

A strong dependence of the reaction rate on the reactor geometry was also established for the APCVD reactor at high reagent concentrations. Figure 10 presents the results obtained in two series of experiments, carried out using reactors of 67 and 14 mm diameter. As can be seen, the maximum growth rate decreases as the diameter of the reactor decreases. The results obtained can be understood if we assume that the film formation is preceded by a volume vapour-phase chemical reaction in the reactor. Therefore, the overall process must be analysed from the standpoint, according to which the synthesis of silicon nitride in the reaction of  $\text{SiCl}_4$  with  $\text{NH}_3$  proceeds as a two-path multistage reaction, controlled by the contributions of both consecutive and concurrent transformations in the vapour phase and on the surface of the growing film. Here, it is important to take into account the specific features of the chemical interactions in the  $\text{SiCl}_4$ – $\text{NH}_3$  system.

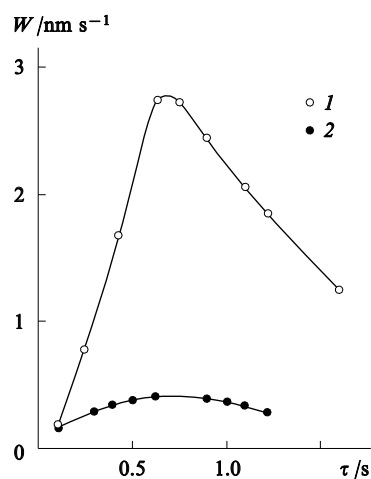
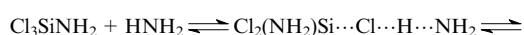
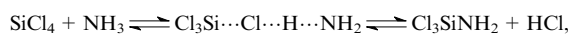
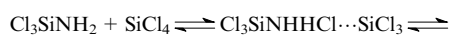


**Figure 10.** Silicon nitride film growth rate plotted vs. residence time for reactors of diameter 67 (1) and 14 mm (2).<sup>42</sup>  
 $[\text{SiCl}_4] = 6.3 \times 10^{-5}$  mol litre<sup>-1</sup>,  $[\text{NH}_3] = 1 \times 10^{-3}$  mol litre<sup>-1</sup>,  $T = 1023$  K.

Lin has shown<sup>17</sup> that the first intermediate product of the vapour-phase reaction is  $\text{SiNH}_2\text{Cl}_3$  and that subsequent reactions result in the formation of  $\text{Si(NH}_2\text{)}_2\text{Cl}$  and  $\text{Si}_2\text{NHCl}_6$ . These features can be explained assuming a multi-stage character for the reactions

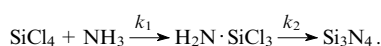


or



The variety of polymeric particles, containing several  $\text{NH}_2$  groups, shows that subsequent reactions proceed as a sequence of random collisions.

One can assume that the vapour-phase reaction results in  $\text{SiNH}_2\text{Cl}_3$ , and in the simplest case, the film growth mechanism can involve two consecutive stages with rate constants  $k_1$  and  $k_2$ :<sup>44</sup>



An expression for the maximum deposition rate in flow reactors, with inclusion of the rate constants for the reaction stages listed above, was derived for the operational regimes in the regions of zero-order reaction with respect to  $\text{NH}_3$ .<sup>44</sup> In its simplified form, it is as follows:

$$W_{\max} \approx k_2[\text{SiCl}_4]_0 \left( \frac{S}{V} \frac{k_2}{k_1} \right)^{[(V/S)(k_1/k_2)-1]^{-1}},$$

where  $[\text{SiCl}_4]_0$  is the concentration of  $\text{SiCl}_4$  at the beginning of the reaction zone and  $S/V$  is the surface-area-to-volume ratio of the reactor. The estimates of the rate constants are listed below:

$$k_1 = 1.3 \times 10^2 \exp\left(-\frac{25}{RT}\right),$$

$$k_2 = 1.5 \times 10^{25} \exp\left(-\frac{75.3}{RT}\right)$$

(here,  $k_1$  is given in  $\text{s}^{-1}$  and  $k_2$  is given in  $\text{molecule cm}^2 \text{s}^{-1}$ ).

### 3. System $\text{SiH}_2\text{Cl}_2 - \text{NH}_3$

The kinetics of interactions in the  $\text{SiH}_2\text{Cl}_2 - \text{NH}_3$  system in various types of reactors is much less studied, compared to other systems.<sup>45–53</sup> The most interesting results were obtained in the studies carried out using isothermal flow LPCVD reactors,<sup>48–50</sup> in which the kinetics of film growth from monosilane, dichlorosilane, dimethyldichlorosilane and silicon tetrachloride was compared directly under identical conditions.

The kinetics of silicon nitride film growth in the ammonolysis of dichlorosilane was investigated in the temperature range 1023–1123 K with variable reagent concentrations. The  $[\text{NH}_3]/[\text{SiH}_2\text{Cl}_2]$  reagent ratio was varied from 1 to 17, the pressure varied between 60 and 1200 Pa and the linear flow rate of the gas mixture was in the range 1450–2870  $\text{cm s}^{-1}$ . In this range of linear flow rates of the gas mixture along the reactor, the shape of the growth rate profiles and the absolute values of the reaction rates were constant, the deposition rate was first-order with respect to dichlorosilane and pseudo zero order with respect to ammonia at large excesses of  $\text{NH}_3$  with respect to  $\text{SiH}_2\text{Cl}_2$ . An empirical expression for the deposition rate (in  $\text{nm s}^{-1}$ ) takes the form:

$$W = 3.15 \times 10^{12} \exp\left(-\frac{152.3}{RT}\right) [\text{SiH}_2\text{Cl}_2].$$

Two possible mechanisms of ammonolysis of dichlorosilane have been proposed.<sup>51–53</sup> One of them is similar to the mechanism of the ammonolysis of  $\text{SiCl}_4$ , involving formation of intermediate products (e.g.,  $\text{SiH}_2\text{NH}_2\text{Cl}$ ) and the other mechanism involves a proton abstraction and the formation of  $\text{SiCl}_2$  as an intermediate. Analysis of the silicon nitride deposition rate profiles obtained for the ammonolysis of  $\text{SiH}_4$ ,  $\text{SiH}_2\text{Cl}_2$  and  $\text{SiCl}_4$  (see Fig. 11 a) reveals

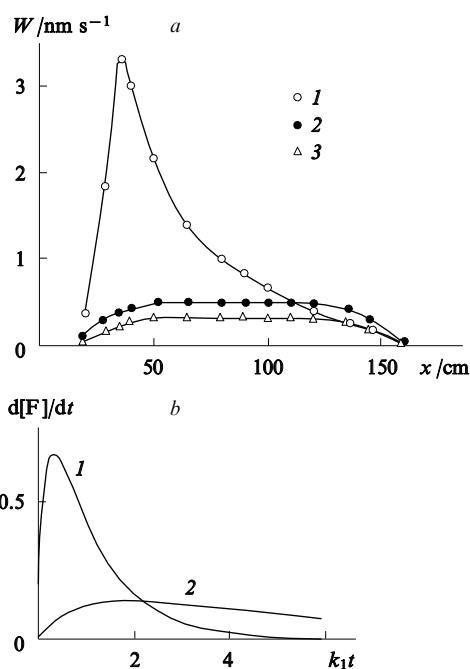


**Figure 11.** Silicon nitride deposition rate profiles obtained for ammonolysis of monosilane (1), dichlorosilane (2) and silicon tetrachloride (3) in low-pressure flow CVD reactor (a) and the deposition rate profiles predicted by the theory of consecutive one-side reactions for  $k_2/k_1 = 5$  (1) and  $k_2/k_1 = 0.2$  (2) (b);<sup>49</sup>

(a): concentration of silicon-containing compound is  $1.86 \times 10^{-6} \text{ mol litre}^{-1}$ , 'ammonia-to-silicon-containing compound' concentration ratio is 17,  $r_r = 61 \text{ mm}$ ,  $T = 1098 \text{ K}$ ,  $P = 333 \text{ Pa}$ ,  $v = 650 \text{ cm s}^{-1}$ .

significant differences between the mechanisms of the ammonolysis of monosilane and its chlorinated derivatives, also giving an indication of the similar mechanisms of ammonolysis of other chlorinated derivatives. Moreover, the profiles for ammonolysis of dimethyldichlorosilane,  $\text{SiH}_2\text{Cl}_2$  and  $\text{SiCl}_4$  are nearly identical, which points to the possibility of forming intermediates similar to  $(\text{CH}_3)_2\text{SiNH}_2\text{Cl}$ . The ammonolyses of  $\text{SiH}_2\text{Cl}_2$  and  $\text{SiCl}_4$  are characterised by similar effective rate constants in the  $W_{\max}$  regions (0.74 and 0.46  $\text{cm s}^{-1}$ , respectively) and conversions (26.6% and 18%, respectively), which are much lower than for the ammonolysis of  $\text{SiH}_4$  (4.9  $\text{cm s}^{-1}$  and 46.5%).

Taking into account the aforementioned observation, the growth of silicon nitride films can be correctly described in terms of a two-step reaction of homogeneous formation and heterogeneous consumption of intermediate products. The dependences of the accumulation of the end product on the reaction time ( $d[F]/dt$ ) (see Fig. 11 b), obtained in the framework of the theory of consecutive one-side first-order reactions



(A is the starting substance, I is the intermediate product and F is the end product) for the different limiting stages, are similar in shape to the curves obtained for the deposition of silicon nitride films (see Fig. 11 a). The limiting stage of the ammonolysis of monosilane is the formation of the intermediate product, while the ammonolysis of chlorinated monosilane derivatives is limited by the stage of heterogeneous consumption of the intermediate product.

### 4. Industrial methods of deposition of silicon nitride films

Since the early 1980s, the most widely used (in electronics) industrial method involves the use of dichlorosilane in flow LPCVD reactors. Typical conditions for the deposition reaction are as follows:  $T \approx 973 \text{ K}$  at a pressure of less than 65 Pa. In this case, the deposition rates are of the order of a few hundredths of a

nanometre per second, and the thickness non-uniformity on wafers of diameters smaller than 200 mm is less than  $\pm 2\%$  at a foreign defect (microparticles of size exceeding  $0.2 \mu\text{m}$ ) level of less than  $0.1 \text{ defect cm}^{-2}$ . The concentration of hydrogen in the films is  $\sim 4 \text{ at.}\%$  and the refractive index varies in the range  $1.96\text{--}2.00$ . As old CVD equipment for electronics is replaced by single-wafer reactors (wafer diameter up to 300 mm) (see Fig. 4b), interest in the ammonolysis of monosilane is retained. This is due to low degree of chloride conversion and correspondingly to the extensive formation of by-products (silicoimides) that poison the vacuum systems of CVD reactors.

Low-temperature deposition of silicon nitride films from mixtures of monosilane, ammonia and/or nitrogen involves plasma activation [most often, the so-called diode systems (see Fig. 4b) are used]<sup>54</sup> and occurs at temperatures below 723 K. In this case, the film composition strongly depends on the temperature and on the ammonia/monosilane ratio. Unfortunately, low-temperature silicon nitride films contain hydrogen, bonded to silicon or nitrogen; the total concentration of hydrogen exceeding  $10^{21} \text{ atom cm}^{-3}$ . Concentration depends on the deposition temperature and, for the  $\text{SiH}_4\text{--NH}_3\text{--N}_2$  system, can be 20 at.%–30 at.% at 573 K and up to 5 at.%–10 at.% at 873 K. Removal of ammonia from monosilane–nitrogen mixtures on increasing in the high-frequency power supplied, allows a 25 at.%–30% reduction of the hydrogen concentration at the same deposition temperature.<sup>55</sup>

At lower temperatures (373–573 K) under plasma activation conditions, it is also possible to use plasma pyrolysis of organo-element compounds that simultaneously contain silicon and nitrogen (hexamethyldisilazane, hexamethylcyclotrisilazane and diethylaminotrimethylsilane). By varying the high-frequency power supplied, one can vary the concentration of  $\text{CH}_3$  groups in the end polymeric material, which is often called 'silicon nitride'. The molecules of the starting compounds contain no Si–H bonds, which are formed during the synthesis<sup>56</sup> due to abstraction of protons and  $\text{CH}_3$  groups from the molecules of the starting compounds, the formation of radicals adsorbed on the surface, followed by proton addition to broken silicon bonds. Thus, fabrication of hydrogen-free films by the plasma pyrolysis of organo-element compounds appears to be impossible.

## V. Deposition of silicon oxynitride films

A number of systems were proposed for the CVD synthesis of SiON films, e.g.,  $\text{SiH}_4\text{--NH}_3\text{--CO}_2$ ,  $\text{SiH}_4\text{--NH}_3\text{--NO}$  and  $\text{SiH}_4\text{--NH}_3\text{--N}_2\text{O}$ .<sup>18, 57</sup> Let us consider the first system in more detail.

In deriving an expression for the deposition rate of films of various chemical compositions, one must use the mole-based units, e.g.,  $\text{mol min}^{-1} \text{ cm}^{-1}$ . Using ellipsometric measurements of the film thickness and the refractive index, one can determine the chemical composition by a linear approximation, assuming that the refractive index,  $RI_{\text{SiON}}$ , of the silicon oxynitride film is defined through the mole fractions of silicon nitride ( $z_1$ ) and silicon dioxide ( $z_2$ ) (the refractive indices of silicon nitride and silicon dioxide are  $RI_n = 2.025$  and  $RI_{\text{ox}} = 1.45$ , respectively):

$$RI_{\text{SiON}} = z_1 RI_n + z_2 RI_{\text{ox}}.$$

The growth rate,  $W_M$  ( $\text{mol min}^{-1}$ ), of silicon oxynitride film can be found from the equation:

$$W_M = \frac{\rho_f S W}{M} 1.67 \times 10^{-11}.$$

Here  $\rho_f$  and  $M$  are the density and the molecular mass (they can be determined with ease using the data listed in Table 4),  $S$  is the surface area of the hot wafer and  $W$  is the growth rate ( $\text{nm s}^{-1}$ ).

Experiments were carried out in a vertical non-isothermal reactor of surface area  $1058 \text{ cm}^2$ , at a gas flow rate of  $1.83 \text{ dm}^3 \text{ s}^{-1}$ , under conditions where the reaction was not

**Table 4.** Characteristics of silicon oxynitride film.<sup>18</sup>

| Refractive index | Molecular mass | Molar refraction | Density / $\text{g cm}^{-3}$ |
|------------------|----------------|------------------|------------------------------|
| 2.025            | 140.0          | 23.03            | 3.09                         |
| 1.9              | 121.6          | 19.46            | 2.91                         |
| 1.8              | 106.4          | 16.51            | 2.75                         |
| 1.7              | 92.0           | 13.71            | 2.59                         |
| 1.6              | 78.4           | 11.07            | 2.42                         |
| 1.5              | 66.4           | 8.74             | 2.23                         |
| 1.45             | 60.0           | 7.50             | 2.15                         |

limited by the mass supply rate. The reaction is first order with respect to monosilane and the deposition rate is independent of the  $\text{NH}_3$  and  $\text{CO}_2$  concentrations in the range from  $10^{-3}$  to  $5 \times 10^2 \text{ M}$ . The empirical dependences of the formation of  $\text{SiO}_2$ ,  $\text{Si}_3\text{N}_4$  and silicon oxynitride SiON at 1123–1323 K are as follows:

$$k_{\text{SiO}_2} = 2.4 \times 10^5 \exp\left(-\frac{100.3}{RT}\right) [\text{SiH}_4], \quad (6)$$

$$k_{\text{Si}_3\text{N}_4} = 22.3 \times 10^5 \exp\left(-\frac{121.2}{RT}\right) [\text{SiH}_4], \quad (7)$$

$$k_{\text{SiON}} = 3.5 \times 10^5 \exp\left(-\frac{98.2}{RT}\right) [\text{SiH}_4].$$

Considering the oxynitride film growth as a reaction following two concurrent paths, viz., ammonolysis of monosilane ( $W_n$ ) and oxidation of monosilane ( $W_{\text{ox}}$ ), the expression for  $W_{\text{SiON}}$  can be written as:

$$W_{\text{SiON}} = W_n + W_{\text{ox}}.$$

Then, assuming that the rate of formation of the structural units  $\text{SiN}_{4/3}$  and  $\text{SiO}_{4/2}$  is proportional to the surface coverage of the  $\text{NH}_3$  and  $\text{CO}_2$  molecules ( $\theta_{\text{NH}_3}$  and  $\theta_{\text{CO}_2}$ , respectively), and taking into account Eqns (6) and (7), one can write

$$W_n = k_{\text{Si}_3\text{N}_4} [\text{SiH}_4] \theta_{\text{NH}_3}^{l_1},$$

$$W_{\text{ox}} = k_{\text{SiO}_2} [\text{SiH}_4] \theta_{\text{CO}_2}^{l_2},$$

where  $l_1$  and  $l_2$  are the reaction orders with respect to their corresponding components. Assuming that  $\text{NH}_3$  and  $\text{CO}_2$  are the most intensely adsorbed species, we get

$$\theta_{\text{NH}_3} = \frac{p_{\text{NH}_3}}{(\alpha_{\text{CO}_2}/\alpha_{\text{NH}_3})p_{\text{CO}_2} + p_{\text{NH}_3}},$$

$$\theta_{\text{CO}_2} = \frac{p_{\text{CO}_2}}{(\alpha_{\text{CO}_2}/\alpha_{\text{NH}_3})p_{\text{NH}_3} + p_{\text{CO}_2}},$$

where  $\alpha_{\text{CO}_2}$  and  $\alpha_{\text{NH}_3}$  are respectively the constants of adsorption equilibrium between  $\text{CO}_2$  and  $\text{NH}_3$ .

Treatment of experimental data using this approach gave the characteristic dependence of the partial rates of formation of structural units of silicon nitride and silicon dioxide, which were used to determine the coefficients  $l_1$  and  $l_2$  ( $l_1 = 0.6$  and  $l_2 = 0.5$ ). Generally, the rates of formation of the corresponding structural units, in the course of silicon oxynitride film growth, differ from the growth rates of the silicon nitride and silicon dioxide films. In particular, the rate of formation of  $\text{SiN}_{4/3}$  in silicon oxynitride is lower than in silicon nitride, while the rate of formation of  $\text{SiO}_{4/2}$  in silicon oxynitride is higher than that in silicon dioxide. However, it should also be noted that these differences are small, being only slightly larger than the scatter of experimental data.

Recently, oxynitride films used as anti-reflecting coatings in electronics have been fabricated from  $\text{SiH}_4\text{--NH}_3\text{--N}_2\text{O--N}_2$  mixtures using low-temperature plasma synthesis. Such methods

allow films of a wide range of compositions to be fabricated by varying the component ratio in the gas mixture.<sup>54</sup>

## VI. Deposition of silicon dioxide films

Silicon dioxide films can be fabricated in the temperature range from a few hundreds of degrees to 1300 K (and higher) by oxidation, pyrolysis, hydrolysis and plasma-enhanced reactions. Below we consider the results of investigations of some most important processes in the CVD synthesis of oxide films.

### 1. Oxidation

Among the practically used CVD reactions, oxidation reactions are the best studied. They are conducted using monosilane, silicon, chlorides and the alkyl and alkoxy derivatives of monosilane as sources of silicon and oxygen, nitrogen oxides, CO<sub>2</sub>, ozone–oxygen mixtures and hydrogen peroxide as oxidants. Low-temperature film deposition (at temperatures below 850 K) is performed using a plasma of the starting components.

#### a. System SiH<sub>4</sub>–O<sub>2</sub>

At present, the SiH<sub>4</sub>–O<sub>2</sub> system is the best studied and most widely used in the synthesis of silicon dioxide films. This system has been the subject of long-term studies in different types of reactors as the method for synthesising of silicon dioxide films at temperatures below 720 K and as the basic system for the synthesis of complex silicate glasses.

The combustion of monosilane was first studied by Shantarovich,<sup>58</sup> who established a chain-radical character for this process. The ‘combustion peninsula’, which determines the range of the temperature and pressure values suitable for reaction in the SiH<sub>4</sub>–O<sub>2</sub> system, is shown in Fig. 12. If the parameters of a system lie outside the ‘combustion peninsula’, the gas mixture is inert and can be kept with no apparent changes as long time as required. Thus, in any case, the reaction products (aerosil, silicon dioxide thin film or both) in the SiH<sub>4</sub>–O<sub>2</sub> system are formed as a result of a branched chain process (BCP). Experimentally, the motion from the outside towards the interior of the ‘combustion peninsula’ (on, *e.g.*, raising the temperature with constant values for the other parameters) will give a stepwise shape to the reaction rate curve. In connection to this, attempts to explain the experimentally observed stepwise temperature dependence of silicon dioxide film deposition rate by invoking the mechanism of a reaction between the adsorbed SiH<sub>4</sub> and O<sub>2</sub> molecules on the silicon or silicon dioxide surface<sup>59,60</sup> (*e.g.*, the Langmuir–Hinshelwood mechanism), seem to be unsubstantiated.

The character of the monosilane oxidation reaction, which proceeds as an SiH<sub>4</sub>–O<sub>2</sub> gas mixture moving along the horizontal tube reactor, is as follows: the reaction rate increases until a maximum thickness of silicon dioxide thin film is achieved,<sup>61</sup> and

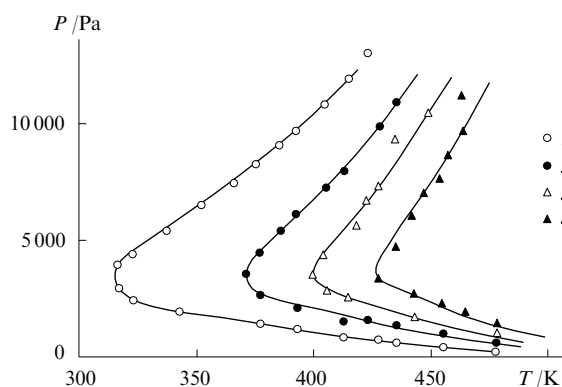


**Figure 12.** ‘Ignition peninsula’ for combustion of monosilane. [SiH<sub>4</sub>] (vol. %): 49 (1), 39 (2), 30 (3) and 14 (4).<sup>58</sup>

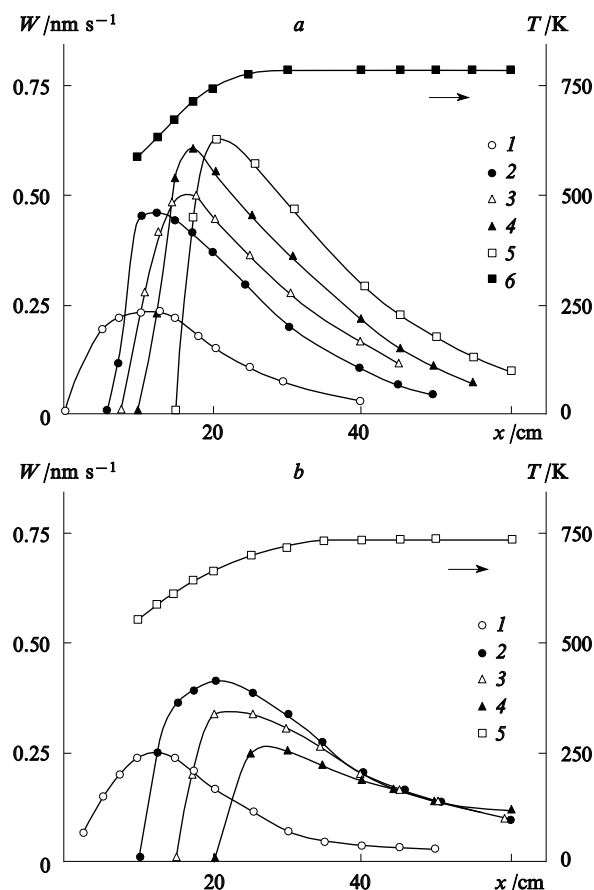


**Figure 13.** Silicon dioxide growth rate profiles along the reactor axis for different temperature profiles. (a) [O<sub>2</sub>]/[SiH<sub>4</sub>] = 10 (1), 30 (2), 50 (3), 100 (4), 300 (5); (b) [O<sub>2</sub>]/[SiH<sub>4</sub>] = 10 (1), 70 (2), 120 (3), 180 (4); [SiH<sub>4</sub>] =  $2.9 \times 10^{-2}$  mol.%, linear flow rate 19 cm s<sup>-1</sup>. Curves 6 (a) and 5 (b) denote the temperature profiles in the reactor.<sup>61</sup>

then rapidly decreases (Fig. 13a,b). A comparison of these dependences with the temperature profile in the reactor showed that the reaction is accelerated as the temperature increases. Also of note is that the initial portions of the curves are shifted towards the inside of the reactor as the [O<sub>2</sub>]/[SiH<sub>4</sub>] ratio increases, *i.e.*, corresponding to the points characterised by higher temperatures.

Note that in this case, the reaction rate at the maximum of the curve is not a characteristic parameter of the process. In particular, Fig. 13a shows that for the reactor with a steep temperature profile, the  $W_{\max}$  value increases as the oxygen concentration in the gas mixture increases. However, in the case of a flattened temperature profile in the reactor (see Fig. 13b), the maximum in the  $W(x)$  dependences initially increases and then decreases as the [O<sub>2</sub>]/[SiH<sub>4</sub>] ratio increases; as a result, we contain a dome-shaped character for the deposition rate dependences, plotted in the  $W_{\max}$ –[O<sub>2</sub>]/[SiH<sub>4</sub>] coordinates.

Using these dependences, we can compare the ignition limits of gas mixtures with the critical parameters determining the formation of silicon dioxide thin films. Data on the degree of monosilane combustion are presented in Fig. 14, and in Fig. 15 we compare the regions of SiO<sub>2</sub> film growth and monosilane combustion. These results show that film growth occurs only under conditions corresponding to monosilane ignition (in this case, the upper ignition limit). The film growth conditions correspond to O<sub>2</sub> and SiH<sub>4</sub> concentrations that are below the corresponding straight lines. Here, we have

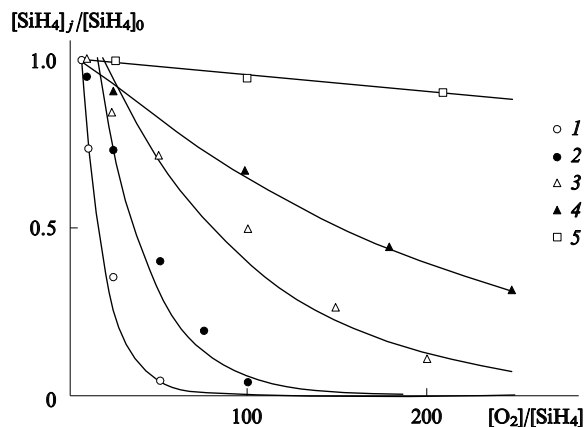


**Figure 14.** Degree of monosilane combustion,  $[\text{SiH}_4]_j/[\text{SiH}_4]_0$ , plotted vs.  $\text{O}_2$  concentration.<sup>18</sup>  
 $T = 573$  (1),  $623$  (2),  $673$  (3),  $693$  (4),  $723$  K (5);  $[\text{SiH}_4] = 8.7 \times 10^{-2}$  mol. %.

$$[\text{O}_2]/[\text{SiH}_4] = A \exp\left(\frac{-33.4}{RT}\right),$$

where  $A$  is the pre-exponent.

By studying the film growth rate distribution along the isothermal reactor zone<sup>62,63</sup> (Fig. 16), it is possible to establish the laws of silicon dioxide film growth under the conditions corresponding to the lower ignition limit. Particular attention should be paid to the regular increase in the growth rate towards the end of the isothermal zone. It becomes more pronounced as the partial pressure of monosilane increases and reflects the acceleration of the reaction due to the development of the branched chain process.

The limiting character of the phenomenon is illustrated in Fig. 17. We can determine the pressure ( $P_1$ ), corresponding to the lower ignition limit of the gas mixture. The expression for  $P_1$  contains the rate constants for the branching ( $k_b$ ) and heterogeneous loss ( $k_d$ ) of the reaction chains

$$P_1 = \frac{k_d}{2k_b f},$$

where  $f$  is the mole fraction of the component involved in the act of branching.<sup>64</sup>

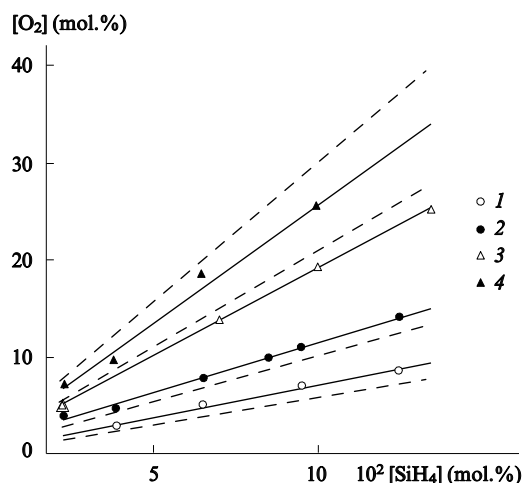


**Figure 15.**  $\text{SiO}_2$  film growth regions (solid lines) and monosilane ignition regions (dashed lines).<sup>18</sup>  
 $T = 573$  (1),  $623$  (2),  $673$  (3),  $693$  K (4).

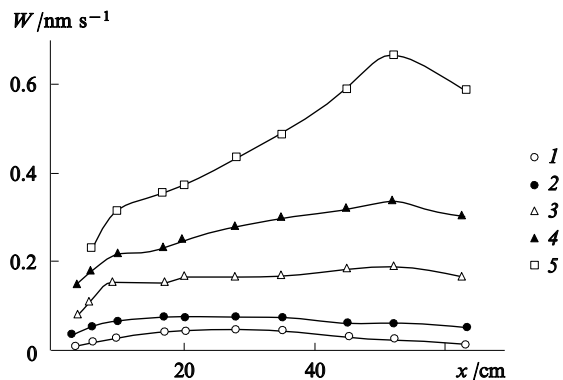


**Figure 16.**  $\text{SiO}_2$  growth rate distribution in a horizontal isothermal reactor.<sup>63</sup>  
 $T = 413$  K, diameter of the reactor is 1.3 cm, the partial pressure of monosilane, Pa: 25.3 (1), 26.7 (2), 32.0 (3), 36.0 (4) and 40.0 (5); gas flow rate is  $0.83 \text{ cm}^3 \text{ s}^{-1}$ ,  $[\text{O}_2]/[\text{SiH}_4] = 2$ .

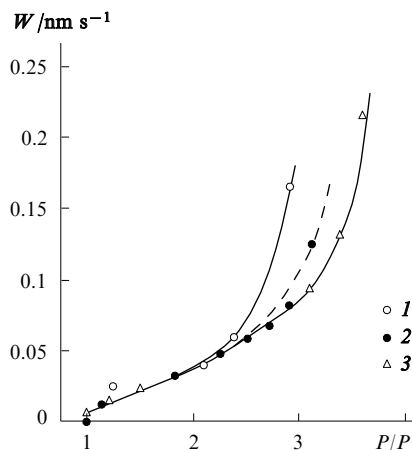


**Figure 17.**  $\text{SiO}_2$  growth rate plotted vs. monosilane pressure in reactors of different diameters.<sup>64</sup>  
Diameter of the reactor/cm: 2 (1), 1.6 (2) and 1.3 (3);  $T = 373$  K;  $[\text{O}_2]/[\text{SiH}_4] = 1$ , gas flow rate is  $0.56 \text{ cm}^3 \text{ s}^{-1}$ .

In practice, the BCP studies usually involve observing the ignition of the reacting gas mixture. A number of unexpected features were disclosed in determining the lower ignition limit from the chemiluminescence of the  $\text{SiH}_4 - \text{O}_2$  mixtures.

Firstly, the position of the lower ignition limit is 'sensitive' to the state of the reactor walls. This manifests itself, in particular, in different  $P_1$  values determined by approaching the limit using a mixture at a pressure lower than  $P_1$  (approach from below), and by approaching the limit using higher pressures (approach from above).

Secondly, a peculiar feature of the combustion of the  $\text{SiH}_4 + \text{O}_2$  mixture is a double ignition under static conditions.<sup>65-67</sup> Using emission spectra, the formation of excited  $\text{OH}^*$  radicals (band at 306.4 nm) in the flame was detected.<sup>66</sup> An EPR study<sup>67</sup> revealed the presence in the flame of hydroxyl groups and oxygen atoms in concentrations of  $10^{13} - 10^{14} \text{ particle cm}^{-3}$ . The active role of oxygen atoms in chain branching processes was proved in the experiments using inhibitors. It is known that the loss rate of oxygen atoms increases in the presence of propylene. For instance, the addition of  $\text{C}_3\text{H}_6$  (1%) increases the lower ignition limit by 40% at 623 K.<sup>62</sup>

Figure 18 shows that the concentrations of oxygen atoms and hydroxyl groups increase as the  $[\text{O}_2]/[\text{SiH}_4]$  ratio increases.<sup>67</sup> The following reactions in the flame are most probable:



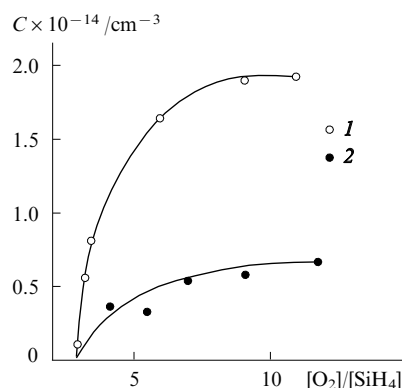
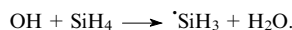
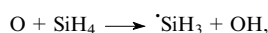


**Figure 18.** Concentration of oxygen atoms (1) and hydroxyl groups (2) plotted vs.  $[O_2]/[SiH_4]$  ratio in the initial mixture in  $SiH_4$  flame.<sup>67</sup> Total pressure is 400 Pa,  $T = 723$  K.



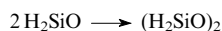
Radicals  $\cdot SiH_3$ , present in the vapour phase, were detected by laser magnetic resonance. The concentration of  $\cdot SiH_3$  radicals in the monosilane flame<sup>68</sup> was  $4 \times 10^{13}$  particle  $cm^{-3}$ . Analysis of the luminescence spectrum showed that the  $\cdot OH$  radicals are in an electronic excited state and the energy of the emission quantum is  $388 \text{ kJ mol}^{-1}$ . This suggests the occurrence of the following reaction



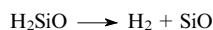
where L is the molecule involved in ternary collision. Indirect measurements showed that  $[O][H] \approx 10^{26} \text{ particle}^2 \text{ cm}^{-6} \text{ s}^{-2}$ . In addition to the particles mentioned above, electronically excited  $SiO^*$  molecules (band  $A'\Pi-X'\Sigma^+$ , emission quantum energy  $504 \text{ kJ mol}^{-1}$ ) were identified using the luminescence spectra. No more reliable data on the composition of the gas phase in the monosilane flame are available at the moment. At the same time it must be remembered that Shantarovich<sup>58</sup> assumed the presence of an intermediate, silanone  $H_2SiO$  ('silicon aldehyde'). Products containing silicon–oxygen double bonds [silanone  $H_2SiO$ , silanoic acid  $HSiOH$  and silicic acid  $(HO)_2SiO$ ] were detected only in an argon matrix at 17 K.<sup>69</sup>

When analysing the data on the kinetics of monosilane oxidation, the possibility of the formation of short-lived products must be taken into account. The inclusion of their properties allows one to establish the mechanism of the formation of finely dispersed aerosil ( $SiO_2$ ) powder, which usually accompanies the growth of  $SiO_2$  films.

Calculations<sup>70</sup> of the following dimerisation reaction



showed that the formation of the four-membered ring occurs barrierlessly and that the enthalpy of reaction is  $\Delta H_{298}^\circ = -441.8 \text{ kJ mol}^{-1}$ . The formation of trimers and tetramers is also characterised by a large exothermic effect. Silanone decomposition by the reaction



was shown<sup>71</sup> to be hampered because its activation energy is  $358.6 \text{ kJ mol}^{-1}$ . Dimerisation of  $SiO$  proceeds barrierlessly.<sup>72</sup> Two more end products,  $H_2$  and  $H_2O$ , were identified in the vapour phase. In relation to this, two possible routes of monosilane combustion are discussed:

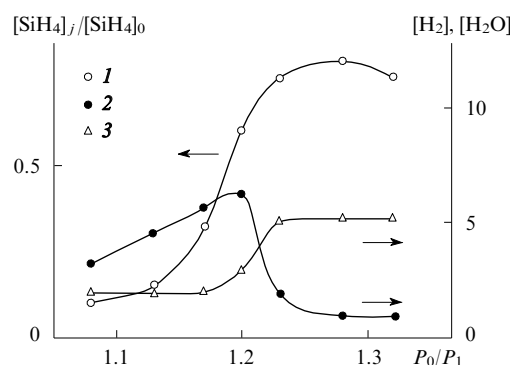
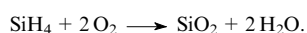
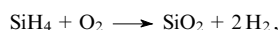
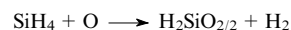


**Figure 19.** Degree of silane combustion  $[SiH_4]_j/[SiH_4]_0$  (1) and yields of the end gaseous products  $H_2$  (2) and  $H_2O$  (3) (rel. u.) plotted vs. the  $P_0/P_1$  ratio for a 9.4%  $SiH_4$  + 64%  $O_2$  + 26.6% He mixture at 423 K and  $P_1 = 203.9$  Pa.<sup>73</sup>

Quite reliable data are available, showing that the formation of water in the vapour phase is not due to subsequent combustion of hydrogen.<sup>73</sup> Analysis of the dependence (see Fig. 19) of the degree of monosilane combustion on the  $P_0/P_1$  ratio ( $P_0$  is the initial pressure in the mixture) shows that the hydrogen/water concentration ratio also varies with the  $P_0/P_1$  parameter. Water molecules can be formed as a result of the vapour-phase reaction and as a product of desorption from the surface of solid  $SiO_2$  particles. For this reason, no exact reaction equation for monosilane combustion has been derived to date.

Atoms and radicals produced in the combustion of monosilane in oxygen in the vapour phase are highly reactive species; their recombination on the surface results in the formation of silicon dioxide structural units. Some types of interactions can be established using the bond dissociation energy values. For instance, the reaction



produces a surface silicon atom bonded to two hydrogen atoms and to the oxide matrix through two bridging oxygen atoms. The reaction requires an energy expenditure for the breaking of two  $Si-H$  bonds; the formation of products will be accompanied by the release of the energy of two  $Si-O$  bonds and the energy of formation of the  $H_2$  molecule. This approach was used for the evaluation of thermal effects for different types of structural units (Table 5).

In analysing these data, considerable attention must be paid to the high thermal effect of forming the main structural unit, the

**Table 5.** Enthalpies of formation of structural units in the  $Si-H-O$  system.<sup>18</sup>

| Structural unit   | Reaction                                             | $-\Delta H$<br>/kJ mol <sup>-1</sup> |
|-------------------|------------------------------------------------------|--------------------------------------|
| $SiO_{4/2}$       | $SiH_4 + O_2 \longrightarrow SiO_{4/2} + 2 H_2$      | 802                                  |
| $H_2SiO_{2/2}$    | $SiH_4 + O_2 \longrightarrow H_2SiO_{2/2} + H_2O$    | 643                                  |
| $SiO_{4/2}$       | $(HO)_2SiO_{2/2} \longrightarrow SiO_{4/2} + H_2$    | 522                                  |
| $SiO_{4/2}$       | $HSiO_{3/2} + OH \longrightarrow SiO_{4/2} + H_2$    | 539                                  |
| $H_2SiO_{2/2}$    | $SiH_4 + O_2 \longrightarrow H_2SiO_{2/2} + H_2$     | 643                                  |
| $H_2SiO_{2/2}$    | $SiH_4 + O \longrightarrow H_2SiO_{2/2} + H_2$       | 647                                  |
| $HSiO_{3/2}$      | $H_2SiO_{2/2} + OH \longrightarrow HSiO_{3/2} + H_2$ | 539                                  |
| $(HO)HSiO_{2/2}$  | $H_2SiO_{2/2} + O \longrightarrow (HO)HSiO_{2/2}$    | 62                                   |
| $(HO)_2SiO_{2/2}$ | $(HO)HSiO_{2/2} + O \longrightarrow (HO)_2SiO_{2/2}$ | 62                                   |
| $SiO_{4/2}$       | $H_2SiO_{2/2} + O \longrightarrow SiO_{4/2} + H_2$   | 647                                  |
| $H_2SiO_{2/2}$    | $SiH_3 + O \longrightarrow H_2SiO_{2/2} + H$         | 581                                  |
| $H_2SiO_{2/2}$    | $SiH_2 + O \longrightarrow H_2SiO_{2/2}$             | 852                                  |
| $SiO_{4/2}$       | $SiH_3 + O_2 \longrightarrow SiO_{4/2} + H + H_2$    | 702                                  |
| $SiO_{4/2}$       | $SiH_2 + O_2 \longrightarrow SiO_{4/2} + H_2$        | 974                                  |

$\text{SiO}_{4/2}$  tetrahedron, and the structural unit  $\text{H}_2\text{SiO}_{2/2}$ , a building block with a two-dimensional chain structure. Account must also be taken of the fact that breaking of single chemical bonds with oxygen atoms is, as a rule, characterised by low activation energies<sup>74</sup> (usually, at most  $16.7 \text{ kJ mol}^{-1}$ ). This suggests that the main direction of reactions is determined by the stages involving oxygen atoms rather than molecules.

The most practically valuable problems in the synthesis of silicon dioxide thin films by the oxidation of monosilane with oxygen are the formation of aerosil, non-stationarity in the deposition process and the porosity of silicon dioxide films.

The essence of the first problem is that the sizes of aerosil microparticles are comparable with or larger than the size of elements of microelectronic devices. Therefore, it is highly probable that a microparticle arriving at the wafer surface during the film synthesis will be a reason for improper operation of the device. In relation to this, the level of microdefects in thin films is one of the most important characteristics of industrial CVD reactors. For instance, at the end of the twentieth century in semiconductor electronics, the level of extra film defects for CVD processes was less than  $0.1 \text{ defect cm}^{-2}$  for the wafer surface at microparticle sizes exceeding  $0.2 \mu\text{m}$ . Using microprobe analysis on the vapour phase in the film synthesis zone, it was established that aerosil microparticles are formed in the oxidation of monosilane by oxygen in all types of reactors.<sup>75–77</sup>

Various studies<sup>63, 78–82</sup> are of interest from the standpoint of determining the conditions for the growth of defect layers. They were carried out at relatively low deposition temperatures ( $373–673 \text{ K}$ ) and reagent pressures ( $< 133 \text{ Pa}$ ) in reactors of different sizes. A qualitative picture of the arrangement of the silicon dioxide film growth and aerosil formation regions, at constant values of other parameters, is shown in Fig. 20. The  $AB$  line in Fig. 20a corresponds to the limiting pressure  $P_1$  (no reaction occurs below  $P_1$ ). At  $P > P_1$ , silicon dioxide films are formed in the region above the portion of the  $AB$  curve (solid line) and below the pressure limiting line (dashed line). Above the dashed line lies the region of aerosil formation. As the temperature decreases, the range of pressures ( $\Delta P = P - P_1$ ) suitable for the fabrication of dioxide films regularly narrows. Below a certain temperature at  $P > P_1$  (where the curve of the limiting pressure is shown as a dashed line) the exclusive reaction product is aerosil.

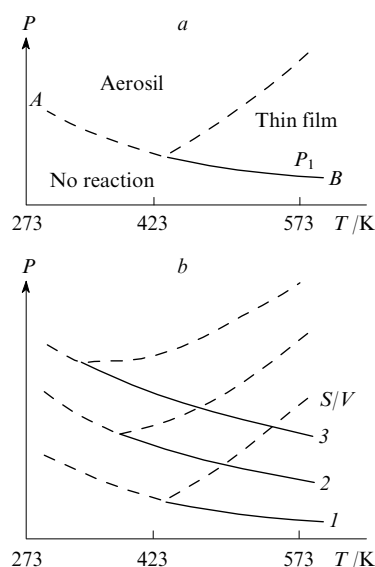


**Figure 20.** Regions of  $\text{SiO}_2$  thin-film growth and aerosil formation in the  $\text{SiH}_4\text{--O}_2$  system (a) and influence of the reactor surface-to-volume ratio on positions of these regions,  $(S/V)_1 < (S/V)_2 < (S/V)_3$  (b). For details, see text.<sup>78</sup>

Analysis of the dependences shown in Fig. 20b reveals a general trend, namely, the growth regions are shifted as the ratio of the inner surface area,  $S$ , to the volume,  $V$ , of the reactor, in the deposition zone, changes. As can be seen, the  $S/V$  parameter increases as the number of the curve increases. The effect of the  $S/V$  ratio on the film growth conditions in reactors of different sizes has been studied in detail.<sup>63</sup> The deposition was performed in quartz tube reactors with horizontally arranged wafers. It was found that at a specified temperature, pressure and  $[\text{O}_2]/[\text{SiH}_4]$  ratio, the  $P_1$  values are inversely proportional to the diameter of the reactor (*i.e.*, they increase with an increase in the  $S/V$  ratio, which is characteristic of the BCP). It is important to note that an increase in the  $S/V$  ratio (decrease in the diameter of the reactor) is accompanied by (i) an increase in the limiting pressure  $P_1$  and (ii) a simultaneous regular shift of the region of formation of silicon dioxide thin films towards low temperatures; moreover, the aerosil formation boundary is also shifted. This is an indication of improved conditions for the synthesis of defect-free thin films.

Thus, only by varying the reactor geometry, is it possible to carry out the reaction in any of the three regions shown in Fig. 20a. By varying the  $S/V$  ratio within certain limits in the film growth region, one can also change the film growth rate (this parameter will decrease with an increase in the  $S/V$  ratio). In practical implementations of the BCP for the fabrication of defect-free silicon dioxide thin films, the  $S/V$  ratio must be increased by exclusion of the 'extra volumes' in reactors by, *e.g.*, filling the gaps on both sides of wafers in the tube reactor (see Fig. 4d) with hollow vessels of the same external diameter as the wafers in order to retain the gas-dynamic parameters of the reactor.

The second and third problems are characteristic of very low-temperature ( $373–473 \text{ K}$ ) conditions for film deposition in the  $\text{SiH}_4\text{--O}_2$  system. When  $\text{SiO}_2$  is deposited at such temperatures, the kinetics of film growth is strongly dependent on the state of the inner surface of the reactor.<sup>78, 79</sup> The state of the surface (first of all, the composition and structure) governs its adsorption capacity and chain loss efficiency. Changes in these properties cause changes in the rates of the heterogeneous stages, branched chain reactions and  $\text{SiO}_2$  film deposition at constant pressure, temperature and concentration of starting reagents. Even if the parameters of the deposition process can be preset and maintained at constant levels, the chemical state of the reactor surface still cannot be controlled, but it is this factor that affects the kinetics of the chain process and leads to non-stationarity of the growth rate in the initial stages. This kind of non-stationarity will be observed until the coverage of the whole reactor surface with a new  $\text{SiO}_2$  film is complete. When the surface of the growing film is covered by the adsorption layer of a specified composition, which is reproduced in the course of further deposition, the growth rate takes a constant value. If deposition begins in a reactor whose surface was preliminarily covered with a silicon dioxide film (so-called 'modified reactor'), theoretically no transient processes would occur. This is not the case however, because the chemical properties of the surface are determined by the composition of the reacting gas mixture, from which the material is formed. Therefore, the surface properties of the newly formed silicon dioxide film will, as a rule, be different from those of the starting oxide, *i.e.*, the transient process will also occur in the modified reactor.

The kinetics of the initial stages of silicon dioxide film growth, until a thickness of  $10–20 \text{ nm}$ , was studied *in situ* using a fast automated ellipsometer.<sup>79</sup> The results obtained were summarised in the form of a diagram plotted in 'pressure of the starting gas mixture ( $P$ )–chain loss efficiency' ( $\beta$ ) coordinates and shown in Fig. 21. The  $\beta$  value characterises the change in the chemical state of the surface in the course of deposition. The  $ab$  curve drawn conditionally (the particular shape of this dependence cannot be obtained from experimental data, but it is known that  $P_1$  increases with increasing  $\beta$ ) shows the change in the limiting pressure  $P_1$  upon an increase in  $\beta$ . Below this curve lies the region corresponding to no reaction. The shaded region meets the quasi-stationary growth conditions. Experiments showed that the process always

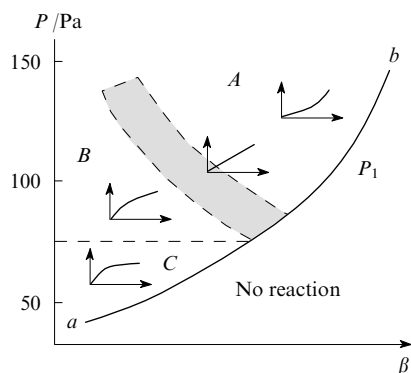


**Figure 21.** Regions with different kinetics of the initial stages of  $\text{SiO}_2$  thin film growth.<sup>78</sup>

For details, see text.  $P_1$  is the limiting pressure.

develops towards quasi-stationary growth. Depending on which direction we move along the curve (to the right or to the left), the  $\beta$  and, correspondingly,  $P_1$  values can decrease or increase.

The shape of the kinetic curves is governed by the initial conditions, *viz.*, the pressure and the chemical state of the surface. In the regions *A*, *B* and *C* (see Fig. 21) we schematically show the kinetic curves which are observed in the initial stages of growth, plotted in the 'film thickness – film growth time' coordinates. Film growth in region *A* occurs with acceleration and in the regions *B* and *C* with retardation. No stationary film growth occurs in region *B* because the growth rate decreases down to zero. Thus, all the experimentally observed shapes of the kinetic curves, which characterise the non-stationarity of the process in its initial stages, are explained by a concept of a transient process of new surface formation on the reactor walls and wafer. The properties of this surface are determined by the deposition conditions.

In studies of the kinetics of film growth until the thickness 100–1000 nm, using a quartz crystal microbalance, it was found that at temperatures below 523 K, the quasi-stationary growth, which follows the dramatic change in the growth rate in the initial stages, is retained until a thickness of 20 to 30 nm. Further increase in the film thickness leads to a monotonic (much slower compared to the changes in the initial stage) decrease in the growth rate.<sup>78</sup> The lower the synthesis temperature and the higher the pressure of the gas mixture, the more pronounced the decrease in the growth rate; in long-term experiments, the growth rate can decrease to zero.

In these experiments, the deposition rate decreases after completion of the initial transient period, in which a  $\text{SiO}_2$  layer is grown in the reactor. This means that retardation of the BCP in the course of film growth is due to other reasons, not associated with the change in the chemical state of the surface. A qualitative explanation for the decrease in the growth rate observed in this thickness range is as follows. Growth of a film is accompanied by the formation of its macro- and microstructure, which are to a great extent determined by the deposition conditions. An adsorption porosimetry study<sup>80</sup> showed that a large number of mesopores of diameter 3 to 10 nm, connected to the surface, were formed in the film under the experimental conditions. The appearance of open pores increases the real surface area of the growing film and the permeability of the film to the diffusion of the sorbed particles towards the near-surface region of the film. Taken altogether, this favours the extension of the heterogeneous reaction zone, leads to more efficient chain loss per unit surface area and, correspondingly, to a decrease in the BCP rate.

This explanation is substantiated by the following experimental results. It was found<sup>80</sup> that the porosity of thin films synthesised at temperatures below 523 K dramatically decreases upon introduction of small amounts of ammonia into the monosilane–oxygen gas mixture. Deposition of these films must not cause

a marked increase in the real surface area. If the deposition rate decreases due to the formation of the porous structure, the growth rate of such films must be independent of time. Indeed, a qualitative difference between the kinetics of thin film growth in the presence and in the absence of ammonia additives was found.<sup>81</sup> In the presence of ammonia the growth rate was independent of time until a thickness of at least 1000 nm was achieved. A constant growth rate of thin films was also observed at temperatures above 523 K because the porosity of the deposited thin film dramatically decreases with increasing synthesis temperature.

Non-stationarity of the growth of silicon dioxide thin films at low temperatures (below 573 K) and low pressures can be explained by the superposition of two processes with different dynamics, a fast process of maximum duration 120 s and a slow one. The fast process is due to the change in chemical state of the surface in the course of deposition. The slow rate decrease process is associated with changes in the real film surface owing to the formation of mesopores connected to the surface in the course of deposition. In addition to the effect of temperature on the porosity of silicon dioxide films, it is also affected by the total pressure in the course of deposition. This fact is illustrated by the dependence of the minimum pore size on the total pressure, obtained at temperatures below 473 K (Fig. 22).

The problem of aerosol formation (see above) gave an impetus to search for methods of control (in fact, inhibition) of the BCP, including the problem of improving the conformality of film deposition on stepwise reliefs. As a possible variant, the effect of such inhibitors as  $\text{C}_2\text{H}_4$ ,  $\text{C}_2\text{H}_6$ ,  $\text{C}_2\text{H}_2$ ,  $\text{NH}_3$ ,  $\text{NO}$  and  $\text{NO}_2$  on the oxidation of monosilane by oxygen was studied.<sup>83,84</sup> As can be seen from Fig. 23,  $\text{C}_2\text{H}_2$  and  $\text{NO}$  have no effect on the reaction,

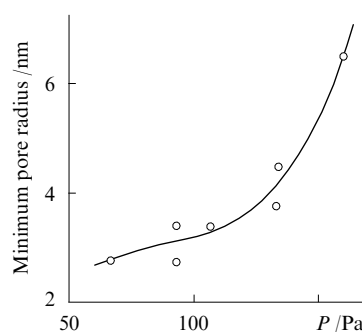


**Figure 22.** Minimum pore radius plotted vs. total pressure during the formation of  $\text{SiO}_2$  layer in the  $\text{SiH}_4$ – $\text{O}_2$  system.<sup>82</sup>

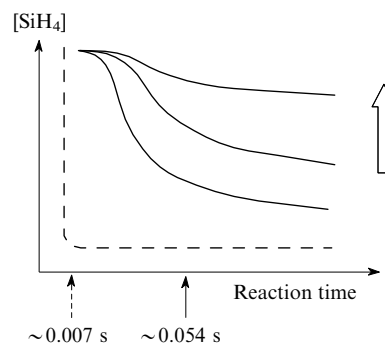


**Figure 23.** Illustration of the effect of the increase in the concentration of inhibitors (large vertical arrow) in the  $\text{SiH}_4$ – $\text{O}_2$  gas mixture on the rate of monosilane consumption.

Dashed line and dashed arrow denote the dynamics and the time of complete consumption of monosilane under inhibitor-free conditions, solid arrow denotes the time corresponding to wafer position in the reactor.<sup>83</sup>

while other compounds inhibit the oxidation of monosilane. In this case the situation on a wafer, whose arrangement in the reactor was characterised by a particular reaction time, is as follows. The silicon dioxide film growth rate correspondingly decreases and the conformality of deposition on the lateral surfaces of gaps in complex-shape reliefs is significantly improved. Nevertheless, it is now impossible to fundamentally improve the quality of deposited silicon dioxide films by the known methods of control of the BCP of monosilane oxidation by oxygen. Consequently, other chemical systems have been the subject of intensive research since the late 1970s.

### b. System $\text{SiH}_4\text{--N}_2\text{O}$

In the  $\text{SiH}_4\text{--N}_2\text{O}$  system,  $\text{SiO}_2$  can be fabricated at temperatures above 773 K (higher than in the case of the  $\text{SiH}_4\text{--O}_2$  system). By varying the  $[\text{N}_2\text{O}]/[\text{SiH}_4]$  ratio it is possible to vary the film composition continuously from amorphous/polycrystalline silicon at  $[\text{N}_2\text{O}] = 0$  to oxygen-doped polycrystalline silicon of composition  $\text{SiO}_y$  ( $y < 2$ ) at  $0.2 < [\text{N}_2\text{O}]/[\text{SiH}_4] < 10$  and further for silicon dioxide at  $[\text{N}_2\text{O}]/[\text{SiH}_4] > 50$ . Strictly speaking, in the first two cases, we are concerned with semiconductor or semi-insulating films rather than dielectric ones; therefore, they are of specific interest.<sup>‡</sup>

In flow LPCVD reactors amorphous silicon films are fabricated at a deposition temperature of  $\sim 823$  K, and polycrystalline silicon films at temperatures above 893 K. The growth rate of polycrystalline silicon depends on the reaction development time (it rapidly decreases starting at 0.05 s). In the initial stages, the deposition rate of polycrystalline silicon films depends strongly on the wafer material. Until a film thickness of  $\sim 22$  nm, the deposition rates are relatively low and therefore we can talk of an induction period in the film growth. This period is determined by the duration of the growth stages of individual nuclei, their outgrowth and their closure into a continuous layer. After completion of the induction period, the growth continues on the surface of polycrystalline silicon film, the growth rate being independent of the characteristics of the wafer material. In a particular range of pressures, the deposition rate is governed by first-order processes with respect to  $\text{SiH}_4$ . The temperature dependence of the growth rate is characterised by an activation energy of  $148.8 \text{ kJ mol}^{-1}$  for low degrees of monosilane conversion and of  $218.2 \text{ kJ mol}^{-1}$  for high conversions. The activation energy at low conversions depends on the wafer material. Pyrolysis of  $\text{SiH}_4$  follows two concurrent paths and results in the formation of reactive silylene ( $\text{SiH}_2$ ) molecules and silyl radicals  $\text{SiH}_3$ . The intermediate products involved are  $\text{Si}_2\text{H}_6$  and  $\text{Si}_3\text{H}_8$ . The presence of  $\text{SiH}_2$  and  $\text{SiH}_3$  in the vapour phase will lead to a more intense adsorption of these species on the growing surface, while the presence of polysilane molecules in the vapour phase favours the formation of silicon clusters in the vapour phase.

At a preset  $\text{SiH}_4$  concentration, the overall growth rate of oxygen-doped polycrystalline silicon ( $\text{SiO}_y$ ) films changes in a complex manner<sup>86</sup> (Fig. 24a). As can be seen, until  $[\text{N}_2\text{O}]/[\text{SiH}_4] = 10$  the growth rate decreases as follows

$$W = \frac{W_{\text{Si}}}{1 + g_{\text{N}_2\text{O}} p_{\text{N}_2\text{O}}},$$

where  $W_{\text{Si}}$  is the growth rate of the polycrystalline silicon film,  $g_{\text{N}_2\text{O}}$  is a constant and  $p_{\text{N}_2\text{O}}$  is the partial pressure of  $\text{N}_2\text{O}$ . At  $[\text{N}_2\text{O}]/[\text{SiH}_4] > 10$ , the growth rate monotonically increases, and at  $0.05 < [\text{N}_2\text{O}]/[\text{SiH}_4] < 0.6$ , the  $y$  value changes almost linearly between 0 and 1.25 (Fig. 24b).<sup>87,88</sup> The film growth rate distribution along the length of the reactor at reaction times no longer than 0.01 s exhibits a characteristic rate maximum; this feature

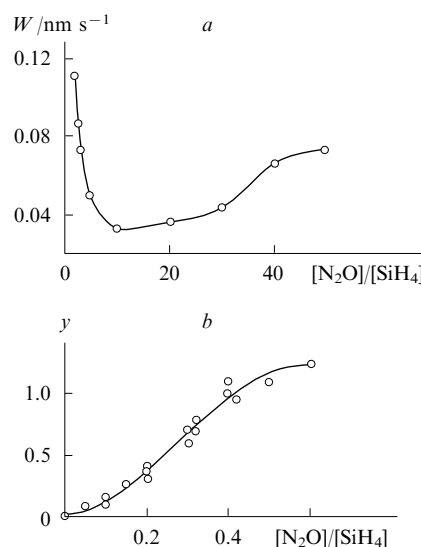


**Figure 24.** Growth rate (a) and oxygen content (b) in silicon-doped  $\text{SiO}_2$  thin films plotted vs.  $[\text{N}_2\text{O}]/[\text{SiH}_4]$  ratio.<sup>86</sup> (a):  $T = 913$  K,  $[\text{SiH}_4] = 8.0 \times 10^{-7} \text{ mol litre}^{-1}$ ; (b):  $T = 923$  K.

permits a quantitative description of the process. The temperature dependence of the deposition rate is characterised by an activation energy of  $140.8 \pm 4.0 \text{ kJ mol}^{-1}$ .

The growth of oxygen-doped polycrystalline silicon films is governed by the laws of the reactions taking place in the adsorption layer. In connection with this mention may be made that a direct experimental proof of the adsorption of  $\text{N}_2\text{O}$  molecules on the silicon dioxide surface was obtained. It is noteworthy that the constants of the adsorption equilibria on the  $\text{SiO}_2$  surface for  $\text{SiH}_4$  and  $\text{N}_2\text{O}$  ( $g_{\text{N}_2\text{O}}$  and  $g_{\text{SiH}_4}$ , respectively) are comparable.<sup>86</sup> The dependence shown in Fig. 24a can be treated as follows: the film growth rate decreases as the pressure of  $\text{N}_2\text{O}$  increases due to the competitive adsorption of  $\text{SiH}_4$  and  $\text{N}_2\text{O}$  onto the same active sites.

The growth of  $\text{SiO}_2$  films in the system under study occurs at  $[\text{N}_2\text{O}]/[\text{SiH}_4] > 50$ .<sup>89–91</sup> The process can conveniently be observed in the temperature range 833–1073 K. The deposition rate profiles along the reactor axis are presented in Fig. 25. Maxima in the deposition rate profiles correspond to the inner part of the reactor; the higher the monosilane concentration in the mixture, the larger the shift of the maximum. The initial portions of the

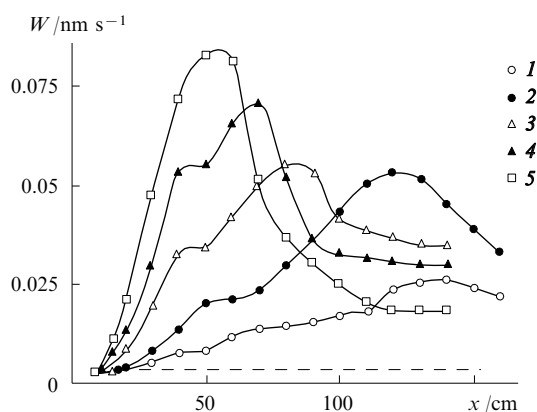


**Figure 25.** Growth rate distribution of  $\text{SiO}_2$  thin films in an atmospheric pressure isothermal reactor.<sup>90</sup> The partial pressure of  $\text{SiH}_4$  is 10.6 Pa; the partial pressure of  $\text{N}_2\text{O}$  /kPa: 2.0 (1), 5.1 (2), 8.1 (3), 15.2 (4) and 30.7 (5). Dashed line denotes the isothermal zone for  $T = 833$  K.

<sup>‡</sup> The readers who are interested in this problem are directed to Refs 18 and 85–88, which present a comprehensive treatment of the growth kinetics of such films.

curves are linear, their slopes being proportional to the pressure of  $N_2O$ . In the temperature range 1023–1073 K the growth rate maxima correspond to the beginning of the isothermal zone; in the inner part of the reactor the growth rates dramatically decrease. From these plots it follows that below 973 K, the rate of the process is described by the expression

$$W = k_1 p_{N_2O(0)} + k_2 (p_{N_2O(0)} - p_{N_2O(x)}),$$

where  $k_1$  and  $k_2$  are the rate constants and  $p_{N_2O(0)}$  and  $p_{N_2O(x)}$  are the partial pressures of  $N_2O$  at the beginning of the isothermal zone and at a point  $x$  on the axis of the reactor, respectively.

This equation reflects the fact that the reaction follows two paths. One of them, with the rate constant  $k_1$ , is responsible for the adsorption mechanism of  $SiO_2$  formation. The other path, characterised by the rate constant  $k_2$ , determines the effect of the vapour-phase reactions on the growth of  $SiO_2$  films. Involvement of the vapour-phase stages of the reaction is directly observed upon introduction of small concentrations of radical inhibitors into the vapour phase. For instance, the addition of less than 1% of ethylene or propylene into the gas mixture causes the growth rate at 873 K to decrease several-fold. The same additives introduced at 1073 K cause only a 20%–25% decrease in the growth rate. The temperature dependence of  $k_1$  is characterised by an activation energy of 196 kJ mol<sup>-1</sup>, the pre-exponent being equal to  $1.7 \times 10^{11}$  Å min<sup>-1</sup> (mm Hg)<sup>-1</sup>.

Thus, the two-path process of  $SiO_2$  film growth involves two concurrent reactions. These are the heterogeneous reaction between adsorbed  $SiH_4$  and  $N_2O$  molecules and the vapour-phase autocatalytic or chain reaction, involving the products of  $N_2O$  decomposition. Most probably, the chain reaction of monosilane oxidation with oxygen, produced in the heterogeneous decomposition of  $N_2O$ , accelerates the overall reaction.

The empirical relationships for evaluating the deposition rates (at  $T = 923$  and 1023 K) in isothermal reactors with a dense cross-vertical arrangement of wafers (with  $\sim 15$  mm spacings) (the deposition rate of  $SiO_2$  is given in nm s<sup>-1</sup>) are as follows:<sup>91</sup>

$$W_{923} = 1.67 \times 10^{-5} p_{SiH_4}^{0.5} p_{N_2O},$$

$$W_{1023} = 5.0 \times 10^{-7} \left( 320 - \frac{p_{N_2O}}{p_{SiH_4}} \right) p_{SiH_4}^{0.5} p_{N_2O}.$$

The assumption of a branched chain component of the oxidation of monosilane by  $N_2O$  (this unambiguously indicates the possibility of formation of the aerosol phase under CVD conditions) was experimentally proved by studies of the conditions for intense nucleation in the vapour phase, using gas mixtures of preset composition.<sup>91</sup> The film surfaces were checked for the presence of microparticles using an optical microscope and by scattering with photons produced by a He-Ne laser (laser light was introduced through transparent windows parallel to the axis of a flow isothermal hot-wall reactor); the light intensity was measured using a photodiode. For a known composition of gas mixture, light scattering began after a specific total pressure in the reactor had been exceeded. Once determined, the pressure values for the mixture compositions under study can be used to calculate the corresponding critical partial pressures of  $N_2O$  and  $SiH_4$ .

A generalised diagram, presented in Fig. 26, shows the regions of formation of reaction products in the form of thin films and aerosol for the deposition temperature 923 K. A correlation between the defects in the deposited film and the growth rate is apparent. Namely, defect-free silicon dioxide films grow in region *I* at rather low rates; region *II* corresponds to the appearance of microparticles on the surface of the silicon dioxide film, growing at a higher rate (the microparticles can be seen in the optical microscope); region *III* corresponds to intense nucleation in the vapour phase, where both the reactor walls and wafers become covered with a powder. The limiting growth rates of 'defect-free' silicon dioxide films in region *I* at the deposition temperatures 923, 1023 and 1123 K were estimated at  $\sim 0.08$ ,  $\sim 0.17$  and  $\sim 0.12$  nm s<sup>-1</sup>, respectively.

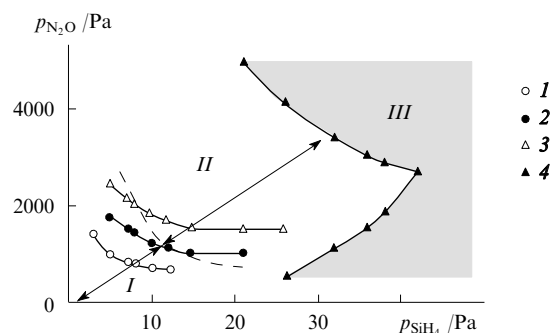
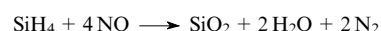


**Figure 26.** Regions of formation of the products of oxidation reaction: defect-free thin film (*I*), defect thin film (*II*) and aerosol (*III*) for the CVD process in the  $SiH_4$ – $N_2O$  system at 923 K.<sup>91</sup>

Growth rate /nm s<sup>-1</sup>: 0.033 (*I*), 0.066 (*II*) and 0.099 (*III*). Dashed line denotes the boundary between the regions *I* and *II* and curve 4 is the boundary of the region of aerosol formation (shaded).

### c. Systems $SiH_4$ – $NO$ and $SiH_4$ – $NO_2$

Depending on the concentration ratio of  $SiH_4$  and  $NO$  in the  $SiH_4$ – $NO$  system, both silicon dioxide (at  $[SiH_4]/[NO] < 0.25$ ) and silicon oxynitride (at  $[SiH_4]/[NO] = 0.5$ – $1.0$ ) films can be fabricated. The reaction



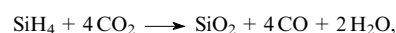
was studied at low degrees of conversion.<sup>92</sup>

The activation energy for this process is 125.4 kJ mol<sup>-1</sup>. Studies on the character of the adsorption processes on the surface of silicon at room temperature and an exposure of 10 Langmuir revealed<sup>93,94</sup> dissociative adsorption of  $NO$  and a monolayer coverage of the surface with the same coverages, equal to 0.5, for both oxygen and nitrogen atoms.

At a temperature of  $\sim 723$  K and a pressure of  $\sim 133$  Pa, the reaction proceeds slowly and obeys the laws of heterogeneous kinetics. As the pressure increases, the reaction is dramatically accelerated and intense chemiluminescence in the vapour phase is observed.<sup>92</sup>

### d. System $SiH_4$ – $CO_2$

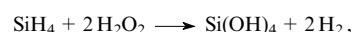
The deposition of silicon dioxide films in the  $SiH_4$ – $CO_2$  system was studied in the temperature range 973–1373 K at  $[CO_2]/[SiH_4] = 100$ .<sup>95,96</sup> The deposition rate increases as the concentrations of both components increase, being higher in argon than in hydrogen. The two possible reaction routes are as follows:



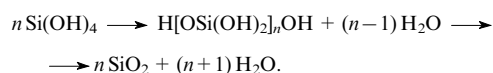
The presence of excess silicon in the  $SiO_2$  films also indicates the occurrence of a concurrent reaction, viz., the thermal decomposition of monosilane.

### e. System $SiH_4$ – $H_2O_2$

The  $SiH_4$ – $H_2O_2$  system, at a deposition temperature similar to room temperature and a reduced pressure, was proposed in order to solve a topical problem of the high-quality filling of gaps between elements with complex reliefs in microelectronic devices.<sup>97</sup> The kinetics of film growth have not been reported as yet, but it was established that the main factor affecting the deposition rate is pressure. It is assumed that the oxidation reaction

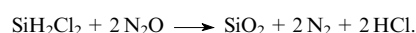


is followed by polymerisation and the formation of a silicon dioxide film:



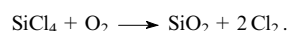
#### f. Oxidation of chlorinated and organic derivatives of monosilane

The  $\text{SiH}_2\text{Cl}_2\text{--N}_2\text{O}$ ,  $(\text{CH}_3)_2\text{SiCl}_2\text{--N}_2\text{O}$ ,  $\text{SiH}_2\text{Cl}_2\text{--O}_2$  and  $(\text{CH}_3)_2\text{SiCl}_2\text{--O}_2$  systems were studied in LPCVD reactors at temperatures 1023–1123 K.<sup>30, 45, 46, 98</sup> However, almost no kinetic data were reported. The first three systems are characterised by very low deposition rates (at most  $0.016\text{ nm s}^{-1}$ ) and a high sensitivity of the deposition processes on the total pressure in the reactor; a feature of the  $\text{SiH}_2\text{Cl}_2\text{--O}_2$  system is an intense aerosol formation. In all of these systems, the film thickness uniformity across the wafer is very low, but only the  $\text{SiH}_2\text{Cl}_2\text{--N}_2\text{O}$  system is used in high-precision technologies. The reaction for this system has the form:



The  $(\text{CH}_3)_2\text{SiCl}_2\text{--O}_2$  system appeared to be the most promising for the fabrication of silicate glass films at admissibly high temperatures, because the deposition rates under identical conditions were nearly an order of magnitude higher.<sup>30, 98</sup> The experiments were carried out using isothermal LPCVD reactors (see Fig. 4 *c, d*) at pressures 260–775 Pa in the temperature range 1023–1123 K. The deposition rate profiles in the reactors exhibited portions characterised by low deposition rate constants (a plateau), after which the growth rates increased. The plateau region became smaller as the pressure and temperature increased. The reaction is nearly first-order with respect to  $(\text{CH}_3)_2\text{SiCl}_2$ , while with respect to  $\text{O}_2$ , the reaction changes from a first-order process to a higher-order one.

$\text{SiCl}_4$  and  $\text{O}_2$  interact at temperatures  $> 1430\text{ K}$ <sup>99, 100</sup> following the reaction:



Reactions at temperatures 1073–1173 K result in thin films of two oxychlorides,  $\text{Si}_2\text{OCl}_6$  and cyclic oxychloride,  $\text{Si}_4\text{O}_4\text{Cl}_8$ . The oxidation of tin and titanium tetrahalides by oxygen at temperatures below 1073 K were also studied in order to obtain tin and titanium oxide films, respectively.<sup>18</sup>

#### g. Systems $\text{C}_2\text{H}_3\text{Cl}_2\text{CH}_3\text{SiH}_2\text{--O}_2$ and $(\text{CH}_3\text{CO}_2)_2(\text{C}_4\text{H}_9\text{O})_2\text{Si--O}_2$

Reactions in the  $\text{C}_2\text{H}_3\text{Cl}_2\text{CH}_3\text{SiH}_2\text{--O}_2$  and  $(\text{CH}_3\text{CO}_2)_2(\text{C}_4\text{H}_9\text{O})_2\text{Si--O}_2$  systems were assumed to be alternatives to the BCP in the low-temperature oxidation of monosilane, but they have found no practical applications because of low deposition rates. A typical deposition rate profile obtained<sup>101</sup> for the former system, at a deposition temperature of  $\sim 673\text{ K}$ , in a flow APCVD reactor, at a  $\text{C}_2\text{H}_3\text{Cl}_2\text{CH}_3\text{SiH}_2$  consumption of  $1.7 \times 10^{-3}\text{ cm}^3\text{ s}^{-1}$ , an oxygen consumption of  $25\text{ cm}^3\text{ s}^{-1}$  and a gas mixture flow rate of  $13\text{ cm}^3\text{ s}^{-1}$ , was similar to the profile shown in Fig. 11 *a*; with a deposition rate in the order of  $0.08\text{ nm s}^{-1}$ , this is two orders of magnitude lower than that for the oxidation of monosilane. The second system<sup>102</sup> exhibited a lowest practically admissible deposition rate of  $\sim 0.17\text{ nm s}^{-1}$ , only at temperatures above 823 K.

#### h. System $(\text{C}_2\text{H}_5\text{O})_4\text{Si--O}_3/\text{O}_2$

The  $(\text{C}_2\text{H}_5\text{O})_4\text{Si--O}_3/\text{O}_2$  system has been widely used in electronic technologies since the mid-1990s. At relatively low deposition temperatures, the growth rate of silicon dioxide films is high, with a low level of side aerosol phenomena. In addition, the system exhibits a unique ‘smoothed’ character in its film growth on stepwise reliefs, which has found practical applications. Unfortunately, there is lack of comprehensive experimental studies of the kinetics of thin film growth in this system, in spite of the availability of much practically useful technological data.

Tetraethoxysilane has long been used as the starting compound in the deposition of silicon dioxide thin films; however, the

information available mainly concerns the pyrolysis of TEOS.<sup>102–106</sup> This reaction proceeds at a noticeable rate at temperatures above 923 K (practically useful temperatures exceed 973 K); detailed consideration of the process being given below. It was also found<sup>104</sup> that in the presence of oxygen, the oxide thin films also grow at lower temperatures, and the maximum deposition rate is achieved at  $\sim 673\text{ K}$  (Fig. 27 *a*). It was assumed that this reaction results in the formation of polymeric structures.

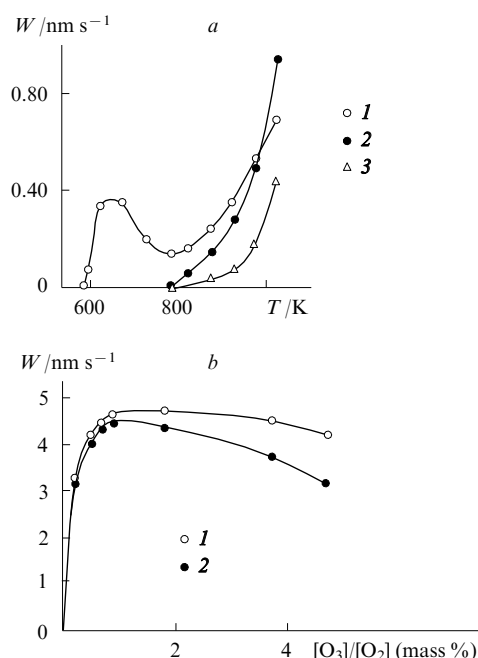


**Figure 27.** Thin-film deposition rate in the TEOS– $\text{O}_2$  (1), TEOS– $\text{H}_2$  (2) and TEOS–Ar (3) systems plotted vs. temperature (*a*) and the  $\text{SiO}_2$  film deposition rate plotted vs. ozone concentration in the gas mixture for the silicon (1) and  $\text{SiO}_2$  thermally grown on silicon (2) wafers (*b*).<sup>107, 108</sup>

Studies<sup>107, 108</sup> on the possibility of a substantial increase in the thin film deposition rate, using ozone–oxygen mixtures containing  $\sim 1$  mass% of ozone as oxidants, for the low-temperature oxidation of TEOS (Fig. 27 *b*) were of great practical interest in the early 1990s. At higher absolute values of growth rate, the temperature dependence of the deposition rate in the presence of ozone retains its shape, shown in Fig. 27 *a* for the TEOS– $\text{O}_2$  system. However, in this case, a practically valuable increase in the growth rate is accompanied by non-stationarity of the film growth in the initial stage of the deposition reaction and by selectivity of thin film growth on the silicon, silicon dioxide and silicon nitride surfaces, which increases as the ozone concentration in the gas mixture increases. An increase in the deposition selectivity is accompanied by improved conformality of deposition and, as a consequence, by the appearance of a smoothed profile for deposited thin films on stepwise reliefs.<sup>108</sup>

The deposition of thin films in the TEOS– $\text{O}_3/\text{O}_2$  system can be considered as a new avenue in the CVD of oxide thin films, and of considerable research interest. However, most studies reported so far have been concerned with the practical aspects of CVD using a few types of industrial reactors. Not only the properties of silicon dioxide thin films, but also the film growth rate,<sup>108–110</sup> deposition selectivity, methods of controlling of this parameter using modified surfaces gas additives<sup>111, 112</sup> and the conformality of thin film deposition on stepwise reliefs, are the main parameters under study.<sup>108–110, 113, 114</sup>

In summarising the data on the growth rates for industrial processes of silicon dioxide thin film deposition at  $\sim 670\text{ K}$  and pressures of 25–100 kPa, with allowance for the fact that the

deposition rate is nearly first order with respect to TEOS and a pseudozero order with respect to  $O_3$ , the effective rate constant for the reaction was found to lie in the range  $0.1\text{--}0.2\text{ cm s}^{-1}$ .

## 2. Pyrolysis reactions

Silicon dioxide, as well as  $Al_2O_3$ ,  $SnO_2$ ,  $TiO_2$ ,  $ZrO_2$ , *etc.*, thin films can be grown by the pyrolysis of vapours of organoelement compounds.<sup>9</sup>  $SiO_2$  deposition is mainly performed by pyrolysis of TEOS.<sup>103–106</sup> Industrial deposition processes of silicon dioxide thin films for electronics in isothermal flow LPCVD reactors<sup>106</sup> make it possible to fabricate films characterised by very low thickness uniformity ( $\sim \pm 2\%$ ), simultaneously on a total of 150 silicon wafers with diameters of up to 300 mm, arranged at a distance of  $\sim 5$  mm from one another. At temperatures above 973 K, the rates of pyrolysis in the presence and absence of oxygen are nearly equal. Nevertheless, oxygen additives are usually used in order to minimise the concentrations of carbon-containing impurities in the deposited silicon dioxide thin film.

The kinetic data characterise the pyrolysis of TEOS as a heterogeneous reaction involving dissociative adsorption of TEOS in the initial stages. It was assumed that monomolecular decomposition can proceed at temperatures above 773 K. The stoichiometry of the pyrolysis reaction remains unknown, because the composition of the side reaction products ( $CO_2$ ,  $CO$ ,  $H_2$ ,  $H_2O$ ,  $C_2H_4$ , *etc.*) has not been exactly determined. The thin film growth rate at 998 K and a total pressure of 46.6 Pa, expressed through the partial pressure of TEOS ( $p_{TEOS}$ ), is described by the equation:

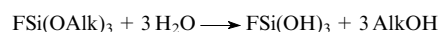
$$W = \frac{k_1 p_{TEOS}^{0.5}}{1 + k_2 p_{TEOS}^{0.5}}.$$

The effective activation energy for the reaction is  $\sim 194.4\text{ kJ mol}^{-1}$  at a total pressure of 33.3 Pa. The equation for the rate constant of pyrolysis (in  $s^{-1}$ ) in an APCVD reactor at 1023–1148 K with  $N_2$  as the medium takes the form:

$$k = 6.38 \times 10^{12} \exp \left( -\frac{238.2}{RT} \right).$$

## 3. Hydrolysis reactions

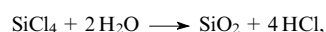
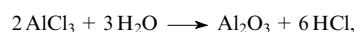
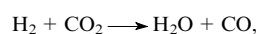
Vapour-phase hydrolysis of silicon, tin and titanium halides can be used to grow thin films of their corresponding dioxides at relatively low temperatures.<sup>115–117</sup> For instance, the interaction of  $SiF_4$  with  $H_2O$  was studied at 753–858 K and gas mixture pressures lying in the range 11.9–93.3 kPa.<sup>115</sup> The growth kinetics of  $SnO_2$  thin films was studied in the temperature range 753–981 K at linear flow rates exceeding  $6\text{ cm s}^{-1}$  (in this case, mass transfer phenomena do not influence the reaction rate).<sup>116</sup> Fluorine-containing silicon dioxide thin films, which have a more complex composition, are fabricated by the hydrolysis of alkoxy halides  $FSi(OAlk)_3$  at room temperature



followed by polymerisation.<sup>118</sup>

The limited use of low-temperature hydrolysis reactions in high-precision technologies for the fabrication of silicon dioxide thin films is mainly due to the low quality of the films produced.

Hydrolysis of  $AlCl_3$  and  $SiCl_4$ – $AlCl_3$  mixtures at temperatures above  $\sim 1123$  K in mixtures with  $CO_2$  and  $H_2$  is described by the following reactions:<sup>119, 120</sup>



which eventually result in  $Al_2O_3$  and  $SiO_2$  or in aluminosilicates (of general formula  $Al_2SiO_5$ ) in co-hydrolysis of halides.

The formation of  $Al_2O_3$  thin films was studied at a pressure of 13.3 kPa in the temperature range 1173–1423 K. The composi-

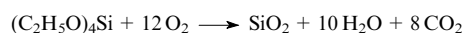
tion of the vapour phase (in mole fractions) was as follows: hydrogen, 0.05–0.95;  $AlCl_3$ , 0.005–0.03;  $CO_2$ , up to 100%.<sup>119</sup> Under these conditions, supersaturation with water vapours varied from 1.01 to 1.20 and supersaturation with  $AlCl_3$  varied from  $10^7$  to  $7.0 \times 10^{11}$ . The kinetic data were obtained under the conditions where the thin film growth rate was independent of the gas flow rate. The reaction rate at 1300 K increased as the partial pressure of  $AlCl_3$  increased, reached a maximum value at  $\sim 133.3$  Pa and then decreased on further increase in the partial pressure of  $AlCl_3$ . The dependence of the growth rate on the partial pressure of  $H_2$  obeyed an identical pattern, with the maximum value reached at  $\sim 7.33$  kPa. The temperature dependence of the process was characterised by an activation energy of  $146.3\text{ kJ mol}^{-1}$ . Most probably, the results obtained correspond to a heterogeneous reaction.

Co-hydrolysis of  $SiCl_4$  and  $AlCl_3$  was studied at temperatures 1123–1373 K, a pressure of 13.3 kPa, gas flow rates in the range  $3.67\text{--}16.7\text{ cm}^3\text{ s}^{-1}$  and mole fractions of 0.006–0.05 for  $SiCl_4$ , 0–0.015 for  $AlCl_3$  and 0.035–0.25 for  $CO_2$ .<sup>120</sup> The deposition rate of the films obtained at deposition temperatures above  $\sim 1273$  K under nearly optimum conditions was higher than  $\sim 1.6 \times 10^{-4}\text{ mg cm}^{-2}\text{ s}^{-1}$ . The activation energy for the deposition of  $SiO_2$ ,  $Al_2O_3$  and aluminosilicates at deposition temperatures above 1273 K was  $\sim 83.6\text{ kJ mol}^{-1}$  and increased to  $\sim 290\text{ kJ mol}^{-1}$  at lower temperatures for hydrolysis of  $SiO_2$ . The most interesting result obtained is a clearly seen linear dependence of the aluminosilicate deposition rate on the mole fraction of  $AlCl_3$  in the mixture, which considerably increases as the reaction temperature decreases; no dependence on the mole fraction of  $SiCl_4$  in the studied range of the experimental conditions was observed.

## 4. Plasma-enhanced oxidation reactions

Fabrication of oxide thin films in the oxidation reactions carried out at low temperatures ( $\sim 670$  K) and pressures of several hundreds of Pa using plasma-enhanced gas mixtures is of paramount practical interest, being in fact a specific field of CVD research. Considerable literature on the subject is available (see, *e.g.*, Refs 4–6, 54–56, 121–124).

The first system used for plasma-enhanced deposition at  $\sim 670$  K was  $SiH_4$ – $N_2O$ . Since the early 1990s the TEOS– $O_2$  system has been used. In principle, low-temperature plasma-enhanced synthesis of oxide films can also be performed using plasma-enhanced pyrolysis of organosilicon compounds (*e.g.*, TEOS, hexamethyldisiloxane, trimethoxychloromethylsilane, *etc.*) in an oxygen-free medium, because these molecules contain Si–O bonds.<sup>54</sup> However, the oxide films obtained contain a considerable amount of carbon, which is undesirable for micro-electronic devices. In this connection a necessary condition for plasma-enhanced synthesis of oxide films of desired quality is the presence of oxidants. In this case, in accord with the equation



even at 12-fold excess of an oxidant with respect to TEOS, the content of carbon in the films obtained can be high (up to  $\sim 3 \times 10^{20}\text{ atom cm}^{-3}$ ) and detectable by secondary ion mass spectrometry (SIMS). It was established that minimisation of the carbon content in the deposited films down to an admissible level of  $\sim 0.3 \times 10^{20}\text{ atom cm}^{-3}$  requires a 30–40-fold excess of oxygen with respect to TEOS.<sup>125</sup>

The deposition rate in the systems under study can be characterised as being first-order with respect to the source of silicon and a pseudozero order with respect to oxidant. The plot of the dependence of the deposition rate on the supplied high-frequency power is a curve with a linear portion followed by a plateau corresponding to the deposition. This permits variation of mechanical strain in the deposited film by varying the high-frequency power. (Optimisation of mechanical strain is of great importance for practical use of dielectric silicon dioxide thin films as passivators of metallisation of electronic devices). The activa-

tion energies for the plasma-enhanced oxidation reactions are  $\sim 10 \text{ kJ mol}^{-1}$ , which suggests that the temperature has little effect on the film growth kinetics.

The effective rate constant for plasma oxidation CVD processes was estimated at  $k_{\text{ef}} > 1$ . By and large, plasma enhanced deposition processes of silicon-containing films are consistent with the classification of CVD processes given in Table 2 and obey the laws of film growth on stepwise reliefs.

### 5. Industrial methods of silicon dioxide film deposition

Depending on the deposition temperature, silicon dioxide films used in electronics are divided into medium-temperature films (920–1000 K) and low-temperature ones ( $\sim 670 \text{ K}$ ); the latter being used for production of wafers containing metallic conductors. A commonly accepted medium-temperature method is oxidative pyrolysis of TEOS in isothermal LPCVD reactors. This industrial process has the best performance and parameters of deposited  $\text{SiO}_2$  films including the conformality of film growth on complex-shape reliefs.

At present, the most widely used industrial low-temperature CVD methods are oxidation of monosilane by oxygen at an atmospheric or low pressure, plasma-enhanced oxidation of TEOS by oxygen and of monosilane by  $\text{N}_2\text{O}$  and oxidation of TEOS by an ozone–oxygen mixture at an atmospheric or reduced pressure. The last-mentioned method is of limited use because of the drawback of the low density of silicon dioxide films, which depends on the properties of the material subjected to deposition. Fast methods of silicon dioxide deposition including plasma-enhanced techniques are mainly used in order to grow films on plane wafers; films on wafers with a complex relief are fabricated using oxidation by ozone–oxygen mixtures.

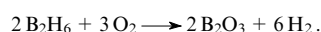
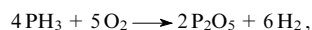
Recently, very dense silicon dioxide thin films with the high-quality (continuous) filling of narrow ( $< 0.2 \mu\text{m}$ ) gaps of a stepwise relief in microelectronic devices have been fabricated using the so-called ‘high-density plasma’ CVD (HDP-CVD) technique, where film deposition in the  $\text{SiH}_4\text{--O}_2$  system at pressures below 1 Pa is combined with sputtering of the material deposited by argon ions.<sup>126</sup> These processes have been comprehensively covered in Refs 32 and 33.

## VII. Deposition of multicomponent silicate glass thin films

Multicomponent dielectric thin films based on glass-forming oxides  $\text{SiO}_2$ ,  $\text{P}_2\text{O}_5$ ,  $\text{B}_2\text{O}_3$  and  $\text{GeO}_2$ , and belonging to silicate glasses, are prepared by CVD techniques and widely used in high-precision technologies as insulators.<sup>3–6, 127, 128</sup> Silicate glasses also possess specific properties, *e.g.*, the ability to help alkali metal ions, undergo a viscous flow at elevated temperatures, *etc.* Such glass films have long been used, but only a few kinetic studies of their growth characteristics are available. The reason for the lack of detailed kinetic studies is that such films were fabricated in industrial reactors only. To some extent this can be explained by the fact that the major component of practically interesting (valuable) compositions of silicate glasses is  $\text{SiO}_2$  (the overall concentration of other oxides is, as a rule, at most 30 mass %). Because of this, the processes of chemical vapour deposition of glasses are usually studied by analysing the changes upon the introduction of the second, third, *etc.*, components in the gas mixtures constituting the source of silicon and oxidant.

Binary phosphosilicate glass (PSG) and ternary borophosphosilicate glass (BPSG) films are best studied and most widely used in electronics.<sup>28, 30, 31, 127–137</sup> A necessary feature of glass film fabrication under the CVD conditions is the use of a strong oxidant. In the absence of the strong oxidant or when using a weak oxidant (*e.g.*,  $\text{N}_2\text{O}$ ), it is impossible to fabricate glass films without the use of excess silicon and carbon and the phosphorus content in the films is at most 1 mass%. It is commonly accepted that the glass-forming oxides ( $\text{SiO}_2$ ,  $\text{B}_2\text{O}_3$  and  $\text{P}_2\text{O}_5$ ) are formed as a result of independent oxidation reactions of hydrides  $\text{SiH}_4$ ,  $\text{PH}_3$

and  $\text{B}_2\text{H}_6$ , esters of silicic, boric, phosphorous and phosphoric acids and boron and phosphorus chlorides under the CVD conditions according to the schemes



However, exact equations of the oxidation reactions are unknown because the compositions of the side products depend on particular CVD conditions and have not been studied in detail (see above).

There are two main methods of fabrication of phosphorus- and boron-containing glass thin films, which are basic to industrial deposition techniques. One of them involves a combination of monosilane and hydrides, chlorides or organic esters at deposition temperatures in the range 620–720 K at atmospheric pressure or at low pressure of reagents. The other uses a combination of TEOS with phosphine or organic esters of boric, phosphorous or phosphoric acids and can be practically implemented in three versions, *viz.*, at 920–100 K and low pressure, at  $\sim 673 \text{ K}$  under PE-CVD conditions and at 670–770 K and atmospheric or reduced pressure of  $\text{O}_3/\text{O}_2$  mixtures (ozone concentration varies from 4 mass % to 12 mass %). The characteristics of five main industrial CVD processes are listed in Table 6. All these methods can be used for fabrication of not only BPSG thin films with boron and phosphorus concentrations of up to  $\sim 6 \text{ mass \%}$ – $8 \text{ mass \%}$  with respect to each element but also silicon dioxide and binary glass films by appropriately combining the starting reagents.

By and large, the glass film deposition processes are similar. They are nearly first order reactions with respect to the silicon-containing compounds and proceed in the presence of a large excess of oxidants, which corresponds to a pseudozero order with respect to the oxidants. The activation energies for the CVD oxidation processes (except for plasma-enhanced processes) reported by different authors lie in the range 62–209  $\text{kJ mol}^{-1}$ , those of the PE processes being an order of magnitude lower.

The influence of phosphorus- and boron-containing compounds on the parameters of the CVD processes of glass films is illustrated in Fig. 28*a*. Here, the ratios of the deposition rates ( $W$ ) of PSG and borosilicate glass (BSG) films to the deposition rate of silicon dioxide ( $W_{\text{SiO}_2}$ ) are plotted *vs.* the change in the mole ratio of the boron or phosphorus compounds to the mole ratio of the silicon compound in the vapour phase.

In the presence of phosphorus-containing compounds the oxidation reactions of silicon compounds are accelerated and their activation energies appreciably decrease (by a factor of 1.3–3). Acceleration of the reactions is favoured by a proportional increase in the phosphorus content in the deposited PSG and BPSG films, by a decrease in the film thickness uniformity and by enhanced formation of aerosol side products. The greatest acceleration of the CVD of silicate glass films (from 3 to 7 times) is achieved when using a mixture of TEOS with  $\text{PH}_3$  while the minimum acceleration is attained for the oxidation of monosilane mixed with any phosphorus compound mentioned above.

The oxidation reactions of monosilane, phosphine and other phosphorus compounds by dioxygen are known to proceed by a branched chain mechanism (see above). Taking into account this fact and the retardation of the oxidation reactions in the order  $\text{PH}_3\text{--PCl}_3\text{--organic esters}$ , the acceleration of the oxidation CVD processes studied clearly indicates their branched chain mechanism. However, boron compounds cause the CVD processes involving monosilane and phosphine to slow down, *i.e.*, inhibit the BCP. This is indicated by a decrease in the glass film deposition rate in the course of the oxidation processes involving monosilane and by a decrease in the phosphorus content in the glass films upon introduction of boron compounds into the starting gas mixtures. On the contrary, relatively slow TEOS oxidation reactions are accelerated upon introduction of boron compounds into the gas mixtures. The effect of the interaction



**Table 6.** Main characteristics of industrial glass film deposition processes.<sup>30–32</sup>

| Characteristic or parameter                                        | CVD technology                                           |                                             |                                               |                |                  |
|--------------------------------------------------------------------|----------------------------------------------------------|---------------------------------------------|-----------------------------------------------|----------------|------------------|
|                                                                    | 1                                                        | 2                                           | 3                                             | 4 (PE-CVD)     | 5 (HDP-CVD)      |
| Reactor type                                                       | see Fig. 4 a,c,d                                         | see Fig. 4 c,d                              | see Fig. 4 b                                  | see Fig. 4 b   | see Ref. 6       |
| Wafer diameter /mm                                                 | 60, 76, 100                                              | 100, 150                                    | 150, 200                                      | 200            | 200              |
| Deposition temperature /K                                          | 670–730                                                  | 970–1130                                    | 710–770                                       | 650–690        | 650–890          |
| Plasma enhancement                                                 | no                                                       | no                                          | no                                            | yes            | yes              |
| Silicon source                                                     | SiH <sub>4</sub>                                         | TEOS                                        | TEOS                                          | TEOS           | SiH <sub>4</sub> |
| Phosphorus and boron sources                                       | PH <sub>3</sub> , B <sub>2</sub> H <sub>6</sub> , esters | PH <sub>3</sub> , PCl <sub>3</sub> , esters | esters                                        | esters         | PH <sub>3</sub>  |
| Oxidant                                                            | O <sub>2</sub>                                           | O <sub>2</sub>                              | O <sub>3</sub> /O <sub>2</sub>                | O <sub>2</sub> | O <sub>2</sub>   |
| Pressure /Pa                                                       | 60–260                                                   | 60–260                                      | (2–10) × 10 <sup>4</sup>                      | 665–1730       | ~0.6             |
| Carrier gas                                                        | N <sub>2</sub> /Ar                                       | Ar                                          | He                                            | N <sub>2</sub> | Ar               |
| Growth rate /nm s <sup>−1</sup>                                    | ~0.5–8 (APCVD reactor),<br>~0.08–0.25 (LPCVD reactor)    | up to ~0.35                                 | 5–10                                          | up to ~17      | ~7               |
| Film thickness uniformity (±%)                                     | < 10                                                     | < 3                                         | < 1.5                                         | < 2            | < 2              |
| Effect of phosphorus compounds on the deposition process           | acceleration                                             | acceleration                                | acceleration                                  | acceleration   | —                |
| Effect of boron compounds on the deposition process                | retardation                                              | acceleration                                | acceleration                                  | acceleration   | —                |
| τ <sub>max</sub> /s                                                | ≤ 0.025                                                  | ~0.05                                       | ~0.05                                         | —              | —                |
| k <sub>ef</sub> /cm s <sup>−1</sup>                                | 2.0–2.6                                                  | 0.8–1.1                                     | 1.1–1.5                                       | 2–5            | —                |
| Surface roughness /nm                                              | ~12 (APCVD reactor),<br>~2.5 (LPCVD reactor)             | —                                           | ~2.1 (APCVD reactor),<br>~0.9 (LPCVD reactor) | 0.8            | 0.5              |
| Conformality (h <sub>2</sub> /h <sub>1</sub> ) (%)                 | 30–40                                                    | 60–80                                       | 60–80                                         | 10–30          | —                |
| Gap-fill test (h <sub>st</sub> /G <sup>2</sup> ) /μm <sup>−1</sup> | —                                                        | —                                           | < 4                                           | < 1            | > 20             |

between the boron and phosphorus compounds in the course of CVD processes on the final parameters of the deposited BPSG thin films can be characterised as follows: phosphorus compounds favour incorporation of boron into the film deposited while boron compounds inhibit the incorporation of phosphorus into the glass thin film.

A good illustration of the influence of acceleration and retardation of CVD processes is provided by Fig. 28 b. A model

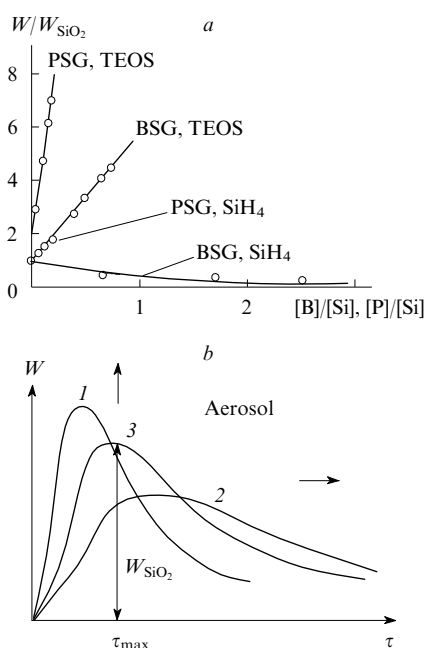


**Figure 28.** Effect of phosphorus- and boron-containing compounds on the parameters of CVD processes (a) and the influence of acceleration (1) and retardation (2) of the oxidation reaction on the shape of the deposition rate profile in a flow reactor (3) (b).<sup>28, 30</sup> For details, see text.

flow reactor is characterised by a generalised SiO<sub>2</sub> deposition rate profile (curve 3) obtained by recalculating the experimental data to the corresponding coordinates. Analysis of the experimental profiles showed that the glass film deposition kinetics is governed by the phosphorus compounds. The presence of phosphorus compounds causes acceleration of the reactions and a shift of the deposition rate profiles to the left (towards shorter residence times) and favours the formation of aerosol reaction products. At the same time the presence of boron compounds causes retardation of the oxidation reactions and a shift of the deposition rate profile to the right; no aerosol particles are observed in this case (see Fig. 28 b). The limiting BPSG growth rates achieved in different deposition processes can be ~1.5–2 times higher than the growth rates listed in Table 6, which favours incorporation of microparticles into the glass films. The directions in which undesired aerosol effects in the deposition of BPSG thin films increase are shown by arrows in Fig. 28 b.

A comparison of various oxidation processes used for glass film deposition showed that in the case of PSG and BPSG the k<sub>ef</sub> value can lie in the range 1.1–2.5 cm s<sup>−1</sup>. Thus, in spite of considerable differences between the deposition of SiO<sub>2</sub> films involving monosilane and TEOS, the kinetic characteristics of these processes are quite similar to those of the deposition processes of glass films of similar compositions.

The problem of the quality of the surfaces of films deposited is topical when one deals with the CVD of glass films involving BCP. The surface roughness of a glass film is characterised (naked-eye observation) using such terms as ‘mirror’, ‘with inclusions’, ‘haze’, etc. The kinetic data on the CVD of glasses can be checked by studying the surface roughness of the BPSG films obtained by different methods using atomic force microscopy.<sup>138</sup> This method has been used in the thin-film surface roughness measurements since the mid-1990s. Comparative studies of the surfaces of glass films of different compositions have revealed some trends.<sup>138</sup> For instance, acceleration of the oxidation reactions by phosphorus compounds makes the glass surfaces rougher while retardation of the same oxidation reactions by boron compounds reduces the surface roughness. The surface roughness of thin films fabricated from TEOS by the methods 3 and 4 (see Table 6) lies in the range

0.8–2 nm. This is on average nearly 2.5 (6) times lower than surface roughness of thin films fabricated from monosilane by the method 1 at atmospheric (low) pressure. This confirms the occurrence of intense vapour-phase processes in the course of CVD involving monosilane. The large difference between the surface roughness of the thin films prepared at low and atmospheric pressures can be explained by substantially different growth rates.

The surface roughness of BSG thin films is about twice lower than those of the PSG and BPSG thin films fabricated under similar conditions. This result clearly indicates a decrease in the intensity of vapour-phase reactions in the presence of boron-containing compounds in the gas mixture. The maximum surface roughness of silicon dioxide films prepared by the oxidation of TEOS by a  $O_3/O_2$  mixture is  $\sim 6$  nm. This value decreases by more than an order of magnitude upon introduction of esters of boric and phosphoric acids to the gas mixture; apparently, in this case the mechanism of the CVD process changes.

Acceleration and retardation of oxidation processes by phosphorus and boron compounds suggests that the oxidation of the gas mixture components involves formation of common intermediates rather than intermediate products of individual reactions. Although the mechanisms of the oxidation reactions proceeding in the course of BPSG fabrication have not been studied so far, the totality of kinetic data on the influence of phosphorus compounds unambiguously points to the similarity of the mechanisms of the PSG and BPSG film deposition reactions involving radicals formed in the interaction between phosphorus-containing compounds and oxidants. This was included in a generalised scheme of the synthesis of oxide films,<sup>28,30</sup> which is based on the concept of multistage and multipath processes of the growth of dielectric films under CVD conditions (see above).

A scheme of the deposition of silicon dioxide and glass films is presented in Fig. 29 (shown is an example of a multicomponent chemical reaction involving TEOS, for which the acceleration effect is most pronounced). Heterogeneous formation of silicon dioxide (route I) proceeds either as pyrolysis of TEOS on the surface at high temperatures or, in the presence of ozone, as a reaction of adsorbed TEOS and ozone at low temperatures. In the latter case the structure of the film deposited is rougher and more porous than the structure of silicon dioxide films fabricated using oxygen as oxidant. This indicates that the silicon dioxide films are more structurally ordered. If boron and phosphorus compounds are introduced in the gas mixture, the process follows a two-stage scheme (route II), which implies homogeneous formation of intermediate products  $I_X$  and  $I_Y$  involving phosphorus-containing radicals (asterisked) followed by heterogeneous transformation of  $I_X$  and  $I_Y$  into the film deposited on the wafer. In the case of PSG

and BPSG, the film growth processes are limited by the stage of homogeneous formation of intermediate products  $I_X$ , whereas the growth of borosilicate glass films following the second route is limited by the heterogeneous stage of consumption of intermediate products  $I_Y$ . Aerosols are formed following route III involving formation of clusters (including those containing boron and phosphorus oxides) in the vapour phase.

A characteristic feature of glassy materials obtained from organic esters is the presence of carbon impurities in the films deposited. For instance, SIMS studies of phosphorus-enriched films prepared by the method 3 (7 mass % of phosphorus and 3 mass % of boron) revealed a uniform distribution of carbon along the film thickness and showed that its content is nearly three times lower than in the films with a similar content of phosphorus (4 mass %) and boron (4.5 mass %), being  $\sim 1.05 \times 10^{19}$  and  $\sim 3.19 \times 10^{19}$  atom  $cm^{-3}$ , respectively. Hydrogen impurities are present in glasses obtained by all deposition techniques. Generally, the content of hydrogen increases if the CVD temperature is below 670 K. The PSG and BPSG thin films freshly deposited by the method 3 and containing 4 mass % of boron and phosphorus are characterised by uniform distribution of hydrogen, its initial content being equal to  $\sim 3 \times 10^{20}$  atom  $cm^{-3}$ . The content of hydrogen in the glass films prepared by the methods 4 and 5 is  $\sim 6 \times 10^{20}$  and  $\sim 4 \times 10^{20}$  atom  $cm^{-3}$ , respectively.

Because of multicomponent composition of silicate glasses, many factors must be controlled. Among them, the most important is the behaviour of the phosphorus and boron components of the glass. Their concentrations and uniformity of distribution across the surfaces of wafers are determined either using destructive methods of spectral analysis, dissolution, *etc.*, or by pre-calibrated non-destructive methods (IR spectroscopy and X-ray fluorescence).

The compositions of the glass thin films prepared by CVD in the presence of a large excess of oxidants are similar to the compositions of stoichiometric glasses, *i.e.*, the films contain silicon, boron and phosphorus oxides  $SiO_2$ ,  $B_2O_3$  and  $P_2O_5$ , respectively. The absence of excess silicon is indicated by the refractive index values of these thin films (from 1.44 to 1.48) measured by ellipsometry. Phosphorus-containing compounds are oxidised to  $P_2O_5$ ; however, in some cases ion chromatography of glasses reveals the presence (less than  $\sim 1$  mass %) of phosphorus in the oxidation state +3, which corresponds to the phosphorus oxide  $P_2O_3$ . This is characteristic of the low-temperature processes of PSG and BPSG deposition from hydrides at low pressure and of the plasma-enhanced deposition techniques involving phosphines under oxidant-deficient conditions (or in the presence of a weak oxidant) at considerable high-frequency power supplied. For the plasma-enhanced glass deposition techniques, it was also reported that the ESCA spectra revealed the formation of not only the P–O (134 eV) but also the Si–P (130 eV) bond. Only phosphorus in the oxidation state +5 is detected in the thin films prepared using the oxidation systems involving organic esters at large excesses of oxidants. No phosphorus in other oxidation states was detected in the PSG thin films deposited in high-density plasma involving hydrides.<sup>139</sup> The use of appropriate synthetic strategy leads to uniform distribution of boron and phosphorus along the thickness of different BPSG thin films; this was confirmed by the results of layer-by-layer SIMS analysis.

Silicate glass thin films possess different properties. First of all, such films differ in degree of structural imperfection (defectness). One must distinguish between two components of this parameter. One component characterises the deposition technique itself (*i.e.*, the state of the equipment and the extent of optimisation of the deposition conditions) and is measured immediately after the deposition. The second component characterises the degree of defect of glasses as a specific property of the glassy material (*e.g.*, BPSG) and manifests itself when the glass film is exposed to atmospheric air. Depending on the glass composition, the value of this component can increase by several orders of

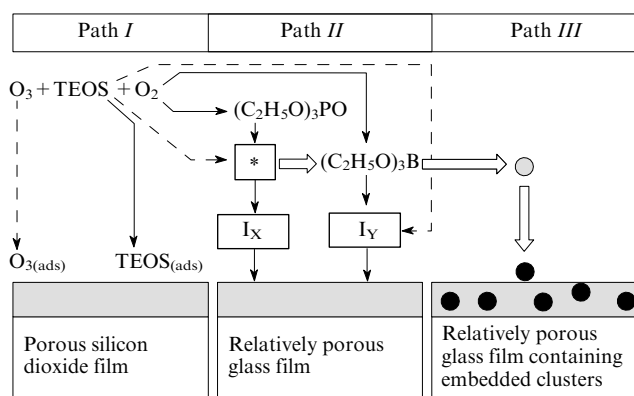
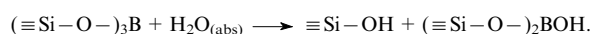
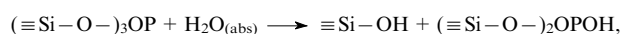


**Figure 29.** Three-path scheme of chemical vapour deposition of  $SiO_2$  and glass films in a chemical system containing organic esters of silicic, boric and phosphoric acids.<sup>28, 132</sup>

magnitude over short time intervals.<sup>134</sup> Problems concerned with the defectness of glass films are summarised in Refs 31 and 133–135.

Different properties of the glass thin films were explained by their different compositions and structures due to the use of a variety of deposition methods. The structure of the BPSG thin films is first of all determined by the boron-to-phosphorus oxide ratio in the glass. The dependence of the reactivity of the BPSG thin films towards, *e.g.*, absorbed water vapours  $\text{H}_2\text{O}_{(\text{abs})}$  present in the air on the film composition can be explained by the presence of boron atoms coordinated to three oxygen atoms ( $\text{BO}_3$ ) in the glass network, in which the silicon and phosphorus oxides are present in the form of tetrahedral  $\text{SiO}_4$  and  $\text{PO}_4$  units. The glass structural fragments ( $\equiv\text{Si}-\text{O}-$ )<sub>3</sub>OP and ( $\equiv\text{Si}-\text{O}-$ )<sub>3</sub>B react with water vapour as follows:



Prolonged interaction between the glass and water vapour and replacement of  $\equiv\text{Si}-\text{O}-$  groups by  $-\text{OH}$  groups lead to gradual leaching of boron and phosphorus from the glass film and formation of droplets containing phosphoric and boric acids on the glass surface. It was shown that the content of boron atoms coordinated to three oxygen atoms decreases with an increase in the concentration of phosphorus oxide in the glass film and that the content of boron atoms coordinated to four oxygen atoms increases. As a result, an increase in the phosphorus-to-boron content ratio in the glass makes the material less reactive towards water vapour in air.

Interrelation between the properties of glasses and specific features of deposition processes can be explained as follows. The most important physical property of glass thin films is their effective density (or its reciprocal, porosity). Unfortunately, no data on the density of the BPSG thin films, measured by direct methods are available in the literature as yet. Based on the totality of data on, in particular, the shrinkage and etch rates of samples in aqueous solutions of hydrofluoric acid, the highest porosity was ascribed to silicon dioxide, PSG, BSG and BPSG thin films fabricated by low-temperature oxidation of organic esters by  $\text{O}_3/\text{O}_2$  following the method 3 (see Table 6). The lowest porosity was ascribed to the thin films of the same glasses, fabricated by the PE-CVD (method 4) and especially the HDP-CVD (method 5) techniques. The highest porosity of the  $\text{SiO}_2$  and BSG thin films fabricated using the method 3 is associated with low  $k_{\text{ef}}$  value. This process was described in the framework of the two-stage scheme of sequential reactions with the heterogeneous limiting stage involving consumption of intermediate products, which is responsible for the formation of disordered glass structures in the course of the CVD process. On the contrary, fast deposition processes described in the framework of the two-stage scheme of sequential reactions with the homogeneous limiting stage involving formation of intermediate products make it possible to grow much more ordered (*i.e.*, dense) thin films.

## VIII. Conclusion

The authors of this review presented the key information on the chemical vapour deposition of layered dielectric materials and on the properties of covalent dielectrics used in electronics. Layered dielectric composites can be used not only in high-precision technologies but also in mechanical engineering, power engineering, medicine, *etc.*, the CVD methods are considered to be quite promising because they provide unique possibilities of deposition of thin and ultrathin coatings with preset properties and high mechanical and adhesive characteristics on surfaces with complex-shape reliefs.

Chemical transformations of reagents on the surface of a growing layer in the course of the CVD process occur within a layer that is somewhat thicker than a monolayer. This is basic to

the definition of the reaction zone concept. For different CVD processes, the thickness of the reaction zone can vary between a few and several tens of Ångströms. Because of the lack of reliable information on the structure of the reaction zone, researchers are forced to employ a traditionally used description of heterogeneous processes, which is based on the concept of an ideal adsorption layer (Langmuir–Hinshelwood or Ealey–Rideal kinetics), which uses physically incorrect models. Further progress in the CVD methods is closely related to the studies on the structure and dynamics of the reaction zone, which govern not only the dynamics and kinetics of the processes but also the main characteristics of the growing layer. Advances in solving the problems considered above are to a great extent due to the use of modern experimental equipment and especially the *in situ* recording techniques used in the course of the CVD processes. These are, *e.g.*, automatic ellipsometry and piezoquartz microbalance methods, which allow the dynamics and (under steady-state conditions) the kinetics of the process to be investigated. The laser heating technique (chemical thermometer) permits separation of the contribution of pure vapour-phase stages while the IR and Raman spectroscopies provide the possibility of monitoring the composition and temperature of the reacting gas flow. Modern methods of investigation of the aerosol phase make it possible to study nucleation in the vapour phase and to control the structural homogeneity of the deposited coatings.

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# Transactinide superheavy elements: isolation and chemical properties in solution<sup>†</sup>

L I Guseva

## Contents

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**Abstract.** Data on the isolation of transactinide elements and their homologues and investigation of their chemical properties in solutions, which were obtained by chromatographic extraction and other methods, are generalised for the first time. Particular attention is given to model experiments on the prediction of the chemical properties and investigation of the relativistic effects of these elements on the basis of the behaviour of homologous elements in solutions containing various complexing ligands. The results and prospects for future research are discussed. The bibliography includes 105 references.

## I. Introduction

In recent years, considerable progress has been made in the synthesis of new transactinide elements (TAEs) or, as they are also called, superheavy elements (SHEs). The elements with atomic numbers  $Z = 114, 115, 116$  and  $118$  and the longest-lived (of the presently known) isotopes of element  $106$  ( $^{265}\text{Sg}$  and  $^{266}\text{Sg}$ ) have been synthesised for the first time in the Flerov Laboratory of Nuclear Reactions of the Joint Institute for Nuclear Research (FLNR JINR, Dubna, Moscow region, Russian Federation).<sup>1–4</sup> The element with  $Z = 113$  was observed in the decay chain of element  $115$ .<sup>2</sup> High stability to various types of nuclear radioactive decay in the vicinity of deformed ( $Z \approx 108, N = 162$ ) and spherical ( $Z = 114, N = 184$ ) nuclear shells was observed experimentally and established by calculations. This fact is indicative of the occurrence of the so-called ‘islands of stability’ among superheavy elements, which has been predicted as early as in the mid-1960s.

During production of new elements, their nuclear physical characteristics ( $T_{1/2}$ , the radioactive decay mode, *etc.*) are generally determined by measuring  $\alpha$  decay or spontaneous fission of the nucleus that formed and the correlations between the decay of parent and daughter radionuclides. However, the exact position of a new element in the Periodic Table should be confirmed by its chemical identification. Investigations of the chemical properties of superheavy elements provide deeper insight into their electronic structures.

Fourteen transactinide elements and  $\sim 70$  their isotopes have been produced. In 1997, IUPAC approved the names and chemical symbols of TAEs with  $Z = 104–109$ . In 2003–2004, the names and chemical symbols of elements  $110$  and  $111$  (Table 1) were approved. Other TAEs have no names. The chemical properties of only two TAEs, *viz.*, rutherfordium and dubnium, were studied in solution. Two experiments on the isolation and chemistry of seaborgium and one investigation of the chemistry of hassium have been carried out. Table 2 lists the isotopes of TAEs, which were studied by chemical methods in solution. The longest-lived  $^{261}\text{Rf}$  isotope ( $T_{1/2} = 78$  s) was discovered in 1970. However, detailed investigations of the chemical properties of rutherfordium in solution were started only in the early 1990s, which was associated with the development of new approaches to the isolation of TAEs. Investigation of the chemistry of transactinide elements and, particularly, of elements with  $Z \geq 106$ , is a complicated and laborious process. The difficulties are associated with very short lifetimes and low production cross-sections of TAEs in reactions with multicharged ions. These experiments are carried out only in a few research centres in the world (see Table 2).

**Table 1.** Names and symbols of transactinide elements.

| Atomic number ( $Z$ ) | Name          | Symbol |
|-----------------------|---------------|--------|
| 104                   | Rutherfordium | Rf     |
| 105                   | Dubnium       | Db     |
| 106                   | Seaborgium    | Sg     |
| 107                   | Bohrium       | Bh     |
| 108                   | Hassium       | Hs     |
| 109                   | Meitnerium    | Mt     |
| 110                   | Darmstadtium  | Ds     |
| 111                   | Roentgenium   | Rg     |

To find the optimum conditions for the isolation and investigation of the chemical properties of these elements, it is necessary to perform preliminary experiments with homologous elements in various systems. In addition, these experiments are required because the relativistic effects in the chemical behaviour of heavy elements can lead to considerable deviations from the general regularities.

The chemical properties of TAEs are studied both in the gas and liquid phases. Studies in the gas phase have the advantage that

L I Guseva V I Vernadsky Institute of Geochemistry and Analytical Chemistry, Russian Academy of Sciences, ul. Kosygina 19, 117975 Moscow, Russian Federation. Fax (7-095) 938 20 54, tel. (7-095) 939 70 80, e-mail: l.i.guseva@inbox.ru

<sup>†</sup> The review is dedicated to the blessed memory of Academician Georgii Nikolaevich Flerov, who has initiated studies on the production and chemical identification of superheavy elements in Russia.

**Table 2.** Isotopes of transactinide elements studied by chemical methods in solution.

| Isotope           | $T_{1/2}$ /s | Production reaction                   | Investigation method        | Research centre (year) | Ref.   |
|-------------------|--------------|---------------------------------------|-----------------------------|------------------------|--------|
| $^{261}\text{Rf}$ | 78           | $^{248}\text{Cm}(^{18}\text{O}, 5n)$  | ion-exchange chromatography | LBL (1970)             | 5      |
|                   | 78           | $^{248}\text{Cm}(^{18}\text{O}, 5n)$  | the same                    | FLNR JINR (1990)       | 6      |
|                   | 78           | $^{248}\text{Cm}(^{18}\text{O}, 5n)$  | "                           | FLNR JINR (1998)       | 7      |
|                   | 78           | $^{248}\text{Cm}(^{18}\text{O}, 5n)$  | "                           | PSI (2000)             | 8      |
|                   | 78           | $^{248}\text{Cm}(^{18}\text{O}, 5n)$  | "                           | JAERI (2002)           | 9      |
|                   | 78           | $^{248}\text{Cm}(^{18}\text{O}, 5n)$  | "                           | JAERI (2004)           | 10     |
|                   | 78           | $^{248}\text{Cm}(^{18}\text{O}, 5n)$  | "                           | GSI (2004)             | 11     |
|                   | 78           | $^{248}\text{Cm}(^{18}\text{O}, 5n)$  | extraction chromatography   | LBL (1980)             | 12     |
|                   | 78           | $^{248}\text{Cm}(^{18}\text{O}, 5n)$  | the same                    | PSI (1998)             | 13     |
|                   | 78           | $^{248}\text{Cm}(^{18}\text{O}, 5n)$  | liquid–liquid extraction    | LBL (1994)             | 14, 15 |
|                   | 78           | $^{248}\text{Cm}(^{18}\text{O}, 5n)$  | the same                    | LBL (1996)             | 16, 17 |
|                   | 78           | $^{248}\text{Cm}(^{18}\text{O}, 5n)$  | adsorption                  | LBL (1996)             | 18     |
|                   | 78           | $^{248}\text{Cm}(^{18}\text{O}, 5n)$  | the same                    | FLNR JINR (2001)       | 19     |
| $^{257}\text{Rf}$ | 3.5          | $^{208}\text{Pb}(^{50}\text{Ti}, n)$  | extraction (on-line)        | LBL (2002)             | 20     |
| $^{262}\text{Db}$ | 34           | $^{249}\text{Bk}(^{18}\text{O}, 5n)$  | adsorption, extraction      | LBL (1988)             | 21     |
|                   | 34           | $^{249}\text{Bk}(^{18}\text{O}, 5n)$  | extraction chromatography   | LBL (1989)             | 22, 23 |
|                   | 34           | $^{249}\text{Bk}(^{18}\text{O}, 5n)$  | the same                    | LBL (1992)             | 24     |
|                   | 34           | $^{249}\text{Bk}(^{18}\text{O}, 5n)$  | "                           | LBL (1999)             | 25     |
| $^{263}\text{Db}$ | 27           | $^{249}\text{Bk}(^{18}\text{O}, 4n)$  | ion-exchange chromatography | LBL (1992)             | 26     |
|                   |              | $^{248}\text{Cm}(^{19}\text{F}, 5n)$  | the same                    | IN2P3-UPS (2002)       | 27     |
| $^{262}\text{Db}$ | 27           | $^{249}\text{Bk}(^{18}\text{O}, 4n)$  | "                           | GSI (2003)             | 28     |
|                   | 34           | $^{248}\text{Cm}(^{19}\text{F}, 5n)$  | "                           | JAERI (2004)           | 29     |
| $^{265}\text{Sg}$ | 7.4          | $^{248}\text{Cm}(^{22}\text{Ne}, 5n)$ | "                           | GSI (1997)             | 30     |
|                   | 7.4          | $^{248}\text{Cm}(^{22}\text{Ne}, 5n)$ | "                           | GSI (1998)             | 31     |
| $^{269}\text{Hs}$ | $\sim 10$    | $^{248}\text{Cm}(^{29}\text{Mg}, 5n)$ | CALLISTO                    | GSI (2004)             | 32     |

**Note.** The following abbreviations are used: LBL is Lawrence Berkley Laboratory (Berkley, USA), PSI is Paul Sherrer Institute (Villigen, Switzerland), JAERI is Japan Atomic Energy Research Institute (Tokai-Mura, Japan), GSI is Gesellschaft für Schwerionenforschung (Darmstadt, Germany), IN2P3-UPS is Institut de Physique Nucleaire, Radiochimie (Orsay, France), CALLISTO is Continuously Working Arrangement for Clusterless Transport of In-situ Produced Volatile Oxides.

TAEs with very short lifetimes can be investigated. Pioneering experiments on the chemistry of TAEs have been carried out by gas chromatography.<sup>33</sup> However, investigations in the gas phase are limited to volatile compounds. Besides, the electronic structures of the valence shells of elements in the gas phase can differ from those in the liquid state, which is reflected in their chemical behaviour.

Model experiments on the isolation and investigation of TAEs in solutions by ion-exchange chromatography in the on-line mode demonstrated the possibility of studying the physicochemical properties of radionuclides with half-lives of  $\sim 5\text{--}10\text{ s}$ .<sup>34, 35</sup> Short-lived radionuclides with half-lives of  $\leq 1\text{ s}$  were isolated and detected using the super fast SISAK III (Short-lived Isotopes Studied by the AKUFVE Technique) extraction system.<sup>36</sup>

In the last decade, investigations of the chemical properties of TAEs have attracted considerable interest. In 2000–2001, studies on the synthesis of TAEs were started in the world-famous Orsay (France) and JAERI (Japan) nuclear research centres, in particular, with the use of ion-exchange chromatography. The number of publications, including relativistic quantum-chemical calculations of the atom states of TAEs in different systems, sharply increased.<sup>37</sup>

In several reviews, experiments on the isolation and the chemical behaviour of TAEs in the gas and liquid phases were analysed (in solutions, the behaviour of only Rf, Db and Sg and their homologues was considered).<sup>38–41</sup> Data on model experiments aimed at studying TAEs in solutions containing various complexing ligands<sup>42–54</sup> are virtually lacking, although these experiments are required to search for the optimum conditions of isolation, prediction of the chemical properties of TAEs and elucidation of the relativistic effects.

The present review provides an overview of the general approaches to the development of procedures for isolation and investigation of the chemical properties of trace amounts of short-lived TAEs in solutions. The possibility of studying the chemical properties of TAEs (speciation of elements in solution, hydrolysis, complexation, valence states, *etc.*), including elements with  $Z \geq 106$ , was demonstrated by investigations of the homologous elements in various systems. The results of the isolation of short-lived isotopes of Hf, Ta, W, Re, Os, Hg, Pb as homologues of Rf, Db, Sg, Bh, Hs and elements 112 and 114, respectively, and studies of their chemical behaviour are considered. Experimental data on the isolation and the chemical properties of Rf, Db and Sg in solution obtained by chromatographic, extraction and other methods are summarised. In the review, it was shown that the relativistic effects can be revealed by performing comparative studies of the behaviour of TAEs and their homologues in solutions containing various complexing ligands. The results of studies and prospects for the use of different methods for the isolation and investigation of the chemical properties of TAEs in solution are discussed.

## II. Principles of production and isolation of transactinide superheavy elements

### 1. Production of heavy and superheavy elements

The first artificial actinide elements were produced primarily by successive neutron capture in high-flux nuclear reactors or underground nuclear explosions in high neutron fluxes. The last element prepared by this method was  $^{257}\text{Fm}$  ( $T_{1/2} \approx 100\text{ days}$ ,  $Z = 100$ ). Heavier nuclei are impossible to produce by this method because of short lifetimes. Transfermium elements have been synthesised

by reactions with multicharged ions at accelerators.<sup>‡</sup> The elements with  $Z = 101–105$  were prepared by so-called ‘hot-fusion’ reactions using bombardment of targets containing heavy isotopes of transuranium elements (from U to Es) with the accelerated  $^{11}\text{B}$ ,  $^{13}\text{C}$ ,  $^{14}\text{N}$ ,  $^{15}\text{N}$ ,  $^{16}\text{O}$ ,  $^{18}\text{O}$ ,  $^{20}\text{Ne}$ ,  $^{22}\text{Ne}$  and  $^{24}\text{Mg}$  ions. The elements with  $Z = 106–112$  were produced by the ‘cold fusion’ reactions of the  $^{208}\text{Pb}$  and  $^{209}\text{Bi}$  nuclei with the ions varying from  $^{54}\text{Cr}$  to  $^{70}\text{Zn}$ . Longer-lived isotopes of Sg, Bh and Hs were synthesised by the reactions  $^{248}\text{Cm}(^{22}\text{Ne}, 4.5\text{n})$ ,  $^{249}\text{Bk}(^{22}\text{Ne}, 4\text{n})$  and  $^{248}\text{Cm}(^{24}\text{Mg}, \text{xn})$ , respectively. The elements with  $Z = 114, 115, 116$  and  $118$  were prepared using heavy isotopes of actinides ( $^{242}\text{Pu}$ ,  $^{244}\text{Pu}$ ,  $^{243}\text{Am}$ ,  $^{248}\text{Cm}$  and  $^{249}\text{Cf}$ ) as the targets and nuclei of the rare  $^{48}\text{Ca}$  isotope as the bombarding particles.

In model experiments, the behaviour of carrier-free short-lived homologous elements is generally studied. These isotopes are also produced by nuclear reactions with multicharged ions at a cyclotron or by uranium fission. With the aim of studying the chemical properties of element 114 using its homologue (lead), a radioisotope generator was constructed to produce the short-lived  $^{211}\text{Pb}$  isotope.<sup>54</sup>

## 2. Specificity of operations with short-lived elements at the tracer scale

Experiments with trace amounts of TAEs bring up the question about the reliability of the results obtained by studying the behaviour of several or even single atoms. The question arises as to whether the behaviour of trace amounts of elements is analogous to their behaviour in macroamounts. The classical law of mass action, which is used for the description of equilibria in chemical reactions, cannot be applied to reactions with single atoms, because one and the same atom cannot exist simultaneously in different species. To solve this problem, an expression equivalent to the law of mass action was proposed.<sup>55,56</sup> In this expression, the concentration (activity, partial pressure) is replaced by the probability of the existence of the species of the element in the corresponding phase (solid, liquid, gas). Therefore, the equilibrium constant (distribution coefficient) between two phases is determined by the probability of the existence of an atom (ion) of the element in a particular phase. Evidently, chromatographic systems, in which transitions of the substance from one phase to another are repeated many times, can be reliably used to study the chemical behaviour of elements at the tracer scale. The classical example supporting this fact is the use of chromatography in experiments on the isolation of 17  $^{256}\text{Md}$  atoms ( $T_{1/2} = 75$  min). The chemical identification of mendelevium was carried out from the peak position on the elution curve from a cation-exchange column with a solution of ammonium  $\alpha$ -hydroxyisobutyrate. The peak of mendelevium exactly coincides with the peak of thulium, which is its chemical analogue.<sup>57</sup> The behaviour of the element in trace amounts was demonstrated<sup>58</sup> to be identical to its behaviour in macroamounts in the absence of additional factors, for example, the influence of loading the resin with a macrocomponent in the chromatographic separation of elements. In my opinion, studies of the chemistry at the microamount level provide the most reliable insights into the chemical properties of elements, because in this case no side processes (polymerisation, disproportionation, *etc.*), which are often observed in experiments with macroamounts, occur.

## 3. Techniques for isolation and determination of short-lived radionuclides formed in reactions with multicharged ions

The techniques for isolation and determination of TAEs and short-lived isotopes of homologous elements, which are produced by nuclear reactions with multicharged ions at accelerators, have been described in detail in the literature.<sup>38–41</sup> The transport of nuclear reaction products from the irradiated target to the corresponding chemical apparatus is generally performed through

a thin capillary using an aerosol gas jet ( $\text{KCl}/\text{H}_2$ , *etc.*). Transactinide elements are isolated and their chemical properties are studied using both the cyclic and continuous (on-line) modes. The former mode involves repeated cycles of isolation, separation and determination of TAEs by correlating the  $\alpha$ – $\alpha$  decays of the parent and daughter radionuclides. The second mode is based on the on-line isolation of short-lived TAEs and separation from radionuclides, which hinder the detection, during their production followed by the long-lived decay product determination.

When isolating TAEs and investigating their behaviour by liquid extraction in the cyclic mode, all chemical operations are carried out manually. The optimum time for one experiment is several minutes. The extraction method was used to isolate  $^{261}\text{Rf}$  and study its chemical properties.<sup>14–17</sup> The process involving chromatographic methods was automated. The Automated Rapid Chemistry Apparatus (ARCA), which includes microcolumns and microprocessor computers, was used to isolate and study Rf,<sup>8–10</sup> Db (see Refs 22, 23, 25 and 26) and Sg.<sup>30,31</sup> This high-precision and expensive apparatus was described in detail in the studies.<sup>38,39,59</sup> The central part of the apparatus consists of an aerosol collector and two magazines each containing twenty  $1.6 \times 8$  mm microcolumns. The columns are packed with the necessary sorbent (ion-exchange resin, extractant on an inert support, *etc.*). A solution in which aerosol is dissolved is delivered to the collector. The resulting solution containing radionuclides (sorbate) is fed to one of the moving microcolumns. The column moves further and another solution (eluate, desorbate) is fed. Then the second column takes the place of the first column, and a new portion of the sorbate containing radionuclides is delivered, *etc.* Solutions eluted from each column are collected on individual supports, dried and directed to  $\alpha$ -spectrometric measurements. The minimum time for each cycle (dissolution of the aerosol, adsorption, elution, desorption and preparation of a source for radiometric measurements) is 45–90 s; 2/3 of this time is spent on the preparation of the source. The automated system makes it possible to perform repeated cycles of isolation of short-lived radionuclides; the number of cycles can be several thousand. However, the possibilities to use the ARCA apparatus for studying the chemistry of SHEs are limited due to very low yields of radionuclides in a unit time and the unreliability of the studies.

The isolation and determination of short-lived isotopes of TAEs in the continuous (on-line) mode holds the most promise. This approach involving ion-exchange chromatography was developed in FLNR JINR.<sup>6,60</sup> The scheme of the apparatus is shown in Fig. 1. The nuclear reaction products are directed to an absorber using an aerosol gas jet. The aerosol is dissolved in the

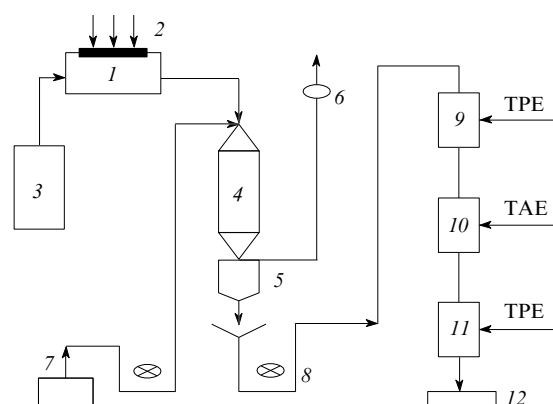


**Figure 1.** Scheme of the continuous radiochemical isolation of TAEs.<sup>6,60</sup> (1) An irradiated target, (2) a heavy ion beam, (3) an aerosol generator ( $\text{KCl}$ ), (4) an absorber, (5) a degasser, (6) a filter, (7) the solution under study, (8) peristaltic pumps, (9) the first cation-exchange column, (10) an anion-exchange column, (11) the second cation-exchange column, (12) an eluate.

<sup>‡</sup> The  $^{254}–^{258}\text{Md}$  isotopes were produced in the reactions  $^{253,254}\text{Es}(\alpha, \text{xn})$ .



solution under study, which is continuously fed to the absorber. Then the solvent containing TAEs and other radionuclides is passed through three ion-exchange columns connected in series. The first (cation-exchange column) is used to separate transactinide elements from actinide (primarily transplutonium) elements (TPEs), which are strongly retained on the cation-exchange resin, whereas TAEs remain in the solution and are sorbed on the second (anion-exchange) column. The decay products of TAEs, *viz.*, late TPEs (No, Fm, Es), are sorbed on the third (cation-exchange) column. Transactinide elements are identified by long-lived decay products after their desorption from the third column and preparation of one sample (source) for  $\alpha$ -spectrometric measurements. Therefore, this method allows one to perform continuous isolation and separation of short-lived TAEs from TPEs produced in nuclear side reactions followed by their detection by long-lived decay products, which are accumulated throughout the experiment. The latter fact is of considerable importance for the isolation of trace amounts of radionuclides (single atoms) with a low production cross-section in nuclear reactions. The method of continuous isolation of TAEs was successfully used to isolate and investigate  $^{261}\text{Rf}$  (see Refs 6, 7, and 60; in the cited studies, the element is called Kurchatovium, Ku) and  $^{262}\text{Db}$  (see Ref. 27) in dilute solutions of hydrofluoric acid. This approach was also used in model experiments on the isolation and investigation of the behaviour of short-lived isotopes of transition d elements (homologues of TAEs). These radionuclides were also determined in the on-line mode using high-resolution HPGe detectors connected to a computer.<sup>34, 35, 43, 44, 46, 48, 52, 61–64</sup>

The super fast SISAK III system, which includes mixers, minicentrifuges and a liquid scintillation detector, was designed for isolation of TAE by extraction and its determination in the on-line mode. Radionuclides are determined in a flowing organic phase. The system was successfully used to separate short-lived radionuclides, including homologues of TAEs.<sup>36, 50, 65–67</sup> The short-lived  $^{257}\text{Rf}$  isotope ( $T_{1/2} \approx 4$  s) was isolated for the first time (in 2001) and chemically identified with the use of the SISAK system.<sup>20</sup>

### III. Isolation and chemical properties of transactinide elements with $Z = 104–118$ and their homologues

#### 1. Rutherfordium

##### a. Theoretical prerequisites

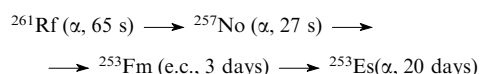
Rutherfordium is the first element in the series of d-transition elements in the seventh period of the Periodic table.<sup>8</sup> Relativistic calculations by the Dirac–Fock method demonstrated<sup>68</sup> that the electronic configuration of an isolated atom of element 104 in the ground state is  $[\text{Rn}]5f^{14}6d^27s^2$ . Therefore, Rf belongs to Group IVB and its chemical properties would be analogous to the properties of Hf and Zr. It was also hypothesised<sup>38</sup> that the electronic configurations  $5f^{14}6d^7s^27p^1$  or  $5f^{14}7s^27p^2$  (after the filled radon shell) can exist. In this cases, rutherfordium can exhibit chemical properties similar to those of p elements (for example, of Pb). However, the lead atom has a completely filled d shell:  $[\text{Xe}]4f^{14}5d^{10}6s^26p^2$ . If only the outer electron shells are taken into account, thorium is also an electronic analogue of rutherfordium:  $[\text{Rn}]f^06d^27s^2$ . Hence, thorium can be considered as a pseudohomologue of rutherfordium. Plutonium is also considered as a pseudohomologue, because Pu(IV) involved in certain systems behaves analogously to Group IVB elements.

§ Hereinafter, the groups of elements are denoted by Roman numerals (I–VIII), which are used in the ‘short-period’ form of the Periodic table. In the ‘long-period’ form of the Periodic table, the groups of elements are denoted by Arabic numerals (1–18).

#### b. Behaviour of Group IVB elements in solution

To isolate rutherfordium and study its chemical properties by ion-exchange chromatography, the behaviour of its homologues and pseudohomologues, *viz.*, Hf, Zr, Th and Pu, was investigated in solutions containing inorganic and organic complexing ligands (upon their sorption on cation- and anion-exchange resins).<sup>6, 8, 42–45, 47, 60, 62, 69</sup>

**Use of cation-exchange resins.** Figure 2 illustrates the influence of the nature and concentration of an acid on the distribution coefficients ( $K_d$ ) of hafnium, thorium, some TPEs, rare-earth elements and strontium upon sorption on Dowex-50  $\times$  8 cation-exchange resin. In these experiments, strontium was studied as a homologue of element 102 (No) produced in the decay chain



(e.c. is electron capture).

A knowledge of the behaviour of No, as well as trivalent TPEs (REEs), which are produced in substantial amounts in the synthesis of TAEs, is of particular importance if the latter are identified from daughter decay products.

Hafnium is virtually not sorbed by the cation-exchange resin from HF,  $\text{H}_3\text{PO}_4$  and  $\text{H}_2\text{C}_2\text{O}_4$  solutions but exhibits high adsorbability in  $\text{H}_2\text{SO}_4$  solutions at a concentration of  $\leq 0.1$  mol litre<sup>-1</sup>. Thorium is much more strongly (compared to Hf) sorbed on the cation-exchange resin, this difference being most pronounced in dilute HF and  $\text{H}_3\text{PO}_4$  solutions. Transplutonium elements, REEs and strontium have large distribution coefficients ( $\geq 10^4–10^6$ ) in acids at concentrations of  $\leq 0.1–0.5$  mol litre<sup>-1</sup>. The degree of sorption of the elements sharply decreases with increasing concentration of the acid due to competitive sorption of  $\text{H}^+$  on the cation-exchange resin.

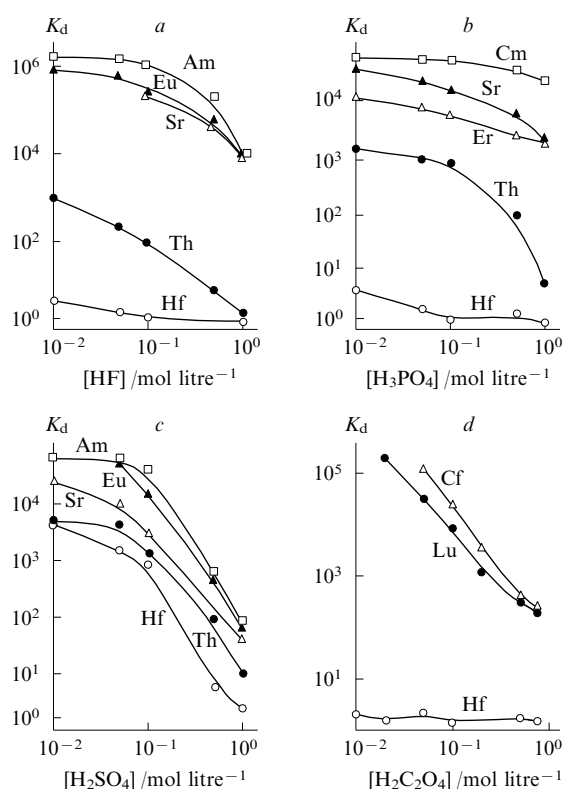


**Figure 2.** Plots of the distribution coefficients of elements *vs.* the acid concentration in solutions for sorption on Dowex-50  $\times$  8 cation-exchange resin.<sup>43, 45, 47</sup>

Acid: (a) HF, (b)  $\text{H}_3\text{PO}_4$ , (c)  $\text{H}_2\text{SO}_4$ , (d)  $\text{H}_2\text{C}_2\text{O}_4$ .

The order of elution of the elements from the cation-exchange resin reflects their tendency to form complexes in solution. The low adsorbability of Hf on the cation-exchange resin is attributable to the fact that transition d elements are more prone to form neutral and negatively charged complexes with  $F^-$ ,  $H_2PO_4^-$  and  $C_2O_4^{2-}$  than with the  $HSO_4^-$  ions. The presence of  $F^-$  anions in  $H_2SO_4$  solutions leads to a sharp decrease in the distribution coefficients of hafnium already at the HF concentration higher than  $5 \times 10^{-4}$  mol litre $^{-1}$ , whereas the distribution coefficients of strontium and TPEs (REEs) remain virtually unchanged (Fig. 3).<sup>45</sup> An analogous behaviour of hafnium and zirconium is observed upon their sorption on the cation-exchange resin from mixed  $HNO_3$ /HF solutions. An increase in the HF concentration from  $5 \times 10^{-4}$  to  $5 \times 10^{-2}$  mol litre $^{-1}$  in 0.1 M  $HNO_3$  solution leads to a decrease in the distribution coefficients of zirconium and hafnium by approximately three orders of magnitude.<sup>8</sup> These data are indicative of the formation of stable neutral and negatively charged complexes of these elements with  $F^-$  ions in solutions containing HF at concentrations of  $\geq 10^{-3}$  mol litre $^{-1}$ . At lower HF concentrations, cationic complexes and various hydrolysed forms adsorbed on the cation-exchange resin can exist. Therefore, the ability of inorganic ligands to form complexes with Hf and Zr increases in the following series  $OH^- > F^- > H_2PO_4^- > HSO_4^-$ .

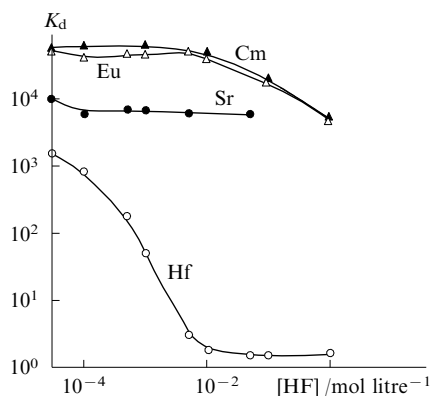


**Figure 3.** Plots of the distribution coefficients of elements vs. the HF concentration in a 0.05 M  $H_2SO_4$  solution for sorption on Dowex-50  $\times$  8 cation-exchange resin.<sup>45, 47</sup>

The difference in the distribution coefficients of Hf, Zr, TPEs (REEs) and Sr is responsible for the high separation factors of these elements on the cation-exchange resin in dilute HF,  $H_3PO_4$ ,  $H_2C_2O_4$  and  $H_2SO_4$ /HF solutions. Hence, these systems can be used to separate Hf and Zr (Rf) from TPEs from large volumes of solutions with purification factors of  $\geq 10^5$ – $10^6$  on small cation-exchange columns in the on-line mode.<sup>6, 42–45, 47</sup> In this case, weakly adsorbed elements (Hf, Zr, Rf) are continuously washed out, whereas TPEs, REEs and Sr (No) remain on the column.

**Use of anion-exchange resins.** The plots of the distribution coefficients of Hf, Sr and TPE (REEs) vs. the concentration of acids upon their adsorption on Dowex-1  $\times$  8 anion-exchange resin from HF,  $H_2SO_4$ ,  $H_3PO_4$  and  $H_2C_2O_4$  solutions are shown in Fig. 4. The distribution coefficients of hafnium and zirconium are rather high ( $> 10^2$ – $10^4$ ), whereas TPEs (REEs) and strontium are virtually not sorbed on the anion-exchange resin from HF,  $H_3PO_4$  and  $H_2SO_4$  solutions but have high adsorbability in dilute  $H_2C_2O_4$  solutions. Sorption of TPEs (REEs) and Sr in  $H_2C_2O_4$  solutions sharply decreases in the presence of small amounts of HCl (Fig. 5). Therefore, anion-exchange columns can be used both to concentrate Rf, Hf and Zr and separate these elements from the daughter radionuclides (TPEs, REEs) in dilute HF,  $H_2SO_4$ ,  $H_3PO_4$ ,  $H_2C_2O_4$ /HCl and  $H_2SO_4$ /HF solutions.<sup>5, 43–47</sup>

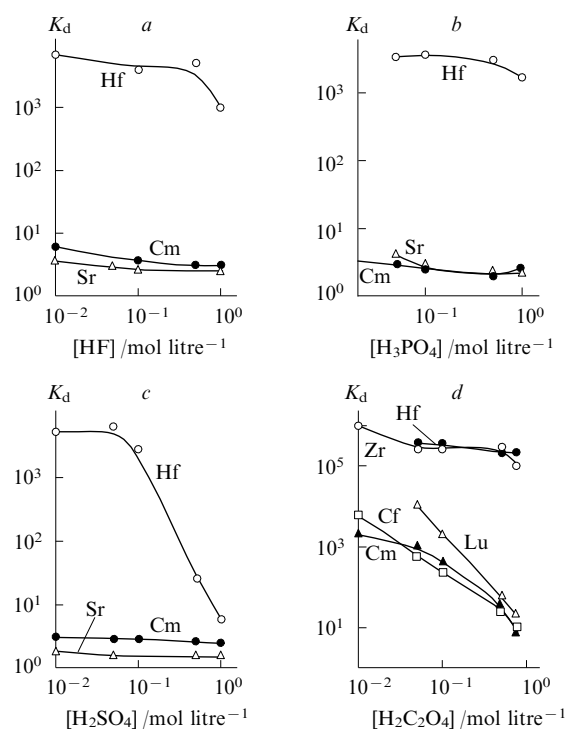


**Figure 4.** Plots of the distribution coefficients of elements vs. the acid concentration in solutions for sorption on Dowex-1  $\times$  8 anion-exchange resin.<sup>43–45, 47</sup>

Acid: (a) HF, (b)  $H_3PO_4$ , (c)  $H_2SO_4$ , (d)  $H_2C_2O_4$ .

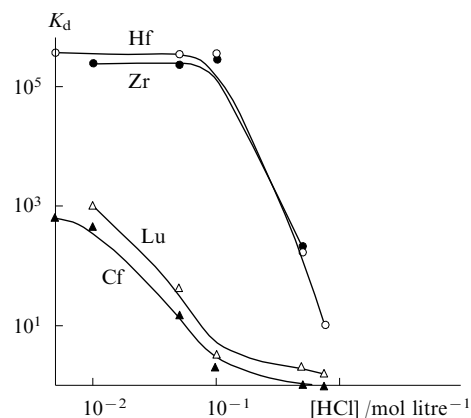


**Figure 5.** Plots of the distribution coefficients of elements vs. the HF concentration in a 0.05 M  $H_2C_2O_4$  solution for sorption on Dowex-1  $\times$  8 anion-exchange resin.<sup>44</sup>

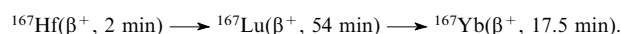
### c. Model experiments

The possibility of using various systems for the isolation of TAEs in the on-line mode was examined in model experiments on the isolation of short-lived hafnium isotopes and investigation of their chemical behaviour under conditions simulating isolation of Rf.<sup>34, 43, 44, 46, 61, 62, 70</sup> The hafnium isotopes were produced by the nuclear reactions  $^{144}\text{Sm}(^{20}\text{Ne}, xn)\text{Hf}$  and  $\text{Gd}(^{18}\text{O}, xn)\text{Hf}$  at the U-400 cyclotron (FLNR JINR). The scheme of isolation was analogous to that presented in Fig. 1. The solution under study containing nuclear reaction products was continuously passed (at a flow rate of  $\sim 2$  ml min $^{-1}$ ) through three  $0.4 \times 4$  cm columns, which were connected in series and filled with Dowex-50  $\times$  8 cation-exchange resin, Dowex-1  $\times$  8 anion-exchange resin and Dowex-50  $\times$  8 cation-exchange resin, respectively.  $\gamma$ -Spectrometric measurements of the columns were carried out in turn both in

**Table 3.** Sorption (from 0.5 M H<sub>3</sub>PO<sub>4</sub> solutions) of hafnium isotopes produced in the reactions Gd(<sup>18</sup>O, xn) and radioactive decay products of hafnium on ion-exchange columns.<sup>43</sup>

| First column, Dowex-50 × 8 |                       |              | Second column, Dowex-1 × 8 |                       |              | Third column, Dowex-50 × 8 |                       |              |
|----------------------------|-----------------------|--------------|----------------------------|-----------------------|--------------|----------------------------|-----------------------|--------------|
| radionuclide               | T <sub>1/2</sub> /min | sorption (%) | radionuclide               | T <sub>1/2</sub> /min | sorption (%) | radionuclide               | T <sub>1/2</sub> /min | sorption (%) |
| <sup>167</sup> Lu          | 54                    | 23           | <sup>165</sup> Hf          | 1.7                   | 100          | <sup>167</sup> Lu          | 54                    | 77           |
| <sup>168</sup> Lu          | 6                     | 2            | <sup>166</sup> Hf          | 6.8                   | 100          | <sup>168</sup> Lu          | 6                     | 98           |
| <sup>167</sup> Yb          | 17.5                  | 10           | <sup>167</sup> Hf          | 2.05                  | 100          | <sup>167</sup> Yb          | 17.5                  | 90           |
|                            |                       |              | <sup>168</sup> Hf          | 25                    | 100          | <sup>169</sup> Yb          | 2.7                   | 100          |
|                            |                       |              | <sup>169</sup> Hf          | 3.2                   | 100          |                            |                       |              |
|                            |                       |              | <sup>170</sup> Hf          | 960                   | 100          |                            |                       |              |

the on-line mode (the solution containing radionuclides was passed through the columns) and in the off-line mode (the flow of the solution was discontinued). Radionuclides of hafnium and its daughter decay products, which were detected on three ion-exchange columns by passing a 0.5 M H<sub>3</sub>PO<sub>4</sub> solution containing the radionuclides, are given in Table 3.<sup>43</sup> The hafnium radionuclides were completely sorbed on the anion-exchange column, whereas its radioactive decay products, REEs (Lu, Yb), were detected primarily on the last column (> 90%), and substantially smaller amounts of the latter products were detected on the first column. Rare-earth elements, which are the daughter radionuclides of Hf, were sorbed on the first cation-exchange column; these radionuclides were produced in the system before the solution was passed through this column. The second cation-exchange (third in order) column sorbed radionuclides produced by the decay of Hf isotopes, which were retained on the anion-exchange column, for example,



Analogous results were obtained in model experiments on the isolation of short-lived Hf isotopes from 0.2 M HF and 0.05 M H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>/0.1 M HCl solutions.<sup>44,46</sup> These experiments demonstrated that the above-mentioned systems can be used for the continuous, on-line, isolation of <sup>261</sup>Rf and its determination by the long-lived decay products, viz., <sup>253</sup>Fm and <sup>253</sup>Es.

A procedure was developed for the determination of the distribution coefficients of Rf between anion-exchange resins and HNO<sub>3</sub>/HF solutions in the on-line mode in the study of short-lived Hf isotopes.<sup>62</sup> The conditions of sorption (the amount and the nature of the anion-exchange resin, the elution rate) were chosen so that the retention time of Hf (Rf) on the column corresponds to the half-life of the radionuclide. Hafnium was found to be sorbed on the anion-exchange resin as the negatively charged HfF<sub>6</sub><sup>2-</sup> complex.

#### d. Isolation of rutherfordium and investigation of its chemical properties

**Chromatographic methods.** As mentioned above, pioneering experiments on the isolation of <sup>261</sup>Rf and investigation of its chemical behaviour in solution were carried out by ion-exchange chromatography, which had been used earlier for the identification of TPEs (LBL, Berkley, USA, 1970).<sup>5</sup> Like zirconium and hafnium, rutherfordium was eluted from a cation-exchange column with a solution of  $\alpha$ -hydroxyisobutyric acid ( $\alpha$ -HIBA) much more rapidly than TPEs. In the experiment, 17  $\alpha$ -decays of <sup>261</sup>Rf (T<sub>1/2</sub> = 65 s) and its daughter radionuclide <sup>257</sup>No (T<sub>1/2</sub> = 25 s) were observed. The second investigation of Rf in solution was published 10 years later, when the first automated apparatus for rapid isolation of short-lived TAEs was constructed.<sup>12</sup>

The behaviour of rutherfordium in HCl solution was studied by the extraction-chromatographic method using columns filled with Aliquat-336 (methyltricapryl ammonium chloride) on an inert support. A 12 M HCl solution containing Rf and Hf radionuclides and trivalent TPEs was passed through a column, which was then washed with a 6 M HCl solution. Transplutonium elements were eluted from the column with a 12 M HCl solution.

The main amounts of Rf and Hf were found in the 6 M HCl fraction. In the experiment, only six  $\alpha$ -decays of <sup>261</sup>Rf and its daughter element (<sup>257</sup>No) were observed. However, the authors of the study<sup>5</sup> concluded that Rf, like Hf and Zr, forms negatively charged complexes in concentrated HCl solution. More recently, the ability of Rf to form negatively charged chloride complexes in concentrated HCl solution was confirmed by the ion-exchange method (JAERI, Japan).<sup>9</sup> The experiments were carried out on an AIDA apparatus (Automated Ion Exchange Separation Apparatus Coupled with the Detection System for Alpha Spectroscopy), which is an improved modification of the above-described ARCA apparatus. It was demonstrated that sorption of Rf, Hf and Zr on CA08Y anion-exchange resin increases with increasing concentration of HCl from 7.0 to 11.5 mol litre<sup>-1</sup> (K<sub>d</sub> may be as large as ~ 10<sup>3</sup>), whereas Th is not sorbed on the anion-exchange resin. The adsorbability of the elements decreases in the series Rf > Zr > Hf, which indicates that Rf is more prone to form negatively charged chloride complexes (compared to Hf and Zr) in concentrated HCl solutions.

The chemical properties of Rf in dilute HF solutions were studied by the above-described method for the continuous isolation of short-lived radionuclides followed by their identification by long-lived decay products (FLNR JINR).<sup>6,60</sup> The <sup>261</sup>Rf isotope was produced using a combined target consisting of <sup>248</sup>Cm and <sup>157</sup>Gd, which was bombarded at the U-400 cyclotron with <sup>18</sup>O ions with an energy of 97–102 MeV and a beam intensity of 4 × 10<sup>12</sup> pps. The scheme of isolation of radionuclides from the irradiated target was analogous to that presented in Fig. 1. A 0.2 M HF solution containing radionuclides was continuously passed at a flow rate of 1.5–2.0 ml min<sup>-1</sup> through three columns (0.4 × 4 cm), which were connected in series and filled with Dowex-50 × 8 cation-exchange resin, Dowex-1 × 8 anion-exchange resin and Dowex-50 × 8 cation-exchange resin, respectively. The first cation-exchange column was replaced from time to time with a new column (after 300 ml of the solution was passed). The time of aerosol transport to the absorber was 5 s. The time during which the solution was passed through the absorber and three ion-exchange columns was no longer than 30 s. Throughout the experiment, radionuclides that appeared in different parts of the system were monitored by radiometry using Ge/Li detectors. The Hf isotopes, which were produced in the Gd(<sup>18</sup>O, xn) reactions, and isotopes of REEs, which were produced by the decay of hafnium, were detected on the anion- and cation-exchange columns, respectively. The total time of irradiation was 24 h. After completion of irradiation, the cation-exchange columns were washed with 6 M HNO<sub>3</sub> solutions, which were analysed for  $\alpha$  and  $\gamma$  activities. The  $\alpha$  spectra of radionuclides desorbed from the first and second cation-exchange columns are shown in Fig. 6. It can be seen that curium isotopes were present in large amounts on the first column (see Fig. 6a). This is accounted for by the fact that the target substance appeared in the system. In addition, the peaks characteristic (in energy of  $\alpha$  particles) of the Cf isotopes, <sup>253</sup>Es, <sup>254</sup>Fm and <sup>255</sup>Fm are clearly seen. The spectrum of the desorbate from the second cation-exchange column (see Fig. 6b) shows only a small amount of Cm isotopes, whereas Cf isotopes are absent, which is indicative

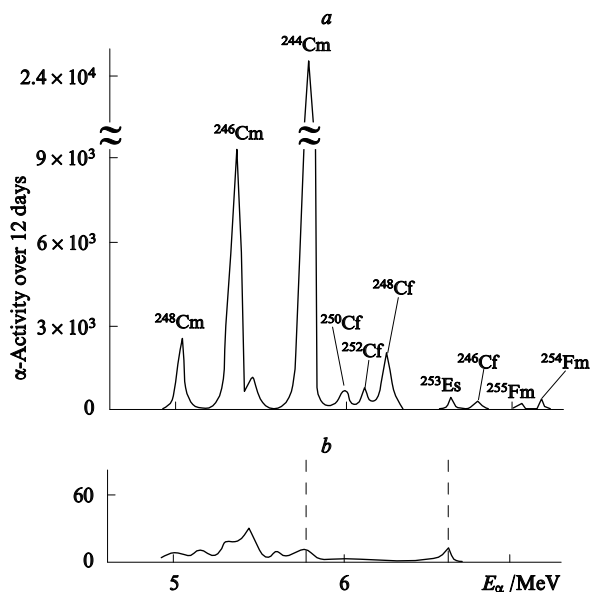
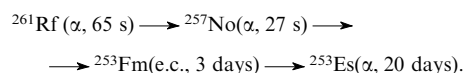


**Figure 6.**  $\alpha$ -Spectra of radionuclides, which were produced in the synthesis of  $^{261}\text{Rf}$ .<sup>6,60</sup> The desorbates from the first (a) and second (b) cation-exchange (Dowex-50  $\times$  8) columns.

of a high degree of purification ( $K_p \approx 10^5$ ) from these radionuclides on the first column. There is a peak in the region of  $^{253}\text{Es}$  (6.63 MeV), whereas  $\alpha$  particles belonging to the  $^{254}\text{Fm}$  and  $^{255}\text{Fm}$  isotopes are not observed. In the time measurements of the  $\alpha$  activity of the desorbate from the second cation-exchange column, the activity first increased and then decreased with  $T_{1/2} = 20$  days, which corresponds to  $T_{1/2}$  for  $^{253}\text{Es}$ . The initial increase is associated with accumulation of  $^{253}\text{Es}$ , which was produced by the  $\beta$  decay of  $^{253}\text{Fm}$  that formed in the chain



The absence of the  $^{254}\text{Fm}$  and  $^{255}\text{Fm}$  isotopes and the presence of the  $^{253}\text{Fm}$  and  $^{253}\text{Es}$  isotopes on the second cation-exchange column unambiguously indicate that the latter isotopes are produced by the decay of  $^{261}\text{Rf}$ , which is retained on the anion-exchange column. Evidently, Rf, like Group IVB elements (Hf and Zr), forms negatively charged complexes in dilute HF solutions. These complexes are not sorbed on the cation-exchange resin but are strongly retained on the anion-exchange resin. A total of  $\sim 500$   $\alpha$  particles belonging to  $^{253}\text{Es}$ , which was produced by the decay of  $^{261}\text{Rf}$ , were detected, which is larger by an order of magnitude than the amount of  $^{261}\text{Rf}$  isolated in other experiments. This is evidence that the method under consideration has advantages in isolating TAEs at the tracer scale and providing reliability of their identification.

The anion-exchange behaviour of Rf, Zr and Hf in 1.9–13.9 M HF solutions was studied using an automated AIDA chemical apparatus.<sup>10</sup> Sorption of Zr and Hf was found to decrease sharply at HF concentrations higher than 8 mol  $\cdot$  litre $^{-1}$ , whereas sorption of Rf decreases gradually already at HF concentrations higher than 4 mol  $\cdot$  litre $^{-1}$ . This difference was accounted for by the formation of less stable fluoride complexes of rutherfordium due to the possible influence of the relativistic effects.<sup>19</sup>

The determination of the distribution coefficients of  $^{261}\text{Rf}$  between Wofatit HS 36 anion-exchange resin and mixed  $\text{HNO}_3/\text{HF}$  solutions in the on-line mode demonstrated that the coefficients for Rf and Hf in 0.1 M  $\text{HNO}_3/0.27$  M HF and 0.2 M  $\text{HNO}_3/0.27$  M HF solutions are of the same order of

magnitude ( $\sim 50$  and  $\sim 15$ , respectively).<sup>7</sup> However, the investigation of sorption of  $^{261}\text{Rf}$  and Hf on Bio-Rad AG1X8 anion-exchange resin (with an ARCA apparatus) showed<sup>8</sup> that the distribution coefficients of Rf and Hf in 0.1 M  $\text{HNO}_3$  solutions containing HF at a concentration of  $1 \times 10^{-2}$ –1.0 mol  $\cdot$  litre $^{-1}$  differ by more than two orders of magnitude. In this case, the degree of sorption of Rf on the anion-exchange resin was very low ( $K_d < 8$ ). Hence, the authors of the study<sup>8</sup> have cast doubt on the results obtained in the study.<sup>7</sup> Moreover, the behaviour of Rf in  $\text{HNO}_3/\text{HF}$  solutions was demonstrated to be analogous to the behaviour of its pseudohomologue Th both on the anion- and cation-exchange resins. However, it is not quite correct to compare the results of the cited studies,<sup>7,8</sup> because anion-exchange resins with different functional groups were used. The low distribution coefficients  $K_d$  (see Ref. 8) of Rf on the anion-exchange resin cannot serve as an evidence for the absence of anionic fluoride complexes of Rf. The presence of  $\text{NO}_3^-$  ions, which are strongly sorbed on the anion-exchange resin, leads to a substantial decrease in radionuclide sorption. The decrease in the  $\text{HNO}_3$  concentration from 0.1 to 0.01 mol  $\cdot$  litre $^{-1}$  was demonstrated<sup>8</sup> to cause an increase in the distribution coefficient of rutherfordium by more than an order of magnitude ( $\geq 10^2$ ) and it becomes similar to  $K_d$  for Hf within the experimental error. Later on, it was found that the presence of  $\text{HNO}_3$  in HF solutions has a much stronger effect on the sorption of Rf on the anion-exchange resin compared to the sorption of Hf or Zr.<sup>11</sup>

The anion-exchange behaviour of rutherfordium in concentrated  $\text{HNO}_3$  solution was studied with the use of an AIDA apparatus.<sup>9</sup> Irradiation of the combined  $^{248}\text{Cm} + \text{natGe} + \text{natGd}$  target (nat is natural) with  $^{18}\text{O}$  ions produced  $^{261}\text{Rf}$  along with the  $^{85}\text{Zr}$  and  $^{169}\text{Hf}$  isotopes. It was found that Rf, like Zr and Hf, is virtually not sorbed on CA08Y anion-exchange resin from 8 M  $\text{HNO}_3$  solution. Preliminary experiments showed that Th and Pu have high adsorbability ( $K_d \geq 10^2$ – $10^3$ ) under the same conditions.

**Extraction methods.** *Extraction with triisooctylamine (TIOA).* Upon isolation of Rf by extraction from 0.5, 4.0 and 8.0 M HF solutions using a 0.25 M TIOA solution in xylene as the extractant<sup>17</sup> (383 experiments), 14  $\alpha$ – $\alpha$  correlations of the  $^{261}\text{Rf}$ – $^{257}\text{No}$  were observed in the organic fraction (only upon extraction from 0.5 M HF solutions). Group IV elements were extracted with TIOA from HF solutions in the series  $\text{Ti} > \text{Zr} \approx \text{Hf} > \text{Rf}$ , i.e., the order varies inversely with their ionic radii ( $\text{Rf} > \text{Hf} \geq \text{Zr} > \text{Ti}$ ), which is indicative of the formation of inner-sphere complexes.

The  $^{261}\text{Rf}$  isotope was extracted from 12 M HCl solutions with 0.1 M and 1.0 M TIOA solutions in benzene.<sup>14</sup> In the organic phase, 20 events with energies of  $\alpha$  particles belonging to  $^{261}\text{Rf}$  and  $^{257}\text{No}$  were observed (only upon extraction with 0.1 M TIOA). Under analogous conditions,  $^{95}\text{Zr}$  and  $^{95}\text{Nb}$  were extracted with  $K_d \geq 10^2$ , whereas  $^{152}\text{Eu}$  and  $^{228}\text{Th}$  were virtually not extracted. Hence, the data on the extraction confirm the results of chromatographic experiments on the formation of negatively charged Rf complexes in concentrated HCl solutions.<sup>9,12</sup>

*Extraction with tributyl phosphate (TBP).* With the aim of studying neutral rutherfordium chloride complexes, extraction of  $^{261}\text{Rf}$ ,  $^{95}\text{Zr}$ ,  $^{169}\text{Hf}$ ,  $^{228}\text{Th}$  and  $^{238}\text{Pu}$  was examined with the use of a TBP solution in benzene as the extractant depending on the concentrations of HCl and the  $\text{Cl}^-$  and  $\text{H}^+$  ions.<sup>15</sup> The Group IVB elements were extracted from 8–12 M HCl solutions with TBP (0.25 mol  $\cdot$  litre $^{-1}$ ) in the following order:  $\text{Zr} > \text{Rf} > \text{Hf}$ . In the case of extraction of  $^{261}\text{Rf}$ ,  $^{95}\text{Zr}$ ,  $^{175}\text{Hf}$ ,  $^{181}\text{Hf}$  and Ti with a 0.35 M TBP solution in benzene from concentrated HCl solutions, the elements were extracted in another order:<sup>16</sup>  $\text{Zr} > \text{Hf} > \text{Rf} > \text{Ti}$ . The distribution coefficients of Rf, Hf and Zr in the TBP/HCl system were determined by extraction chromatography (using an automated ARCA apparatus).<sup>13</sup> In 8 M HCl solutions, the distribution coefficients of Rf, Hf and Zr are 150, 53 and 1180, respectively. Therefore, the extractability of Group IV elements and their tendency to form neutral chloride

complexes decrease in the series  $Zr > Rf > Hf$ , which was observed experimentally<sup>15</sup> and predicted theoretically.<sup>71</sup>

Rutherfordium was not extracted from 7.75–12 M HBr solutions with the use of a 0.35 M TBP solution in benzene as the extractant.<sup>16</sup> However, the degree of isolation by extraction in the presence of LiBr was  $\sim 90\%$ . Extraction of Group IV elements from HBr solutions decreases in the series  $Zr > Hf > Rf \approx Ti$ , which was also observed for extraction from HCl solutions.<sup>16</sup>

**Extraction with dibutylphosphoric acid (DBPA).** The extraction method in the on-line mode with the use of the SISAK system was employed for the first time for the isolation of the short-lived  $^{257}Rf$  isotope ( $T_{1/2} \approx 4$  s) produced in the nuclear reaction  $^{208}Pb(^{50}Ti, n)^{257}Rf$ . Before chemical determinations, Rf was separated from other radionuclides in a gas-filled separator.<sup>20</sup> This made it possible to decrease the amounts of fission products and radionuclides, which were produced in multinucleon transfer reactions, by more than three orders of magnitude and optimize the on-line isolation and determination of  $^{257}Rf$ . The  $^{257}Rf$  isotope was extracted with a 0.25 M DBPA solution in toluene from 6 M  $HNO_3$ . The experiment time was  $\sim 18$  h, and 5  $\alpha$ - $\alpha$  correlations assigned to the  $^{257}Rf$ – $^{253}No$  pair were observed in the organic phase. Under these conditions, the behaviour of Rf is analogous to the behaviour of its light homologues, *viz.*, Zr and Hf.

**Adsorption methods.** The adsorption method combined with extraction by thenoyltrifluoroacetone (TTA) was developed for studying chelate Rf complexes in the investigation of the adsorption of Hf and Zr on a hydrophobised glass surface from 0.01 M and 1 M HCl solutions saturated with TTA.<sup>72</sup> Short-lived Rf and Hf isotopes were synthesised in the reactions  $^{248}Cm/^{152}Gd(^{18}O, 5n)$  and  $^{261}Rf/^{165}Hf^{19}$  at the U-400 cyclotron (FLNR JINR). The experiment was carried out for 16 h, during which 600 sorption cycles of radionuclide isolation were carried out and five  $\alpha$  decays of  $^{261}Rf$  were observed. All events were observed only for adsorption from 0.01 M HCl solutions with thenoyltrifluoroacetone. The short-lived  $^{168}Hf$  isotope was virtually equally sorbed from 0.01 M and 1.0 M HCl solutions (87% and 82%, respectively). It appeared that the behaviour of  $Rf^{4+}$  in the HCl–TTA system differs from the behaviour of its homologues and resembles the behaviour of  $Po^{4+}$ ,  $Sn^{4+}$  and  $Ti^{4+}$ , which form neutral complexes with TTA only in weakly acidic solutions.<sup>19</sup>

To study the hydrolysis of Rf, the ability of Group IVB elements to be adsorbed on glasses treated with transition metal ferrocyanides was investigated.<sup>18</sup> Cobalt ferrocyanides show high selectivity to the tetravalent  $Zr^{4+}$ ,  $Hf^{4+}$  and  $Th^{4+}$  cations and low selectivity to their hydrolysed  $M(OH)_3^+$  or  $M(OH)_2^{2+}$  forms. A substantial decrease in the sorption of Rf on cobalt ferrocyanide was observed already at HCl concentrations lower than 3 mol litre<sup>-1</sup>, whereas sorption of Zr and Hf decreased only at HCl concentrations lower than 1 and 0.5 mol litre<sup>-1</sup>, respectively. Consequently, hydrolysis increases in the series  $Hf < Zr < Rf$ . This behaviour of Rf was accounted for by the influence of the relativistic effect due to which the  $Rf^{4+}$  ion in aqueous solution has a coordination number of 6, whereas the coordination number of Zr and Hf is 8. However, this conclusion is inconsistent with theoretical and experimental data,<sup>73</sup> according to which the tendency of Group IVB elements to be hydrolysed increases in the reverse order,  $Rf < Hf < Zr$ , *i.e.*, in accordance with the change in the ionic radii of the elements.

## 2. Dubnium

### a. Theoretical prerequisites

The electronic configuration of an isolated atom of element 105 in the ground state should be  $[Rn]5f^{14}6d^37s^2$ . The Group VB elements Nb and Ta are chemical homologues of dubnium, and Pa is a pseudohomologue. Relativistic calculations by the Dirac–Fock method demonstrated that 7p electrons are absent in the ground state of the atom.<sup>74</sup> Therefore, no substantial deviations in the chemical behaviour of element 105 associated with relativistic effects are expected. In solution, the main oxida-

tion state of Db would be +5, although Db can also exist in lower oxidation states in the presence of strong reducing agents.<sup>75</sup>

### b. Isolation of dubnium and investigation of its chemical properties

Pioneering experiments on the isolation of element 105 and investigation of its chemical properties (earlier, this element was called hanium, Ha) in solution were carried out with the  $^{262}Db$  isotope ( $T_{1/2} = 34$  s), which was produced by the nuclear reaction  $^{249}Bk(^{18}O, 5n)$  (LBL).<sup>21</sup> When studying the chemistry of dubnium, sorption on the glass surface from fuming  $HNO_3$  solutions characteristic of Group VB elements and extraction with methyl isobutyl ketone (MIBK) from mixed  $HNO_3/HF$  solutions were investigated. Both series of experiments were carried out manually. Dubnium was adsorbed from a 15 M  $HNO_3$  solution. In 800 experiments on glass, 24  $\alpha$ - $\alpha$  decays of  $^{262}Db$  and its daughter element  $^{258}Lr$  ( $T_{1/2} = 4.3$  s) were observed. Under identical conditions, the degree of sorption of Nb and Ta was 42% and 80%, respectively. By contrast, Group IVB elements (Zr, Hf) were not sorbed. However, upon extraction of dubnium with MIBK from 3.8 M  $HNO_3/1.1$  M HF solutions (335 experiments), no events of  $\alpha$  decay or spontaneous fission of  $^{262}Db$  or  $^{258}Lr$  in the organic fraction were observed. In the authors' opinion, this behaviour of Db could be associated with the formation of unextractable doubly charged complexes  $DbF_2^{2-}$  or mixed oxyfluoride complexes. Under analogous conditions, tantalum forms singly charged  $TaF_6^-$  complexes, which are well extracted by MIBK. The possibility of relativistic stabilisation of 7s orbitals and, as a consequence, the formation of  $Db^{3+}$ , which is not extracted by MIBK, is also not ruled out.

**Extraction chromatography methods.** Extraction of dubnium with TIOA from HCl solution in the presence of small amounts of HF was studied using an ARCA apparatus.<sup>22,23</sup> The  $^{262}Db$  isotope was sorbed on a column containing TIOA on an inert support from a 12 M HCl/0.02 M HF solution. Then the column was successively washed with 4 M HCl/0.02 M HF (Pa–Nb fraction) and 6 M  $HNO_3/0.015$  M HF (Ta fraction). The  $\alpha$  activity of the  $^{262}Db$ – $^{258}Lr$  pair was found primarily in the Pa–Nb fraction. Therefore, the Group V elements are extracted with TIOA in the series  $Ta > Nb > Db > Pa$ . In the studies,<sup>22,23</sup> the 'non-tantalum' behaviour of dubnium was attributed to the fact that this element, like Nb and Pa, forms the oxyhalide or hydroxy halide complexes  $[NbOCl_4]^-$  and  $[PaOCl_4]^-$  or  $[Pa(OH)_2Cl_4]^-$ , whereas tantalum forms the purely halide complex  $[TaCl_6]^-$  under these conditions. However, this explanation is not fully explicit because the fact that HCl solutions contain the strong complexing ligand ( $F^-$  ions) is ignored.

With the aim of examining the similarity between the chemical properties of Db and Pa, a series of experiments on the extraction of Db, Pa and Nb with diisobutylcarbinol, which is a selective extractant for Pa, was carried out.<sup>24</sup> Radionuclides were sorbed on a column with diisobutylcarbinol from a 7 M HBr solution, and the column was then successively washed with a 6 M HCl/0.02 M HF solution (Nb fraction) and a 0.5 M HCl solution (Pa fraction). The investigation revealed the following series:  $Pa > Nb > Db$ . This series does not confirm the similarity in the behaviour of Db and Pa observed upon their extraction with TIOA.

The extraction behaviour of Group VB elements on a column with Aliquat-336 from pure HCl, HF and HBr solutions using an ARCA apparatus was studied in detail.<sup>25</sup> It was found that the elements were extracted from 6 M HCl solutions in the series  $Pa \gg Nb \geq Db > Ta$ . In a 4 M HF solution, dubnium was sorbed on an anion-exchange column with the distribution coefficients  $K_d > 570$ . These coefficients are similar to those for Nb and Ta ( $\geq 10^3$ ). By contrast, Pa is sorbed only to a small extent ( $K_d \approx 19$ ) under these conditions. Therefore, the Group V elements were extracted from 4 M HF solutions with Aliquat in the following series:  $Ta \geq Nb > Db > Pa$ . The degree of extraction of the Group V elements from solutions of hydrohalic acids decreases in the series  $HF > HCl > HBr$ .<sup>25</sup> These characteristic

features are consistent with the results of relativistic calculations on the stability of negatively charged halide complexes of Group V elements.<sup>71, 76</sup>

**Ion-exchange method.** The ion-exchange method in the on-line mode was used to isolate dubnium and study its behaviour in dilute HF solutions.<sup>27</sup> The <sup>262</sup>Db isotope was produced by the nuclear reaction (<sup>248</sup>Cm, xn <sup>19</sup>F) at the accelerator at the Institute of Nuclear Physics (Orsay, France). A 0.2 M HF solution containing nuclear reaction products was gradually passed through three ion-exchange columns filled with a cation-exchange resin (Bio Rad AG 50W × 8), a macroporous anion-exchange resin (Bio Rad AG MP1) and a cation-exchange resin (AG50W × 8), respectively. A high degree of purification of Db from actinide elements was achieved on the first column, Db was adsorbed on the second column, and its decay products were retained on the third column. The <sup>262</sup>Db isotope was identified by the long-lived decay product <sup>254</sup>Fm (*T*<sub>1/2</sub> = 3.24 h) after its desorption from the third cation-exchange column. It was demonstrated that <sup>262</sup>Db, which could be produced by the reaction <sup>248</sup>Cm + <sup>19</sup>F, was virtually completely (67 atoms) sorbed on the second (anion-exchange) column. A preliminary investigation of the behaviour of Group V elements on AG MP1 anion-exchange resin in HF solutions demonstrated that the elements in the HF concentration range of 0.01–0.3 mol litre<sup>−1</sup> are sorbed in the series Ta ≫ Pa > Nb with the distribution coefficients of ≥10<sup>4</sup>. The authors of the study<sup>27</sup> believed that Db, like its homologues Ta and Nb and pseudohomologue Pa, forms negatively charged complexes in dilute HF solutions, and these complexes are strongly sorbed on the anion-exchange resin.

**Anion-exchange method.** The anion-exchange behaviour of Db and its homologues and also of Pa in concentrated HF solutions was studied<sup>29</sup> with the use of an AIDA apparatus. In 14 M HF solutions, *K*<sub>d</sub> values are 35 for Db, 150 for Nb, 175 for Ta and 18 for Pa. Therefore, the order of sorption is the same as that observed for extraction with Aliquat (reagents containing identical functional groups) from 4 M HF solutions.<sup>25</sup> However, the distribution coefficients for Db on the anion-exchange resin in 14 M HF solutions are closer to those for Pa, whereas the distribution coefficients of Db for extraction from 4 M HF solutions are close to those of Nb and Ta (see above).

**Cation-exchange method.** The <sup>263</sup>Db (*T*<sub>1/2</sub> = 27 s) isotope, which was produced in the reaction <sup>249</sup>Bk (<sup>18</sup>O, 4n), was isolated and chemically identified with the use of α-hydroxyisobutyric acid as the eluent. The experiments were carried out on an ARCA apparatus. During elution of radionuclides, dubnium was washed out together with Nb, Ta and Pa from a cation-exchange column with a solution of α-HIBA within the first four seconds, unlike tri- and tetravalent radionuclides. In the authors' opinion,<sup>26</sup> the pentavalent state of dubnium is the most stable in solution.

The cation-exchange method combined with extraction was used to prove a new decay branch of <sup>263</sup>Db through electron capture and to identify <sup>263</sup>Rf.<sup>28</sup> After elution of <sup>263</sup>Db from the cation-exchange column with α-HIBA, the eluate was transferred into a 9 M HCl solution, from which radionuclides were extracted with a TBP–cyclohexane mixture. In the extractant, spontaneous fission of <sup>263</sup>Rf (*T*<sub>1/2</sub> = 20 min) was observed; the latter isotope could be produced only by the decay <sup>263</sup>Db(e.c.) → <sup>263</sup>Rf(s.f.).<sup>†</sup>

Model experiments demonstrated that dubnium can be isolated by extraction with trioctylamine (TOA) from solutions of α-hydroxyisobutyric and lactic acids in the on-line mode using the SISAK system.<sup>67</sup>

### 3. Seaborgium

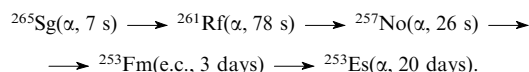
#### a. Theoretical prerequisites

Calculations by the Dirac–Fock method predicted<sup>68</sup> the 5f<sup>14</sup>6d<sup>4</sup>7s<sup>2</sup> electronic configuration for a free neutral atom of element 106 in the ground state, *i.e.*, this element belongs to Group VIB. Tungsten and molybdenum are homologues of seaborgium

and U is its pseudohomologue. In aqueous solutions, Sg<sup>6+</sup> would be expected to be the most stable oxidation state of seaborgium, although the possibility of the existence of the tetravalent state in the absence of complexing ligands cannot be ruled out.<sup>77</sup> The characteristic feature of elements belonging to this group is that they form oxygen-containing compounds in aqueous solutions through strong M–O covalent bonds.

#### b. Behaviour of Group VIB elements in solutions

To identify seaborgium by chemical methods, it is necessary to separate it from daughter radionuclides, which can be produced both by nuclear reactions in the synthesis and the radioactive decay



With the aim of finding the optimum conditions for the isolation and identification of seaborgium based on its daughter decay products, the ion-exchange behaviour of its homologues, *viz.*, W and Mo, and homologues of rutherfordium and nobelium, *viz.*, Hf and Sr, respectively, the pseudohomologue U and some TPEs (Cm) and REEs (Eu) in dilute H<sub>2</sub>SO<sub>4</sub> and H<sub>2</sub>SO<sub>4</sub>/HF solutions was studied.<sup>51</sup> The effect of the H<sub>2</sub>SO<sub>4</sub> concentration on the distribution coefficients of the elements upon their sorption on cation- and anion-exchange resins is illustrated in Fig. 7. Tungsten is sorbed only to a small extent on cation-exchange resins from solutions containing H<sub>2</sub>SO<sub>4</sub> at concentrations lower than 0.1 mol litre<sup>−1</sup>, whereas the distribution coefficients of U, Hf, Sr, Cm and Eu are ≥10<sup>3</sup>–10<sup>4</sup> (see Fig. 7a). Tungsten, hafnium and uranium are sorbed on anion-exchange resins with distribution coefficients larger than 10<sup>2</sup>–10<sup>3</sup>, whereas Sr, Cf and Eu are virtually not sorbed from these solutions (see Fig. 7b). Therefore, cation-exchange columns can be used to separate W (Sg) from daughter elements, *viz.*, Hf (Rf), Sr (No) and REEs (TPEs), and from U in the on-line mode. Anion-exchange columns can be used to concentrate Group IV–VI elements and separate them from di- and trivalent elements. Since the presence of small amounts of HF in dilute H<sub>2</sub>SO<sub>4</sub> solutions has only a slight effect on the sorption of W, Hf, Sr, TPEs and U,<sup>51</sup> these solutions can also be used to isolate and study seaborgium.

Sorption of Group IV–VI elements on Dowex-50 × 8 cation-exchange resin and Dowex-1 × 8 anion-exchange resin from mixed HCl/HF solutions has been studied in detail.<sup>69</sup> It was demonstrated that Group VI and V elements can be separated from Group IV elements in the on-line mode with the use of 0.05–0.1 M HCl solutions containing 1 × 10<sup>−3</sup> mol litre<sup>−1</sup> HF.

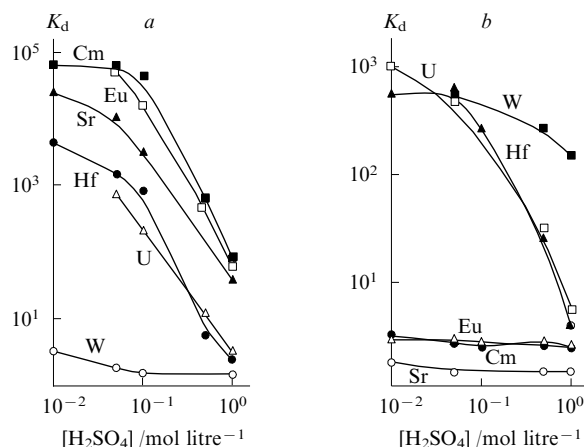


**Figure 7.** Plots of the distribution coefficients of elements vs. the H<sub>2</sub>SO<sub>4</sub> concentration for sorption on Dowex-50 × 8 cation-exchange resin (a) and Dowex-1 × 8 anion-exchange resin (b).<sup>51</sup>

<sup>†</sup> s.f. is spontaneous fission.

The possibility of determining the distribution coefficients of Sg and the compositions of complexes in HCl/HF and HNO<sub>3</sub>/HF solutions was examined by studying the sorption of W and Mo on anion-exchange resins containing various functional groups.<sup>63, 78</sup> The sorption selectivity and the separation factor of W and Mo were demonstrated to depend strongly on the composition of the solution and the nature of the functional groups of the ion-exchange resin. The optimum conditions for the separation of the W–Mo pair in the on-line mode were found.

To isolate seaborgium with the use of the SISAK extraction system, extraction of <sup>176</sup>W, <sup>177</sup>W, <sup>99</sup>Mo, U, Th, Am, Cm, La, Ce, Tb, Lu and Hf from HNO<sub>3</sub>, H<sub>3</sub>PO<sub>4</sub> and H<sub>2</sub>SO<sub>4</sub> solutions was studied<sup>79, 80</sup> using Aliquat-336 and TOA. The optimum conditions for the separation of Group VI elements and U from TPEs, REEs and Hf were found. The extraction of elements in different oxidation states decreases in the series  $M^{4+} > MO^{2+} > M^{3+}$ .

### c. Model experiments

**Ion-exchange methods.** Short-lived tungsten isotopes, which were produced in the nuclear reactions Sm (<sup>24</sup>Mg, xn) at a cyclotron, and Mo, Zr, Ba and REE radionuclides produced by fission of <sup>235</sup>U were isolated in model experiments and their chemical behaviour in dilute H<sub>2</sub>SO<sub>4</sub>, H<sub>2</sub>SO<sub>4</sub>/HF,<sup>52</sup> HF (see Refs 34, 46 and 48) and HCl/HF solutions<sup>61</sup> was studied. The radionuclides were isolated and determined in the on-line mode using two–three ion-exchange columns. Table 4 lists the tungsten isotopes and products of their radioactive decay, which were determined on columns during elution with a 0.05 M H<sub>2</sub>SO<sub>4</sub> solution containing the radionuclides. The Hf and REE isotopes, which were produced by the decay of tungsten before the solution was fed into the column, were sorbed on the first (cation-exchange) column. The tungsten isotopes and products of their radioactive decay, viz., the ‘daughter’ (tantalum) and ‘granddaughter’ (hafnium) isotopes, adsorbed on the second (anion-exchange) column. The ‘great-granddaughter’ isotopes (Lu and Yb, respectively) were retained on the third (cation-exchange) column. The <sup>168</sup>W, <sup>169</sup>W and <sup>172</sup>W isotopes were found on the anion-exchange resin, but the shorter-lived <sup>167</sup>W isotope ( $T_{1/2} = 19.3$  s) was not detected because of the lack (at that instant) of data on the  $\gamma$ -radiation energies of this radionuclide. However, the presence of the <sup>167</sup>Ta, <sup>167</sup>Hf, <sup>167</sup>Lu and <sup>167</sup>Yb radionuclides, which could be produced only by successive  $\beta^+$ -decays of <sup>167</sup>W, on the anion-exchange column and the second cation-exchange column, provides evidence that this isotope was also present on the anion-exchange column.

Therefore, the short-lived parent radionuclide was chemically identified based on the genetic relationship to longer-lived decay products. The results of model experiments suggest that <sup>265</sup>Sg ( $T_{1/2} = 7 \pm 3.3$  s) can be isolated and its chemical properties can be studied in the on-line mode followed by the identification with

the longer-lived decay products <sup>261</sup>Rf, <sup>253</sup>Fm and <sup>253</sup>Es, which can be accumulated on anion-exchange or cation-exchange columns.

**Extraction method.** Tungsten and molybdenum as homologues of Sg were isolated by on-line extraction using the SISAK system.<sup>67</sup> It was demonstrated that the degree of extraction of Group VI and V elements with TOA from solutions of  $\alpha$ -hydroxyisobutyric or lactic acids is 80% (or higher), whereas Group IV elements (Hf) and REEs remain in the aqueous phase. The best separation was achieved by extraction from 1 M  $\alpha$ -HIBA solutions at pH 1–2 with the use of 0.046 M TOA as the extractant.

### d. Isolation of seaborgium and investigation of its chemical properties

The first experiments on the isolation of seaborgium and investigation of its behaviour in solution were carried out after the ‘long-lived’ <sup>265</sup>Sg ( $T_{1/2} = 7 \pm 3$  s) and <sup>266</sup>Sg ( $T_{1/2} = 20 \pm 16$  s) isotopes had been synthesised in FLNR JINR,<sup>4</sup> although the <sup>263</sup>106 isotope ( $T_{1/2} = 0.9$  s) was discovered as early as 1974. The <sup>265</sup>Sg and <sup>266</sup>Sg isotopes were produced in the nuclear reaction <sup>248</sup>Cm + <sup>22</sup>Ne at the Unilac Accelerator Facility (Darmstadt, Germany).<sup>30</sup> Seaborgium was separated from other radionuclides on the ARCA apparatus using chromatographic columns (1.6 × 8 mm) filled with Aminex A-6 cation-exchange resin (17  $\mu$ m). A 0.1 M HNO<sub>3</sub>/5 × 10<sup>−4</sup> M HF solution was used as the eluent. The seaborgium fractions were collected during the first ten seconds. Preliminary experiments showed that, under these conditions, the degree of elution of tungsten from the column was 85%, whereas trivalent actinides, Group IV elements and uranium remained on the column; 4000 cycles of isolation and determination of seaborgium were carried out. Three pairs of  $\alpha$ – $\alpha$  correlated decays for <sup>261</sup>Rf and <sup>257</sup>No, which are the daughter decay products of <sup>265</sup>Sg, were observed. The <sup>265</sup>Sg isotope ( $T_{1/2} \approx 7$  s) was not detected directly because the total time consumed for the chemical operations was 38–45 s. These results suggest that seaborgium exists in solution in the stable hexavalent state and, like its light homologues, viz., tungsten and molybdenum, forms neutral (SgO<sub>2</sub>F<sub>2</sub>) or anionic (SgO<sub>2</sub>F<sub>3</sub><sup>−</sup>) oxyhalide complexes. The existence of ‘seaborgates’ SgO<sub>4</sub><sup>−</sup>, by analogy with molybdates and tungstates, cannot be ruled out as well.<sup>30</sup>

Another series of experiments on the isolation of seaborgium was carried out with the use of HF-free 0.1 M HNO<sub>3</sub> solutions as the eluent.<sup>31</sup> The <sup>265</sup>Sg and <sup>169</sup>W isotopes were produced simultaneously by bombardment of the combined <sup>248</sup>Cm + Gd target with <sup>22</sup>Ne ions. All other experimental conditions were identical to those used in the earlier experiment.<sup>30</sup> The first portions of the eluate (0.1 M HNO<sub>3</sub>) contained ~60% of <sup>169</sup>W; only one  $\alpha$ – $\alpha$  decay pair corresponding to <sup>261</sup>Rf–<sup>257</sup>No was observed. However, according to the estimates,<sup>31</sup> five  $\alpha$ – $\alpha$  correlated events were expected. Based on this fact, the authors hypothesised that in dilute HNO<sub>3</sub> solution, seaborgium gives the positively charged hydrolysed Sg(OH)<sub>4</sub>(H<sub>2</sub>O)<sub>2</sub><sup>+</sup> or Sg(OH)<sub>5</sub>(H<sub>2</sub>O)<sup>+</sup> species, which are sorbed on cation-exchange resins. In such solutions, the behaviour of seaborgium is similar to that of uranium. Tungsten forms primarily the neutral WO<sub>2</sub>(OH)<sub>2</sub> compounds, which remain in solution.<sup>31</sup>

**Table 4.** Distribution of tungsten isotopes produced in the nuclear reactions Sm(<sup>24</sup>Mg, xn) and radioactive decay products of tungsten on ion-exchange columns (from 0.05 M H<sub>2</sub>SO<sub>4</sub> solutions); the measurements were carried out in the on-line mode.<sup>48, 52</sup>

| First column,<br>Dowex-50 × 8 cation-<br>exchange resin |           | Second column,<br>Dowex-1 × 8 anion-<br>exchange resin |           | Third column,<br>Dowex-50 × 8 cation-<br>exchange resin |           |
|---------------------------------------------------------|-----------|--------------------------------------------------------|-----------|---------------------------------------------------------|-----------|
| isotope                                                 | $T_{1/2}$ | isotope                                                | $T_{1/2}$ | isotope                                                 | $T_{1/2}$ |
| <sup>167</sup> Hf                                       | 2.05 min  | <sup>168</sup> W                                       | 53.0 s    | <sup>167</sup> Lu                                       | —         |
| <sup>169</sup> Hf                                       | 3.2 min   | <sup>169</sup> W                                       | 1.3 min   | <sup>168</sup> Lu                                       | —         |
| <sup>167</sup> Lu                                       | 52.0 min  | <sup>172</sup> W                                       | 6.7 min   | <sup>167</sup> Yb                                       | —         |
| <sup>168</sup> Lu                                       | 6.0 min   | <sup>167</sup> Ta                                      | 1.4 min   | <sup>169</sup> Yb                                       | 46 s      |
| <sup>169</sup> Lu                                       | 2.7 min   | <sup>169</sup> Ta                                      | 4.9 min   |                                                         |           |
| <sup>167</sup> Yb                                       | 17.5 min  | <sup>170</sup> Ta                                      | 6.8 min   |                                                         |           |
|                                                         |           | <sup>172</sup> Ta                                      | 38.8 min  |                                                         |           |
|                                                         |           | <sup>167</sup> Hf                                      | —         |                                                         |           |

## 4. Bohrium and hassium

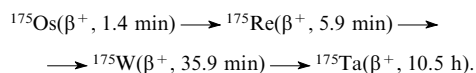
### a. Theoretical prerequisites

It was predicted<sup>68</sup> that the configurations of the outer electron shells of elements 107 and 108 are 6d<sup>5</sup>7s<sup>2</sup> and 6d<sup>6</sup>7s<sup>2</sup>, respectively. Therefore, Bh and Hs belong to Groups VIIB and VIIIB, respectively. Rhenium and technetium are the chemical homologues of Bh. Osmium and ruthenium are the chemical analogues of Hs. The characteristic feature of elements of these groups is that they can exist in various oxidation states. In particular, the stable states +7, +5 and +3 were predicted for Bh.<sup>77</sup> Since the highest oxidation state within the group is stabilised on going to heavier elements, bohrium, by analogy with rhenium, would be expected to occur in aqueous solution in the heptavalent oxidation state as the BhO<sub>4</sub><sup>−</sup> oxy anion. Evidently, hassium, by analogy with

osmium, can exhibit the maximum oxidation state of +8 (volatile tetroxide  $\text{OsO}_4$ ) and a lower valence state in aqueous solution.

### b. Model experiments

**Ion-exchange methods.** Model experiments on the isolation of the short-lived osmium and rhenium isotopes under conditions simulating isolation of Hs and Bh, respectively, were carried out at the U-400 cyclotron in FLNR JINR. Osmium radionuclides were produced in the nuclear reactions  $^{nat}\text{Dy}(^{20}\text{Ne}, xn)^{172-178}\text{Os}$ . Rhenium and tungsten isotopes were present in the system as decay products of osmium, for example,



The isolation was carried out from 0.05 M  $\text{H}_2\text{SO}_4$  and 0.05 M  $\text{HCl}$  solutions in the on-line mode with the use of ion-exchange columns connected in series (cation-exchange resin – anion-exchange resin – cation-exchange resin).<sup>53, 64</sup> In both systems, Os and Re were not sorbed on the cation-exchange resin, but were strongly retained on the anion-exchange column, which is indicative of the presence of neutral or negatively charged forms of the elements in these solutions. Table 5 lists the nuclear physical characteristics of the radionuclides detected on the anion-exchange column (the on-line mode) when passing a 0.05 M  $\text{HCl}$  solution through the column.<sup>64</sup> Short-lived osmium isotopes with  $T_{1/2} = 16\text{--}55 \text{ s}$  were isolated. There is a genetic relationship between the osmium isotopes and the daughter decay products of rhenium and tungsten. Hence, these systems can be used to isolate Hs and Bh in the on-line mode.

The possibility of identifying the valence states and speciation of Hs and Bh in dilute  $\text{HCl}$  solutions was demonstrated in the study of the sorption of Os and Re on various sorbents (in the on-line mode).<sup>64</sup> Dowex-50  $\times 8$  cation-exchange resin, Dowex-1  $\times 8$  anion-exchange resin, mixed  $\text{K}_2\text{Ni}[\text{Fe}(\text{CN})_6]$  ferrocyanide and tri-*n*-octylphosphine oxide (TOPO) containing a sorbent on an inert support were used in the study. During the experiment, the order in which the columns containing various sorbents were connected was varied. Figure 8 shows the  $\gamma$  spectra of three columns connected in series: the cation-exchange resin, ferrocyanide and the anion-exchange resin. The spectra were measured when a solution of radionuclides in 0.05 M  $\text{HCl}$  was passed through these columns. Osmium, rhenium and tungsten radionuclides were sorbed only on the anion-exchange column. These radionuclides were not observed on the columns with the cation-exchange resin and ferrocyanide. The radionuclides were also absent in the solutions after they have been passed through the anion-exchange column.<sup>64</sup> Since only the  $\text{Os}^{3+}$  and  $(\text{OsO}_2)^{2+}$  cations are sorbed on the cation-exchange resin and ferrocyanide from dilute  $\text{HCl}$  solutions,<sup>81</sup>  $\text{Os}^{4+}$  were, evidently, present in the model experiment as the major form, that sorbed on the anion-exchange resin as  $(\text{OsCl}_6)^{2-}$ . When the columns were connected in the cation-

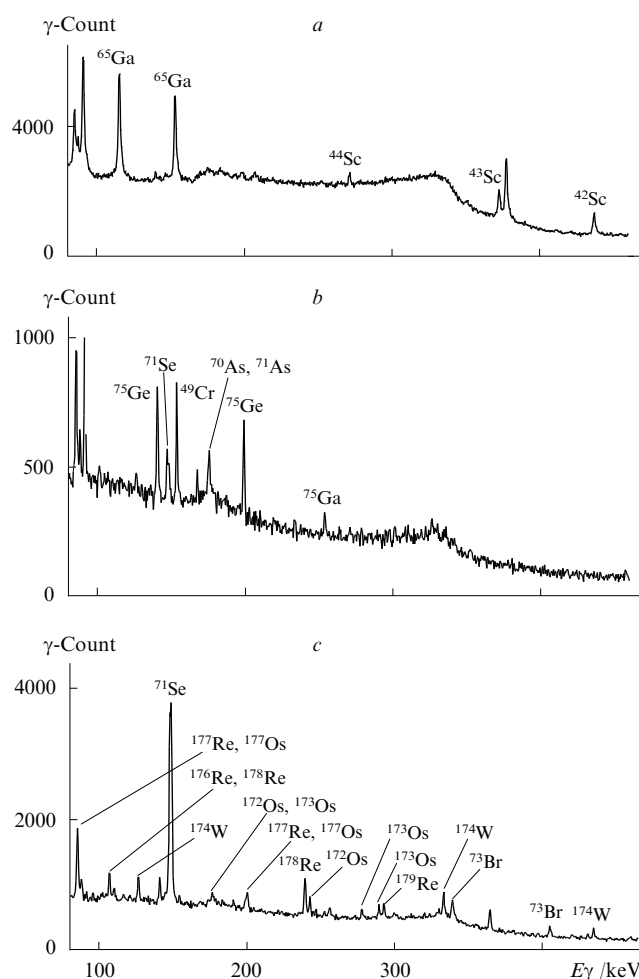


**Figure 8.**  $\gamma$ -Spectra of three columns connected in series and filled with Dowex-50 (a),  $\text{K}_2\text{Ni}[\text{Fe}(\text{CN})_6]$  (b) and Dowex-1 (c), which were measured when passing a 0.05 M  $\text{HCl}$  solution containing radionuclides (in model experiments with osmium and rhenium isotopes).<sup>64</sup>

exchange resin – TOPO – anion-exchange resin series, the osmium isotopes were also found only on the anion-exchange column, whereas Re was detected primarily on the anion-exchange column and, partially, on the TOPO-containing column.<sup>64</sup> In weakly acidic solutions, Re exists in the stable anionic  $\text{ReO}_4^-$  form, which is not sorbed on the cation-exchange resin, but is strongly retained both on the anion-exchange resin and the TOPO-containing sorbent to form the  $3(\text{TOPO})\text{H}_3\text{O}^+ + \text{ReO}_4^-$  or  $(\text{TOPO})\text{H}^+ + \text{ReO}_4^-$  solvates.

**Table 5.** Nuclear-physical characteristics of osmium, rhenium and tungsten isotopes detected on an anion-exchange column when passing a 0.05 M  $\text{HCl}$  solution.<sup>64</sup>

| Osmium            |           |                       | Rhenium           |           |                       | Tungsten         |           |                       |
|-------------------|-----------|-----------------------|-------------------|-----------|-----------------------|------------------|-----------|-----------------------|
| isotope           | $T_{1/2}$ | $E_\gamma/\text{keV}$ | isotope           | $T_{1/2}$ | $E_\gamma/\text{keV}$ | isotope          | $T_{1/2}$ | $E_\gamma/\text{keV}$ |
| $^{172}\text{Os}$ | 19.0 s    | 240, 254              | $^{172}\text{Re}$ | 55.0 s    | 123, 254              | $^{172}\text{W}$ | 6.7 min   | 154, 175              |
| $^{173}\text{Os}$ | 16.0 s    | 285, 187              | $^{173}\text{Re}$ | 1.9 min   | 181, 373              | $^{173}\text{W}$ | 8.0 min   | 459, 175              |
| $^{174}\text{Os}$ | 44.0 s    | 118, 138              | —                 | —         | —                     | $^{174}\text{W}$ | 29.4 min  | 125, 136              |
| $^{175}\text{Os}$ | 1.4 min   | 125, 181              | $^{175}\text{Re}$ | 5.0 min   | 185                   | $^{175}\text{W}$ | 34.9 min  | 166                   |
| $^{176}\text{Os}$ | 3.6 min   | 776, 857              | $^{176}\text{Re}$ | 5.7 min   | 109, 240              | $^{176}\text{W}$ | 2.5 h     | 100.2                 |
| $^{177}\text{Os}$ | 3.0 min   | 85, 196               | $^{177}\text{Re}$ | 14.0 min  | 84, 197               | —                | —         | —                     |
| $^{178}\text{Os}$ | 5.0 min   | 533, 594              | $^{178}\text{Re}$ | 13.2 min  | 106, 237              | —                | —         | —                     |
| $^{179}\text{Os}$ | 6.3 min   | 218                   | $^{179}\text{Re}$ | 19.5 min  | 290, 430              | —                | —         | —                     |



In the study, it was shown that Re and Tc (homologues of Bh) can be separated from Nb and Ta on a cation-exchange column with the use of mixed  $\text{HNO}_3/\text{HF}$  solutions (at 75 °C) as the eluent.<sup>49</sup>

**Extraction method.** The extraction method for the separation of Re and Tc in  $\text{HNO}_3$  solution from Nb, Ta, actinides and other elements using a 0.05 M TOA solution in toluene was developed with the aim of isolating Bh in the SISAK system.<sup>50</sup> In the study of Re and Tc, a selective method was developed for the isolation of Bh by extraction with TOA from solutions of  $\alpha$ -hydroxyisobutyric acid in the presence of an oxidising agent ( $\text{NaBrO}_3$ ).<sup>82</sup>

No experiments on the isolation of Bh from solution were carried out. The  $^{267}\text{Bh}$  isotope ( $T_{1/2} \approx 17$  s), which was produced by the reaction  $^{249}\text{Bk}(^{22}\text{Ne}, 4n)$  as the volatile oxychloride  $\text{BhO}_3\text{Cl}$ , was isolated by gas chromatography.<sup>83</sup> The long-lived  $^{269}\text{Hs}$  ( $T_{1/2} \approx 10$  s) and  $^{270}\text{Hs}$  ( $T_{1/2} = 2-7$  s) isotopes were isolated for the first time as the volatile tetroxide  $\text{HsO}_4$ .<sup>84</sup>

In the CALLISTO project, hassium was studied in the liquid phase using a new procedure for the isolation and transport of volatile nuclear reaction products in an aerosol-free gas flow.<sup>32, 85</sup> The  $^{269}\text{Hs}$  isotope produced in the nuclear reaction  $^{248}\text{Cm}(^{26}\text{Mg}, 5n)$  was oxidised to a volatile oxide (apparently,  $\text{HsO}_4$ ) in the gas flow ( $\text{O}_2 + \text{He}$ ) and transferred to a special device, in which  $\text{HsO}_4$  was trapped and Hs was detected. The device contained a stainless steel plate, which was coated with a thin NaOH film and located a distance of 1 mm from 16 silicon detectors. In the experiment, six  $6\alpha-\alpha$  correlations were observed in the decay chain of  $^{269}\text{Hs}$ . It was hypothesised<sup>32</sup> that octavalent hassium was isolated as sodium hassate  $\text{Na}_2[\text{HsO}_4(\text{OH})_2]$ , by analogy with  $\text{OsO}_4$ , whose dissolution in NaOH affords osmate  $\text{Na}_2[\text{OsO}_4(\text{OH})_2]$ .

## 5. Meitnerium and darmstadtium

Relativistic calculations for elements 109 and 110<sup>68</sup> predicted the  $5f^{14}6d^77s^2$  and  $5f^{14}6d^97s^1$  electronic configurations, respectively, for their neutral atoms in the free state. Therefore, Mt and Ds belong to Group VIII platinum elements. Iridium and platinum are the chemical homologues of meitnerium and darmstadtium, respectively. In recent years, the ‘long-period’ form of the Periodic table has gained increasing acceptance. In my opinion, this form reflects the chemical similarity, in particular, between the platinum-group elements, to a lesser extent compared to the ‘short-period’ form. In the ‘long-period’ form, elements 109 and 110 are placed in the ninth and tenth groups, respectively.

The characteristic feature of platinum elements is that they can form complexes with various ligands in solution.

No attempts to study the chemical properties of Mt and Ds in the liquid and gas phases have been reported. Apparently, this is associated with the very short lifetimes of the  $^{266}\text{Mt}$  ( $T_{1/2} = 5$  ms) and  $^{269}\text{Ds}$  ( $T_{1/2} = 393$   $\mu\text{s}$ ) isotopes, which were produced by the nuclear reactions  $^{209}\text{Bi}(^{58}\text{Fe}, n)$  and  $^{208}\text{Pb}(^{62}\text{Ni}, n)$ , respectively.

## 6. Roentgenium and element 112

### Theoretical prerequisites

According to the general regularities, elements 111 and 112 can be assigned, respectively, to Groups IB and IIB (or Groups 11 and 12 in the ‘long-period form’) of the seventh period. Gold and mercury are the chemical homologues of elements 111 and 112, respectively. Group IB and IIB elements have a completely filled  $d^{10}$  electron shell. Hence, these elements are characterised by a lower diversity of valence states compared to other groups of transition d elements. The presence of the  $d^{10}$  shell is responsible for the chemical inertness of metals and their tendency to form intermetallic compounds. Another specific feature of these elements is the formation of compounds with covalent bonds. Relativistic calculations predicted that the most stable oxidation states of elements 111 and 112 are +3 and +2, respectively. In the metallic state, element 112 may be highly volatile by analogy with noble gases.<sup>86, 87</sup>

Data on the chemical properties of element 111 are lacking.

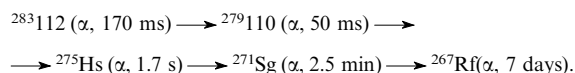
### b. Model experiments

Model experiments on the isolation of element 112 from solution were carried out with the use of short-lived Hg isotopes in the on-line mode.<sup>88</sup> It was demonstrated that Hg is strongly adsorbed from 0.05 M  $\text{H}_2\text{SO}_4$  solution on a column, which is filled with glass granules treated with silver.

### c. Isolation of element 112

Element 112 has only been isolated in the gas phase (FLNR JINR).<sup>89, 90</sup> The  $^{283}112$  isotope (s.f.,  $T_{1/2} = 3$  min.) was produced simultaneously with the short-lived  $^{185}\text{Hg}$  isotope ( $\alpha$ ,  $T_{1/2} = 49$  s) in the reactions  $^{238}\text{U} + \text{Nd}(^{48}\text{Ca}, xn)$  at the U-400 cyclotron. The nuclear reaction products in the gas flow (He) were passed to a counting apparatus consisting of a system of semiconducting detectors with a gold coating and an ionisation chamber, which recorded  $\alpha$  decay and spontaneous fission. Compared to Hg, element 112 interacts much more weakly with gold, and its chemical behaviour is more similar to that of Rn under the conditions used.<sup>90</sup>

It was predicted<sup>91</sup> that the  $\alpha$  decay of element 112 can occur to form the following chain:



In experiments on the synthesis of element 112 by the reaction  $^{238}\text{U}(^{48}\text{Ca}, xn)$  (FLNR JINR, in 2004), a chain of four successive  $\alpha$  decays was observed. The chain was terminated to give spontaneously fissionable  $^{267}\text{Rf}$  isotope ( $T_{1/2} \approx 3$  h) as the final product.<sup>92</sup> The occurrence of such decay chains offers possibilities of isolating element 112, studying its chemistry in solution in the on-line mode and determining it based on long-lived decay products.

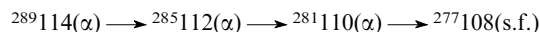
## 7. Elements 113 and 114

### a. Synthesis and theoretical prerequisites

Data on the synthesis of element 113 are lacking. However,  $\alpha$  activity with  $T_{1/2} = 0.5$  s was observed in the decay chain of element 115, and this activity was assigned to element 113.<sup>2</sup>

Element 114 has attracted particular interest because of the theoretical predictions of ‘islands of stability’ for  $Z = 114$  and  $N = 184$ . Considerable attention has been given to a search for this element in nature, because calculations predicted that the lifetime of this radionuclide may be comparable with the age of the Earth. However, numerous investigations did not give positive results, and studies in this field were terminated. According to the modern concept,<sup>91</sup> even-even isotopes of elements 108 and 110 with a closed spherical shell ( $N = 180-184$ ) should be even more stable. Hence, studies aimed at searching for SHEs in nature will be continued.

In 1998–1999, element 114 was synthesised in the reactions  $^{244}\text{Pu}(^{48}\text{Ca}, 3-4n)$  and  $^{242}\text{Pu}(^{48}\text{Ca}, 3n)$  at the U-400 cyclotron (FLNR JINR).<sup>1</sup> The  $\alpha$  decay chain



and two identical decay chains of the  $^{288}114$  isotope were observed. These chains afforded finally the spontaneously fissioning  $^{280}110$  isotope. Therefore, the effect of stabilisation of the neutron-excessive nuclei with  $Z = 114$  ( $N = 175, 174, 173$ ) in the vicinity of the closed neutron shell  $N = 184$  was established experimentally (earlier, this effect was predicted theoretically).

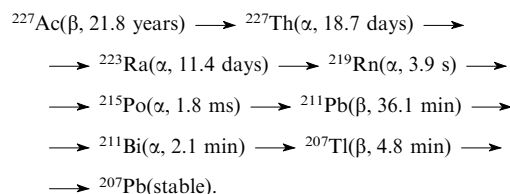
After filling the d shell of transition elements 111 and 112, the p shell of the subsequent elements begins to be filled. Hence, elements 113 and 114 belong to the so-called ‘post-transition’ or p elements. The valence electrons of these elements occupy the ns and np sublevels. Thallium and lead are homologues of elements 113 and 114, respectively. It was predicted<sup>93</sup> that  $113^{+1}$  and  $114^{+2}$  are the most stable oxidation states. In addition, due to relativistic effects, element  $114^{+2}$  should exhibit stronger complexing properties than  $\text{Pb}^{+2}$  and, under particular conditions, would be similar to  $\text{Hg}^{+2}$ .

No experiments on the isolation of element 113 and investigation of its chemical properties have been carried out.

### b. Model experiments

Model experiments on the isolation of element 114 and investigation of its chemical properties were carried out using its homologue, viz., Pb.<sup>54,94,95</sup> To produce the short-lived carrier-free <sup>211</sup>Pb isotope ( $T_{1/2} = 36.1$  min) a simple and efficient procedure was developed for the on-line isolation of this element from parent radionuclides (based on the same principle as a radioisotope generator).

**Construction of the generator.** The <sup>211</sup>Pb isotope belongs to the main branch of the decay chain of the actinide family



The repeated isolation of the <sup>211</sup>Pb isotope was carried out with the use of a small cation-exchange column on which <sup>227</sup>Ac or <sup>223</sup>Ra was sorbed, while the short-lived <sup>211</sup>Pb isotope was washed out with a solution of an appropriate composition. The scheme of the generator and the elution curves of <sup>211</sup>Pb using solutions of various compositions are shown in Fig. 9.

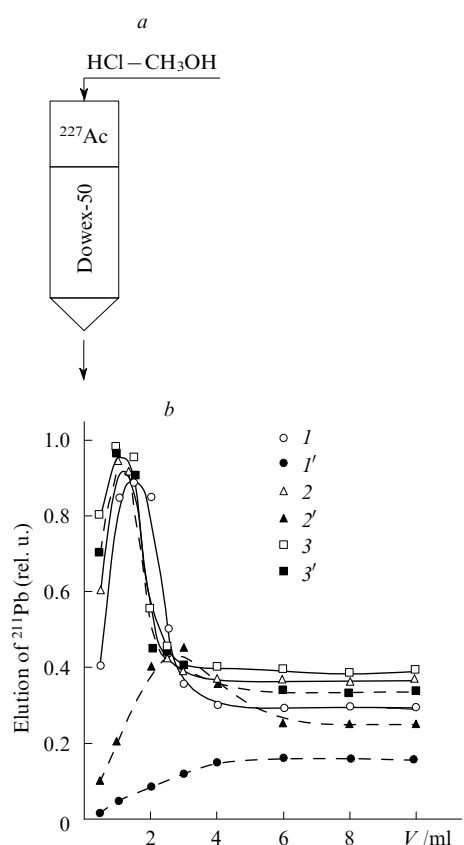


**Figure 9.** The generator of <sup>211</sup>Pb; 0.4 × 5 cm cation-exchange column (a) and the elution curves of <sup>211</sup>Pb with 1 M and 0.5 M HCl solutions (solid and dashed lines, respectively) containing CH<sub>3</sub>OH (b).<sup>94</sup> [CH<sub>3</sub>OH] (%): (1, 1') 0, (2, 2') 80, (3, 3') 90.

**Investigation of the ion-exchange behaviour of Pb. Cation-exchange resin.** With the aim of finding the optimum conditions for elution of <sup>211</sup>Pb and stronger retention of the parent radionuclides sorbed on a cation-exchange column, the static and

dynamic characteristics of sorption of elements were examined depending on the composition of the solution, the concentration of the acid (HCl, HBr) and the nature of the solvent (alcohols, ketones, etc.). The distribution coefficients of actinide elements and Ra were demonstrated to be higher in the presence of an organic solvent, whereas the distribution coefficients of Pb, on the contrary, decrease due to strong complexation in aqueous-organic solutions. In HBr solutions, the distribution coefficients of Pb are lower than those in HCl solutions due to the formation of more stable bromide complexes. The distribution coefficients of actinide elements in aqueous-organic solutions of HCl and HBr are larger than  $K_d$  for lead by four orders of magnitude, which allows the repeated elution of <sup>211</sup>Pb from a generator over a long period of time. The purification factors of <sup>211</sup>Pb from actinides are  $> 10^5 - 10^6$ .<sup>54,94,95</sup>

**Anion-exchange resin.** Lead is characterised by low adsorbability on anion-exchange resins from 1–2 M HCl solutions ( $K_d \approx 30$ ) and high adsorbability from HBr solutions ( $K_d \geq 10^3$ ) (Fig. 10). These facts support the conclusion that anionic bromide complexes of lead are more stable than the corresponding chloride complexes. In the presence of organic solvents, the sorption of lead on anion-exchange resins from HCl solutions sharply increases.<sup>54,95</sup> Due to the high distribution coefficients of Pb in dilute HBr solutions and aqueous-methanolic HCl solutions, lead can be concentrated on small anion-exchange columns with simultaneous separation from Hf and actinides, which are not sorbed on anion-exchange resins under these conditions.

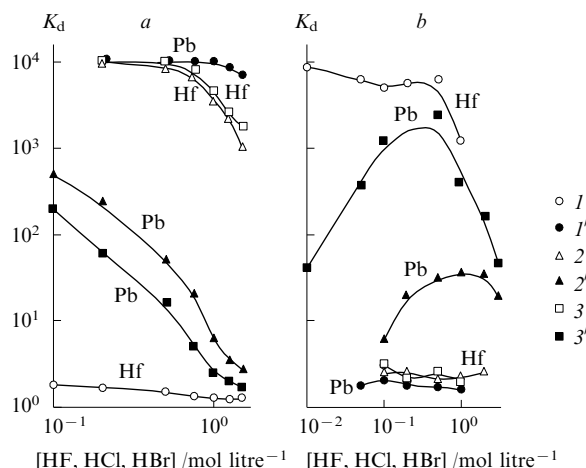


**Figure 10.** Plots of the distribution coefficients of Hf (1, 2, 3) and Pb (1', 2', 3') vs. the concentration and nature of acid for sorption on Dowex-50 × 8 cation-exchange resin (a) and Dowex-1 × 8 anion-exchange resin (b). (1, 1') HF, (2, 2') HCl, (3, 3') HBr.

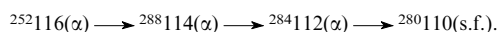
Experiments on the isolation of the short-lived <sup>211</sup>Pb isotope from a generator and investigation of its chemical behaviour by repeated elution from a cation-exchange column with solutions of various compositions are, in fact, model experiments on the isolation of element 114 and investigation of its chemistry in the on-line mode. In experiments performed in FLNR JINR (in 2004), two chains were observed in the synthesis of element 114 in the reaction <sup>242</sup>Pu(<sup>48</sup>Ca, 3n).<sup>92</sup> These chains consist of four and five successive  $\alpha$  decays and are completed by the spontaneous fission of <sup>271</sup>Sg ( $T_{1/2} = 2.4^{+4}_{-1}$  min) and <sup>267</sup>Rf ( $T_{1/2} = 3.3$  h), respectively. Evidently, on-line isolation followed by identification of longer-lived decay products can be used for element 114.

## 8. Elements 115 and 116

Element 115 was synthesised in the nuclear reaction <sup>243</sup>Am(<sup>48</sup>Ca, xn)<sup>291-xn</sup>115 at the U-400 cyclotron (FLNR JINR, in

2003).<sup>2</sup> For the  $^{288}115$  isotope ( $T_{1/2} \approx 87$  ms), which was produced in channels with evaporation of three neutrons, three identical chains of five successive  $\alpha$  decays giving finally  $^{268}\text{Db}$  (s.f.,  $T_{1/2} = 16^{+19}_{-6}$  h) were observed. For the  $^{287}115$  isotope ( $T_{1/2} \approx 32$  ms), which was produced in the reaction upon evaporation of four neutrons, a chain of four successive  $\alpha$  decays completed by the spontaneous fission of  $^{267}\text{Db}$  (s.f., 73 min) was observed.

Element 116 was synthesised in the same laboratory (in 2000–2001) by the nuclear reaction  $^{248}\text{Cm}(^{48}\text{Ca}, 4n)$ .<sup>3</sup> Three identical decay chains corresponding to the isotope were observed:



Therefore, in addition to the discovery of new element 116, the discovery of element 114, which has been synthesised earlier by the reaction  $^{244}\text{Pu}(^{48}\text{Ca}, 4n)$ ,<sup>1</sup> was confirmed. More recently (in 2004), three more isotopes of element 116 with masses 290–293 were produced by the reactions  $^{245}\text{Cm}$ ,  $^{248}\text{Cm} + ^{48}\text{Ca}$ .<sup>92</sup>

According to the general regularities of the filling of electron shells, elements 115 and 116 can be assigned to p elements, and Bi and Po are, respectively, their chemical homologues. Relativistic calculations demonstrated that element 115 is rather stable in the oxidation state of +1 and the chemical properties of element 115 are to a certain extent similar to the properties of  $\text{Tl}^+$ . The most stable oxidation state of element 116 is +2.<sup>96</sup>

In the studies,<sup>97,98</sup>  $^{268}\text{Db}$  was isolated as the terminal decay product of element 115, which was produced in the reaction  $^{243}\text{Am}(^{48}\text{Ca}, 3n)$  at the U-400 cyclotron (FLNR JINR). The products of the nuclear reactions were collected in the surface layer of a copper catcher block. Radionuclides were separated from macroamounts of copper by precipitation of  $\text{La}(\text{OH})_3$  with ammonia. Group V elements were separated from actinides and lanthanides on a cation-exchange column filled with Dowex-50  $\times$  8 with the use of a 1 M HF solution as the eluent. The eluent was evaporated on a polyethylene film (0.4  $\mu\text{m}$  thick), which was placed between a pair of semiconducting detectors surrounded by  $^3\text{He}$  counters for measuring  $\alpha$  particles, fission fragments and neutrons. Fifteen events of spontaneous fission with  $T_{1/2} = 32^{+11}_{-7}$  h were observed, and they were assigned to the  $^{268}\text{Db}$  isotope. These results are in good agreement with the results of physical experiments on the synthesis of element 115, where the  $^{268}\text{Db}$  isotope was observed for the first time after five successive  $\alpha$  decays of the parent nucleus of the  $^{288}115$  isotope.<sup>2,92</sup> Therefore, the formation of element 115 in the reaction  $^{243}\text{Am} + ^{48}\text{Ca}$  and the formation of element 113 in the decay chain of element 115 were confirmed.

The chemical identification of element 116 has not been described.

## 9. Elements 117 and 118

Data on the synthesis of element 117 are lacking. Element 118 was produced by the reaction  $^{208}\text{Pb} + ^{83}\text{Kr}$  (LBL)<sup>99</sup> (more recently, these data were not confirmed). In the Laboratory of Nuclear Reactions of the Joint Institutes of Nuclear Research, element 118 was synthesised in the reaction  $^{249}\text{Cf} + ^{48}\text{Ca}$ .<sup>92,100</sup>

According to the general regularities, element 117 can be assigned to the halides with pronounced metallic properties, and At is a chemical homologue of this element. It was predicted that element 117 is more stable in the oxidation state of +3 than in the oxidation state of +1 due to relativistic effects. In certain solutions, the behaviour of element 117 may be similar to that of  $\text{Au}^{+3}$ .<sup>77</sup> Element 118 has a completed outer electron shell and should belong to the noble gases. In going from light to heavier analogues, the inertness of noble gases decreases. Hence, the reactivity of element 118 would be expected to be higher. In particular, its solubility in water would be expected to be higher compared to other inert gases.

## IV. Conclusion

In the last 10–15 years, considerable progress has been made in isolating TAEs and investigating their chemical properties in solution. A high-precision automated apparatus has been constructed and is being improved. This apparatus allows one to perform repeated isolation, separation and determination of transactinide elements. An efficient method has been developed for the on-line isolation of TAEs and investigation of their chemical properties during the production in nuclear reactions followed by their identification with long-lived decay products. New approaches to the isolation of short-lived isotopes of TAEs ( $^{257}\text{Rf}$ ,  $^{269}\text{Hs}$ , elements 112 and 115) on the tracer scale have been devised. These approaches are based on the use of separators, transport of radionuclides from the irradiated target in an aerosol-free gas flow, *etc.*

The behaviour of Rf and Db in solutions of hydrohalic acids has been thoroughly studied by chromatographic and extraction methods. It has been established with a high degree of assurance that Rf and Db form negatively charged complexes in dilute HF solutions and concentrated HCl solutions. It has been demonstrated that the stability of Rf and Db complexes with halide ions increases in the series  $\text{Br}^- < \text{Cl}^- < \text{F}^-$ , *i.e.*, in the order characteristic of Group IVB and VB elements. However, the results of comparative investigations of the stabilities of halide complexes of elements belonging to the same group by determining the distribution coefficients or the elution (extraction) order of elements are ambiguous and sometimes contradictory. The discrepancies can be attributed to various factors, primarily, to the low statistics and the possible losses of trace amounts of elements in the different steps of their isolation. Hence, conclusions about the behaviour of seaborgium in  $\text{HNO}_3$  solutions, which have been made on the basis of the detection of one atom, are unjustified. Short-lived radionuclides are generally determined only in one phase and at one concentration. When operating with a limited number of atoms, errors, for example, in the determination of the distribution coefficients may be larger than 100%.

In studies of the behaviour of homologous elements, the optimum conditions were found for isolation of TAEs with  $Z = 104$ –108, 112 and 114 and investigation of their chemical properties in solutions containing various inorganic and organic complexing ligands ( $\text{F}^-$ ,  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{H}_2\text{PO}_4^-$ ,  $\text{HSO}_4^-$ ,  $\text{C}_2\text{O}_4^{2-}$ , TOA, TBP, TOPO, *etc.*) in the on-line mode by chromatographic and extraction methods. The ability of inorganic ligands to form complexes with Group IVB and VB elements increases in the following series  $\text{OH}^- > \text{F}^- > \text{H}_2\text{PO}_4^- > \text{HSO}_4^- > \text{Cl}^- > \text{Br}^-$ . Investigations of the behaviour of short-lived rhenium and osmium isotopes in dilute HCl solutions using various sorbents demonstrated that the species and oxidation states of Bh and Hs can be determined. Homologous elements are widely used to test and construct new systems for the isolation and investigation of the chemical properties of TAE in solution. Model experiments on the extraction of short-lived zirconium and hafnium isotopes (homologues of rutherfordium) with macrocyclic ligands from solutions of mineral acids were carried out.<sup>101</sup> Zirconium and hafnium were separated by extraction with TOA in  $\text{H}_2\text{SO}_4$  solutions using the SISAK system.<sup>102</sup> A new method for the isolation and identification of superheavy elements by electrochemical deposition in systems containing several working electrodes made of different materials is in the development stage.<sup>103</sup>

An investigation of the relativistic effects in heavy element chemistry is a fundamental problem of modern radiochemistry. The influence of the relativistic effect of the electron shells of heavy atoms on the chemical properties of TAEs remains an open question. First experimental results, in which 'deviations' in the extraction and ion-exchange behaviour of dubnium and rutherfordium compared to the behaviour of their light homologues have been observed and assigned to the influence of the relativistic effects, have been revised and call for further study. The absence of unambiguous evidence for the influence of these effects is asso-

ciated with the difficulty of revealing substantial differences in the behaviour of elements belonging to the same group due to the similarity of their chemical properties and unreliable statistics. Moreover, regularities in the behaviour of elements observed in studies of extraction and ion exchange, *i.e.*, the distribution coefficients, do not always reflect the order in which the stability of the complexes changes. Depending on the nature and concentration of the ligand, the character of the resulting complex (inner- or outer-sphere complexes) and the nature of the sorbent (an extractant, a solvent) and, consequently, the adsorption (extraction) mechanism, an inversion in the behaviour of elements with similar chemical properties can be observed.

In my opinion, investigations of systems in which heavy elements can exhibit substantially different chemical properties (for example, in solutions containing various complexing ligands) have the most promise for revealing relativistic effects. As mentioned above, relativistic calculations predicted that the Rf atom can have the  $5f^{14}6d7s^27p^1$  or  $5f^{14}7s^27p^2$  electronic configuration along with the  $[Rn]5f^{14}6d^27s^2$  configuration. Evidently, under particular conditions (for example, in the presence of stabilising ligands), Rf can exhibit properties typical of p elements (Pb, Bi). In solutions of hydrohalic acids, Group IVB d elements form complexes whose stability increases from Br to F. For p elements, inverse dependence is observed, *i.e.*, the stability of halide complexes increases in the series  $F < Cl < Br$ .<sup>104, 105</sup> Actually, comparative studies of the ion-exchange behaviour of Hf and Pb in dilute solutions of hydrohalic acids demonstrated that Hf is strongly sorbed on cation-exchange resins from HCl and HBr solutions and is not sorbed from HF solutions. In contrast, Pb is more strongly sorbed on cation-exchange resins from HF solutions and is sorbed to a lesser extent from HCl and HBr solutions (see Fig. 10a). An inverse situation is observed for sorption on anion-exchange resins (see Fig. 10b). The results presented in Fig. 10 correlate well with the stability constants of halide complexes of hafnium and lead. As demonstrated above, Rf is not sorbed on cation-exchange resins from solutions containing HF at concentrations higher than  $0.1 \text{ mol litre}^{-1}$ , but it is strongly retained on anion-exchange resins (*i.e.*, its behaviour is analogous to that of Group IVB d elements). Evidently, investigations of the ion-exchange behaviour of Rf in dilute HBr solutions can reveal the extent to which this element exhibits the properties characteristic of p elements.

Studies of the behaviour of TAEs in different oxidation states in the presence of oxidising (or reducing) agents or by electrochemical oxidation (reduction) in the course of their isolation also hold promise for elucidating the relativistic effects. In this case, the distribution coefficients should be substantially different, due to which the experiments can be performed in the on-line mode.

The relatively long half-lives of some TAEs with  $Z \geq 106$  allow one to study the chemical properties of these elements in solution. However, the main problem is that SHEs are produced in very low yields in a unit of time (for example,  $1 \text{ atom h}^{-1}$  for Sg), and the yields sharply decrease with increasing  $Z$  ( $1 \text{ atom day}^{-1}$  for element 112). In this connection, methods based on the on-line isolation of TAEs during their synthesis hold the most promise. In the near future, one would expect that new longer-lived isotopes of SHEs in the vicinity of the 'islands of stability' will be discovered. Hence, the development of efficient procedures for the isolation and investigation of such isotopes on the basis of studies of the behaviour of their homologues is of primary importance.

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# Phenylaza- and benzoazacrown compounds with a nitrogen atom conjugated with a benzene ring

S P Gromov, S N Dmitrieva, M V Churakova

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**Abstract.** Data on the synthesis and properties of aza- and diazacrown compounds containing a phenyl group at a nitrogen atom or an *o*-phenylene fragment annelated to the macrocycle are generalised. The functional derivatives of these compounds and their heteroanalogues with O, S and N atoms are considered. The bibliography includes 217 references.

## I. Introduction

Crown compounds bind metal cations, organic cations and neutral molecules through multidentate coordination to heteroatoms incorporated in the macrocycle. Due to this feature, they are used successfully as selective ligands,<sup>1,2</sup> for extraction and separation of metal cations,<sup>3,4</sup> for ion transport through membranes, in ion selective electrodes,<sup>5</sup> as phase transfer catalysts and as synzymes that simulate enzymic activity,<sup>6</sup> in photosensitive systems,<sup>7–12</sup> etc.

Crown ethers in which one or two oxygen atoms have been replaced by nitrogen atoms are referred to as azacrown ethers or azacrown compounds; if the number of nitrogen atoms in the macrocycle is greater than two, the latter name is used most often. In addition to the IUPAC names, two special nomenclatures are used to designate azacrown compounds. According to one of them, developed by Pedersen in 1967,<sup>13</sup> the total number of macrocycle units (the size) is indicated ahead of the word 'crown' and the total number of heteroatoms is indicated after this word. In the case of nitrogen analogues, the positions of nitrogen atoms are numbered separately, precede the whole compound name and are accompanied by the prefix '(di-, tri-, etc.) aza' (for example, 1,10-diaza-18-crown-6 ether). The second nomenclature was proposed by Busch in 1972.<sup>14</sup> In this case, the macrocycle size is given

in square brackets, this is followed by an indication of the type of heteroatoms, with their number given as the subscript (e.g., [15]N<sub>4</sub>O or [14]N<sub>4</sub>; the last macrocycle is called cyclam).

The interest in azacrown derivatives persists, first of all, due to their extensive practical use. In particular, diazacrown compounds are important intermediates in the synthesis of cryptands. Azacrown compounds attract the attention of researchers in many fields due to their unusual complexing properties, intermediate between the properties of crown ethers, which firmly bind alkali and alkaline earth metal ions, and the properties of cyclams, which form stable complexes with heavy and transition metal ions.

Apart from the traditional applications of azacrown compounds, of special interest is the use of those fragments, in which the nitrogen atom is conjugated with the chromophore, as parts of photosensitive, chromogenic, fluorescent and photochromic ligands. These compounds can form the heart of optical sensors for metal and ammonium ions, optical information recording systems, photoswitched molecular devices and machines for molecular electronics, transporting agents for the photocontrolled membrane transport of metal cations, etc. For this reason, we summarise here the data on the synthesis of several classes of azacrown compounds in which the macrocycle nitrogen atom is conjugated with the benzene ring.

A number of reviews on the methods of synthesis of azacrown compounds have been published. Two of these consider crown ether analogues containing only nitrogen atoms as heteroatoms and cover a period from 1967 to 1987.<sup>15,16</sup> The most comprehensive data on the synthesis of azacrown compounds with different sets of heteroatoms were reported by Bradshaw *et al.* in a monograph<sup>17</sup> published in 1993. Among the latest studies, noteworthy is the review<sup>18</sup> devoted to the synthesis of fused aza- and thiaazacrown compounds. However, none of the published reviews consider specially the synthesis of azacrown compounds in which at least one nitrogen atom of the macrocycle is conjugated with a benzene ring; no systematic data are currently available on this topic.

This review is devoted to the synthesis and chemical properties of azacrown compounds based on macrocycles of various sizes (starting with the smallest, nine-membered one) containing three or more heteroatoms. A special feature of the molecules of these compounds is the presence of not more than two phenyl or annelated *o*-phenylene fragments linked to the macrocycle

S P Gromov, S N Dmitrieva, M V Churakova Photochemistry Centre of the Russian Academy of Sciences, ul. Novatorov 7a, 119421 Moscow, Russian Federation. Fax (7-095) 936 12 55, tel. (7-095) 936 3850, e-mail: gromov@photonics.ru (S P Gromov), dmitrieva@photonics.ru (S N Dmitrieva), churakova@photonics.ru (M V Churakova)

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through nitrogen; the other heteroatoms may be represented by O, S and N atoms. The azacrown compounds having heteroaromatic substituents, organoelement (P-, As- and Se-containing) and organometallic derivatives or polymers containing phenylaza or benzoazacrown compounds are beyond the scope of this review. Several examples are related to the synthesis and modification of benzoannulated cryptands. The review covers the publications from the late 1960s to 2003 and includes some studies published in 2004.

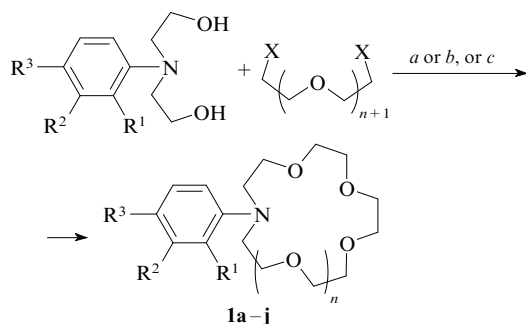
## II. *N*-Phenylazacrown compounds

There are three main approaches to the synthesis of phenylazacrown compounds differing by the type of reaction used, which include the condensation of two fragments, aromatic nucleophilic substitution and cross-coupling.

### 1. Methods based on the condensation of two fragments

The base-induced condensation of *N*-aryldiethanolamines or their derivatives with oligoethylene glycols or their aza or thia analogues is a widely used method for the synthesis of *N*-phenylazacrown compounds. Using this method, Vögtle and Dix performed the first synthesis<sup>19,20</sup> of *N*-phenylaza-15(18)-crown-5(6) ethers. With dichlorides as the electrophilic component, NaOH is used most often as the base, while in the case of ditoluenesulfonate this is NaH.<sup>19–21</sup>

Phenylazacrown ethers **1c–i** containing Me, MeO, Cl or NO<sub>2</sub> groups in the *ortho*- or *para*-position of the benzene ring were prepared by condensation of *N*-aryldiethanolamine with oligoethylene glycol dimethanesulfonates (or ditoluenesulfonates) in the presence of sodium hydride<sup>22–26</sup> or with dichlorides in the presence of sodium hydroxide,<sup>27–29</sup> while 3-nitrophenylaza-15-crown-5 ether **1j** was synthesised using sodium *tert*-butoxide as the base.<sup>30</sup> The use of derivatives with hard oxygen-containing leaving groups (ditoluenesulfonates, dimethanesulfonates) and strong bases (sodium hydride and *tert*-butoxide) allows one to synthesise *N*-arylazacrown ether derivatives **1** in higher yields than the use of dichlorides in the presence of alkali.

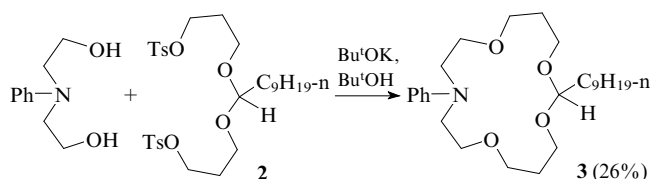


(a) NaOH, dioxane; (b) NaH, THF; (c) Bu<sup>t</sup>ONa, dioxane.

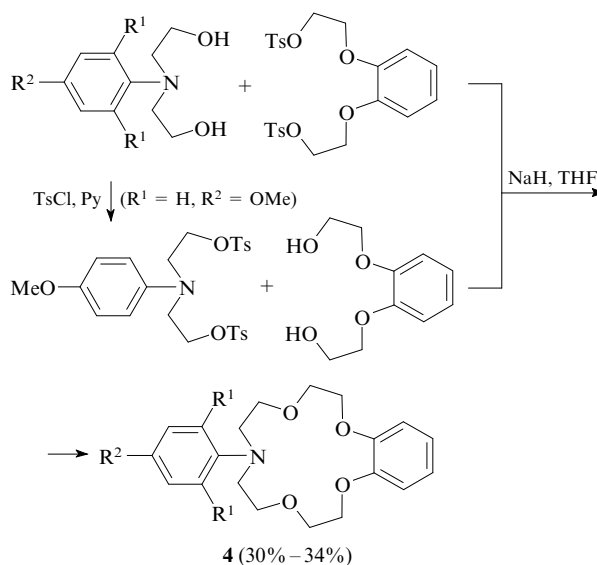
| Compound <b>1</b> | X   | R <sup>1</sup> | R <sup>2</sup>  | R <sup>3</sup>  | n | Yield (%) |
|-------------------|-----|----------------|-----------------|-----------------|---|-----------|
| <b>a</b>          | Cl  | H              | H               | H               | 1 | 16        |
|                   | OTs | H              | H               | H               | 1 | 50        |
| <b>b</b>          | Cl  | H              | H               | H               | 2 | 13        |
| <b>c</b>          | Cl  | OMe            | H               | H               | 1 | 16        |
|                   | OMs | OMe            | H               | H               | 1 | 38        |
|                   | OTs | OMe            | H               | H               | 1 | 35        |
| <b>d</b>          | OMs | H              | H               | OMe             | 1 | 30        |
| <b>e</b>          | OMs | OMe            | H               | H               | 2 | 41        |
| <b>f</b>          | OMs | H              | H               | Me              | 1 | —         |
| <b>g</b>          | OMs | H              | H               | Cl              | 1 | —         |
| <b>h</b>          | OTs | H              | H               | NO <sub>2</sub> | 0 | 55        |
| <b>i</b>          | OTs | H              | H               | NO <sub>2</sub> | 1 | 70        |
| <b>j</b>          | OTs | H              | NO <sub>2</sub> | H               | 1 | 38        |

Ms is MeSO<sub>2</sub>, Ts is 4-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>.

The same method was utilised to obtain azacrown ether **3** with a long alkyl chain from *N*-phenyldiethanolamine and ditoluenesulfonate **2** under the action of potassium *tert*-butoxide.<sup>31</sup>

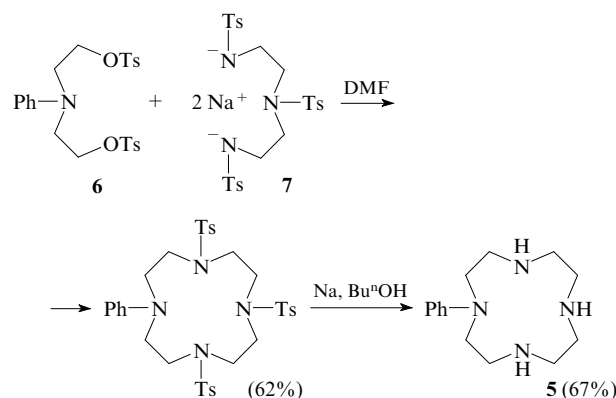


Using a similar procedure, a series of benzophenylazacrown ethers **4** have been prepared (with NaH as the base).<sup>32</sup> Interestingly, the methoxy derivative **4** (R<sup>1</sup> = H, R<sup>2</sup> = OMe) was also prepared using an alternative method of synthesis, namely, from *N*-aryldiethanolamine ditoluenesulfonate and the corresponding diol. The yields of products **4** were moderate in all cases.



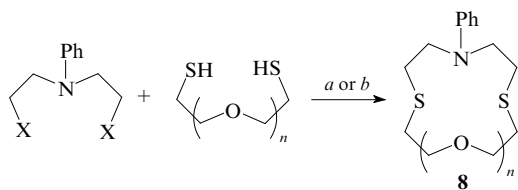
R<sup>1</sup> = H, Me; R<sup>2</sup> = H, OMe, Me, Bu<sup>t</sup>.

*N*-Phenyltetraazacrown compound **5** was obtained by the reaction of ditoluenesulfonate **6** with the disodium salt of tritosylamide **7**. The tosyl groups were removed by refluxing with sodium metal in *n*-butanol.<sup>33</sup>



The condensation of *N*-phenyldiethanolamide dichlorides, ditoluenesulfonates or dimethanesulfonates with dithiols under the action of sodium hydroxide or potassium carbonate gave *N*-phenyldithiaazacrown compounds **8** (for the derivative with X = OMs, *n* = 1, the yield was 40%).<sup>34–37</sup>

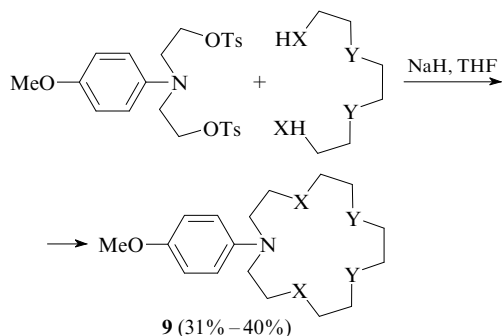




$n = 1, 2$ ;  $X = \text{Cl, OTs, OMs}$ ;

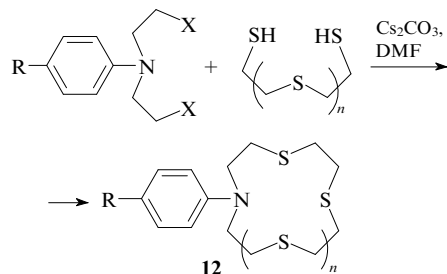
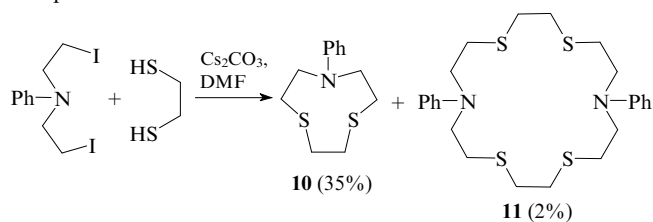
(a)  $\text{NaOH}$ , dioxane– $\text{Bu}^t\text{OH}$ ; (b)  $\text{K}_2\text{CO}_3$ ,  $\text{MeCN}$ .

Compounds **9**, containing oxygen and sulfur atoms in various combinations in the macrocycle, have been prepared.<sup>32</sup> The starting compounds used for this purpose were *N*-(4-methoxyphenyl)diethanolamine ditoluenesulfonate and diols or dithiols.



$X, Y = \text{O, S}$ .

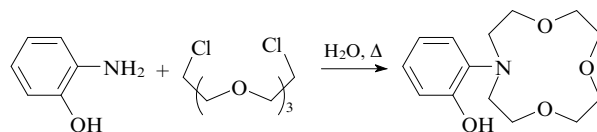
*N*-Phenylpolythiaazacrown compounds with two, three or four sulfur atoms in the macrocycle have been obtained by the reactions of dithiols with  $\alpha,\omega$ -dihalides in the presence of caesium carbonate in DMF.<sup>38–40</sup> In the synthesis of dithiaaza-9-crown-3 compound **10**, the product of [2 + 2]-condensation of both reactants, compound **11**, was also isolated, although the reaction was carried out under high dilution conditions in order to avoid the condensation.<sup>38</sup> Higher yields of trithiaaza-12-crown-4 and tetra-thiaaza-15-crown-5 compounds **12** compared to those of macrocycle **10** were attributed to the greater steric strain in the latter compound.



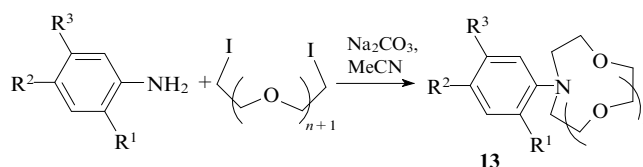
| R  | X  | n | Yield (%) |
|----|----|---|-----------|
| H  | I  | 1 | 52        |
| H  | I  | 2 | 61        |
| Br | Cl | 1 | 53        |

Yet another version of the condensation of two fragments is the cyclodialkylation of anilines.<sup>22, 24, 41–53</sup> This approach is usually employed to prepare *N*-phenylazacrown ethers with small rings. An early study<sup>41</sup> describes the synthesis (without indication of the yields) of *N*-(2-hydroxyphenyl)aza-12-crown-4

ether by the reaction of *o*-aminophenol with the dichloride prepared from tetraethylene glycol on refluxing in water.

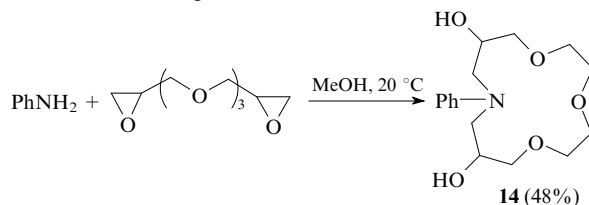


The reaction of aniline and its derivatives with the diiodides prepared from tri-, tetra- or pentaethylene glycols in the presence of sodium carbonate in acetonitrile resulted in the synthesis of arylazacrown ethers **13**.<sup>22, 24, 42–50</sup>

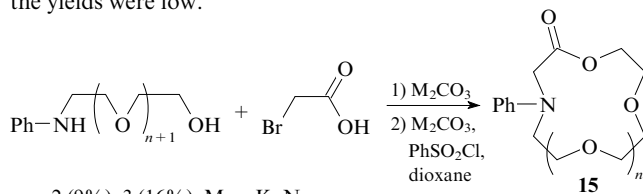


| R <sup>1</sup> | R <sup>2</sup> | R <sup>3</sup> | n   | Yield (%) |
|----------------|----------------|----------------|-----|-----------|
| H              | OMe            | H              | 1   | 13        |
| H              | H              | H              | 2   | 51        |
| OMe            | H              | H              | 2   | 26        |
| H              | H              | OMe            | 2   | 40        |
| H              | CN             | H              | 2   | 45        |
| H              | H              | OBn            | 2   | —         |
| OMe            | H              | OMe            | 2   | —         |
| H              | NHAc           | H              | 2–3 | 26–42     |
| H              | NHAc           | NHAc           | 2   | 42        |

*N*-Phenylaza-14-crown-4 ether **14**, which contains two hydroxyl groups in the macroheterocycle, is formed upon the reaction of aniline with diethylene glycol diglycidyl ether in methanol at room temperature.<sup>51, 52</sup>



The synthesis of *N*-phenyl-3-oxoaza-15(18)-crown-5(6) ethers **15** by the two-step condensation of *N*-(polyoxyethylene)anilines with bromoacetic acid has been described;<sup>53</sup> first, the reaction is induced by sodium or potassium carbonate and then by the carbonate and benzenesulfonyl chloride in dioxane. However, the yields were low.



$n = 2$  (9%), 3 (16%);  $M = \text{K, Na}$ .

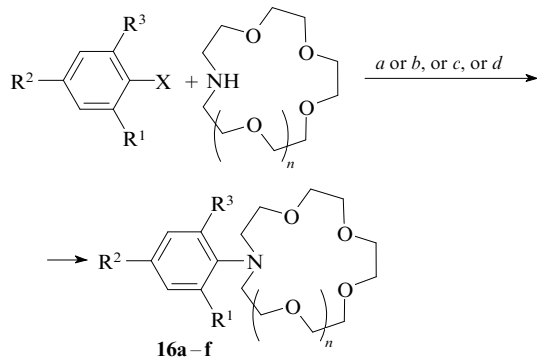
Unsubstituted *N*-phenylazacrown compounds have been used to prepare various chromo- and fluoroionophores,<sup>54–57</sup> in particular, azo dyes<sup>20, 25, 26, 37</sup> and squaric acid derivatives).<sup>58</sup>

## 2. The introduction of a macrocyclic fragment by aromatic nucleophilic substitution

Many derivatives of *N*-phenylazacrown compounds have been obtained by arylation of the nitrogen atom in the macrocycle. Halobenzenes containing electron-withdrawing substituents are employed most often for this purpose.

Arylazacrown ethers **16a–e** have been prepared by the reaction of aza-15-crown-5 ether with various fluoro- and

chloro-substituted benzenes (Table 1). The process conditions (heating of a reactant mixture in a polar solvent or in a neutral solvent under the action of a base) depend on the nature of the arylating reagent. Dinitrophenyl derivatives **16f** (see Table 1) with various macrocycle sizes are formed in high yields in the reaction of 2,4-dinitrochlorobenzene with *N*-unsubstituted azacrown ethers in the presence of tetrabutylammonium acetate in diethyl ether.<sup>62, 63</sup>

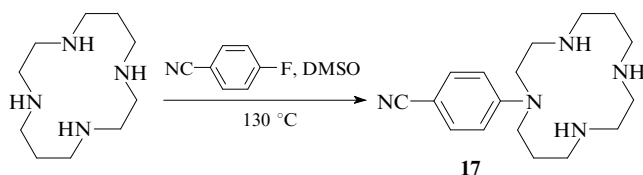


(a) DMSO; (b) Et<sub>3</sub>N, PhH; (c) Py; (d) AcONBu<sub>4</sub>, Et<sub>2</sub>O.

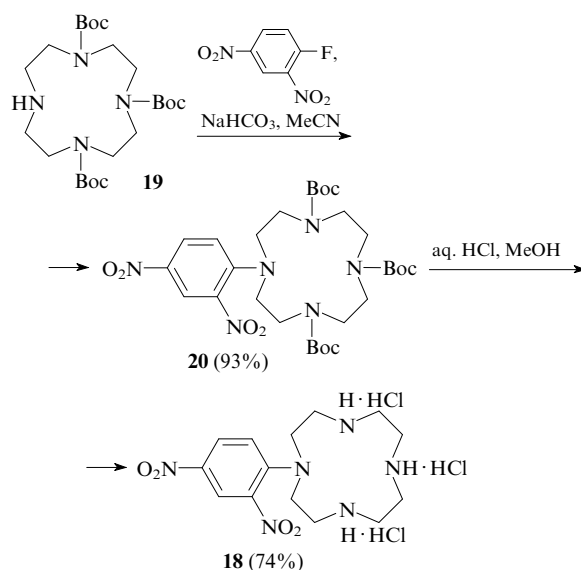
**Table 1.** Preparation of *N*-arylazacrown ethers by arylation.

| Com-<br>pound <b>16</b> | X  | R <sup>1</sup>    | R <sup>2</sup>     | R <sup>3</sup>  | <i>n</i> | Reaction<br>conditions | Yield<br>(%) | Ref.   |
|-------------------------|----|-------------------|--------------------|-----------------|----------|------------------------|--------------|--------|
| <b>a</b>                | F  | H                 | CN                 | H               | 1        | <i>a</i>               | 70           | 46     |
| <b>b</b>                | F  | H                 | NO <sub>2</sub>    | H               | 1        | <i>a</i>               | —            | 59     |
| <b>c</b>                | Cl | Bz                | NO <sub>2</sub>    | NO <sub>2</sub> | 1        | <i>b</i>               | 84           | 60     |
| <b>d</b>                | Cl | NO <sub>2</sub>   | CO <sub>2</sub> Me | NO <sub>2</sub> | 1        | <i>b</i>               | 77           | 60     |
| <b>e</b>                | Cl | CO <sub>2</sub> H | NO <sub>2</sub>    | H               | 1        | <i>c</i>               | 26           | 61     |
| <b>f</b>                | Cl | NO <sub>2</sub>   | NO <sub>2</sub>    | H               | 0–2      | <i>d</i>               | ~95          | 62, 63 |

The synthesis of (4-cyanophenyl)cyclam **17** from cyclam and 4-fluorobenzonitrile has been reported;<sup>64</sup> however, the product yield is not indicated in the publication.



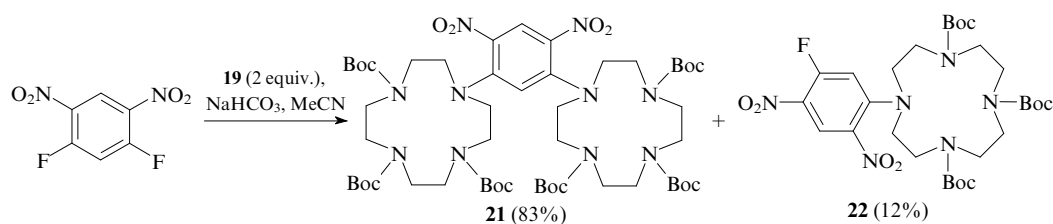
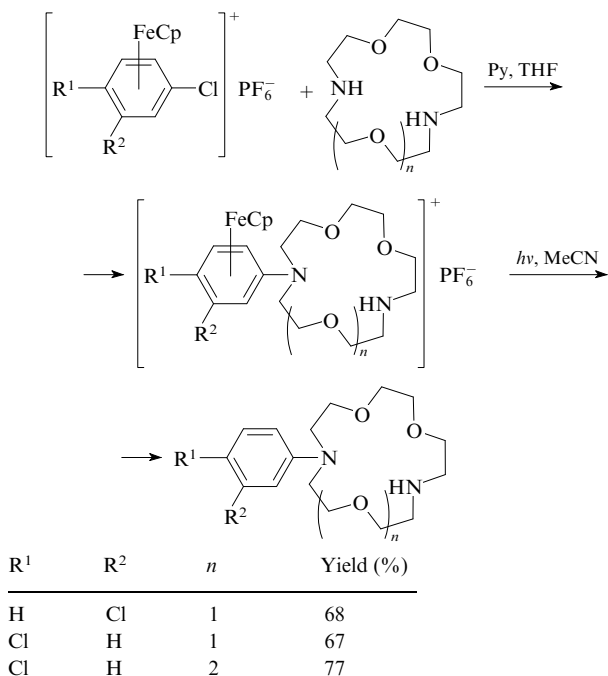
2',4'-Dinitrophenylcyclen **18** was prepared in two stages and characterised as the trihydrochloride. The reaction of 1-fluoro-2,4-dinitrobenzene with cyclen **19** was carried out in the presence of sodium hydrogen carbonate and was followed by treatment of compound **20** with hydrochloric acid in methanol.<sup>65</sup>



Boc is *tert*-butoxycarbonyl.

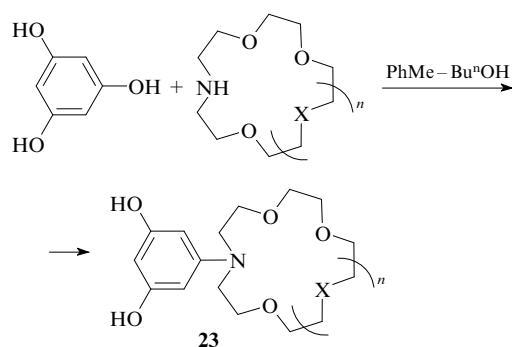
Bis(azacrown) compounds can be synthesised from dihalobenzenes. For example, the reaction of 1,5-difluoro-2,4-dinitrobenzene with two equivalents of cyclen **19** yields mainly bis(cyclen) **21**. A small amount of cyclen **22** was also isolated (Scheme 1).<sup>66</sup>

The *meta*- and *para*-chloro derivatives of phenyldiazacrown ethers were synthesised by the reaction of the dichlorobenzene complex with cyclopentadienyliron hexafluorophosphate and diazacrown ether. The subsequent demetallation of the compounds formed was attained by irradiation with a halogen quartz lamp (100 W).<sup>67</sup>



Scheme 1

The refluxing of a mixture of aza-15(18)-crown-5(6) ethers (or diaza-15-crown-5 ether) with phloroglucinol with azeotropic removal of water gave rise to *N*-(3,5-dihydroxyphenyl)azacrown ethers **23**.<sup>68–70</sup>



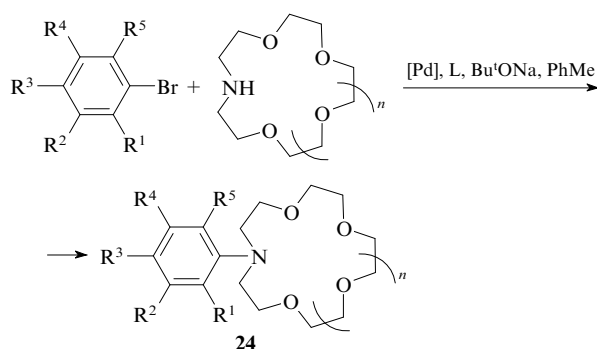
X = O:  $n = 1$  (16%), 2; X = NCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>OMe-2,  $n = 1$ .

Compounds **23** condense with squaric acid to give squarelium dyes.<sup>68, 70</sup>

### 3. Cross-coupling reactions

In recent years, a new approach to the preparation of the compounds in question, based on palladium-catalysed *N*-arylation of azacrown ethers, has been developed.<sup>66, 71–73</sup> The reaction is normally carried out in toluene in the presence of sodium *tert*-butoxide. The advantage of this method is the possibility of using non-activated or sterically hindered aryl halides.

The cross-coupling of azacrown ethers catalysed by systems including a palladium complex ([Pd]) and a phosphine ligand (L) was first carried out for 4-nitro- and 4-cyanobromobenzenes. Aza-18(15,12)-crown-6(5,4) ethers were used to give arylazacrown compounds **24** (Table 2, method A).<sup>71</sup> The highest product yields (57%–88%) were observed when a mixture of Pd(OAc)<sub>2</sub> and PPh<sub>3</sub> was used as the catalyst.

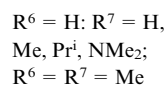


A large series of *N*-phenylaza-15-crown-5 ethers **24** with various substituents in the benzene ring have been synthesised from aza-15-crown-5 ether and aryl bromides *via* the palladium-catalysed Buchwald–Hartwig amination (see Table 2, method B).<sup>72</sup> It was demonstrated that a combination of Pd<sub>2</sub>(dba)<sub>3</sub> and electron-excessive sterically hindered biphenyl-based phosphine is an efficient system for the catalysed coupling of aza-15-crown-5 ether with both electron-deficient and electron-excessive aryl bromides. The reaction occurs under mild conditions, the product yields being 75%–91%. Compounds **24** containing a substituent in the *ortho*-position were also prepared using this catalyst system, although the yields were lower (~40%).

The cross-coupling of cyclen **19** with mono- and dihalobenzenes resulted in the isolation of *N*-aryl-substituted (**25**) and phenylene-bridged cyclens **26** in moderate yields.<sup>66</sup> In the former case, toluene, THF, bromobenzene and a toluene–18-crown-6 mixture were used as solvents.

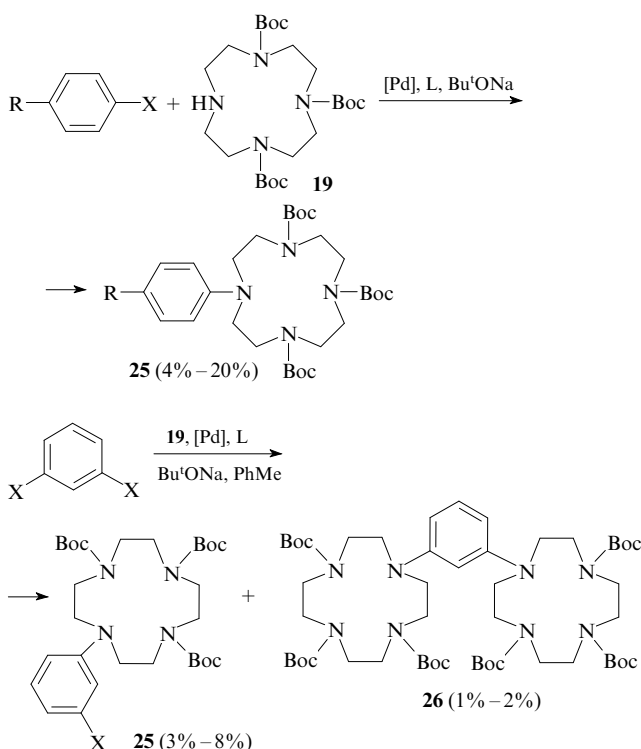
**Table 2.** Preparation of *N*-arylazacrown ethers by cross-coupling.

| Method | [Pd]                                           | L                                                                                    | R <sup>1</sup> –R <sup>5</sup>                                                                                                                                                                              | <i>n</i> |
|--------|------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| A      | Pd(dba) <sub>2</sub> ,<br>Pd(OAc) <sub>2</sub> | P(Tol- <i>o</i> ) <sub>3</sub> , PBu <sub>3</sub> <sup>t</sup> ,<br>PPh <sub>3</sub> | R <sup>1</sup> = R <sup>2</sup> = R <sup>3</sup> = R <sup>5</sup> = H, R <sup>4</sup> = NO <sub>2</sub>                                                                                                     | 0–2      |
|        |                                                |                                                                                      | R <sup>1</sup> = R <sup>2</sup> = R <sup>3</sup> = R <sup>5</sup> = H, R <sup>4</sup> = CN                                                                                                                  | 2        |
|        |                                                |                                                                                      |                                                                                                                                                                                                             |          |
| B      | Pd <sub>2</sub> (dba) <sub>3</sub>             |                                                                                      | R <sup>1</sup> = H, Me, Et, OMe, CF <sub>3</sub> , Cl; R <sup>2</sup> = H, Me, OMe; R <sup>3</sup> = H, Bu <sup>t</sup> , OMe, CF <sub>3</sub> , NMe <sub>2</sub> ; R <sup>4</sup> = R <sup>5</sup> = H, Me | 1        |
|        |                                                |                                                                                      |                                                                                                                                                                                                             |          |
|        |                                                |                                                                                      |                                                                                                                                                                                                             |          |



R<sup>6</sup> = H; R<sup>7</sup> = H, Me, Pr<sup>i</sup>, NMe<sub>2</sub>; R<sup>6</sup> = R<sup>7</sup> = Me

(Tol-*o*) is *o*-tolyl, dba is dibenzylideneacetone, Cy is cyclohexyl.



X = I, Br; R = H, NO<sub>2</sub>, CH(OCH<sub>2</sub>CH<sub>2</sub>O), CHO; [Pd] = Pd<sub>2</sub>(dba)<sub>3</sub>, Pd(OAc)<sub>2</sub>; L = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 1,1'-bis(diphenylphosphino)ferrocene (DPPF), PPh<sub>3</sub>, 2-(di-*tert*-butylphosphino)biphenyl.

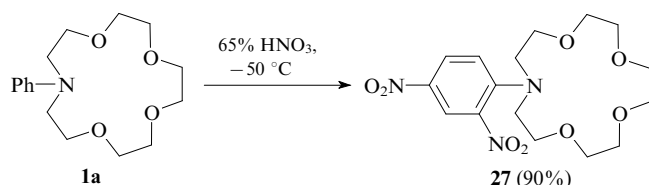
(4-Cyanophenyl)cyclam **17** (see Section II.2) is also formed upon arylation of cyclam with 4-bromobenzonitrile in the presence of the Pd(dba)<sub>2</sub>–1-(*R*)-(1-methoxyethyl)-2-(*S*)-diphenylphosphinoferrocene (PPF-OMe) catalyst system and sodium *tert*-butoxide (yield 22%).<sup>73</sup>

### III. Functional derivatives of *N*-phenylazacrown compounds

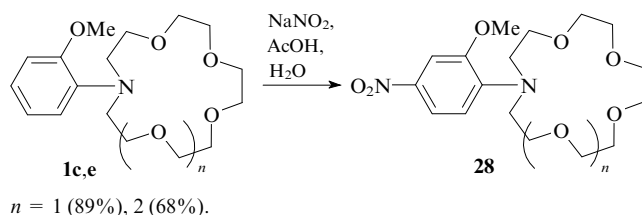
Many functional derivatives of *N*-phenylazacrown compounds are formed during the construction of the macrocycle (see Section II). An alternative way is to introduce functional groups into the benzene ring of pre-formed *N*-phenylazacrown compounds *via* electrophilic substitution or to modify the existing substituents. Reactions of this type are presented below.

#### 1. Nitro, nitroso and amino derivatives of *N*-phenylazacrown compounds

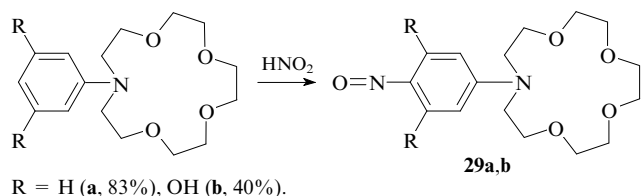
Direct nitration of *N*-phenylaza-15-crown-5 ether **1a** with nitric acid at low temperature resulted in the 2,4-dinitrophenyl derivative **27**.<sup>63</sup>



When *N*-(*o*-methoxyphenyl)aza-15(18)-crown-5(6) ethers **1c,e** were made to react with sodium nitrite in aqueous AcOH, nitration products **28** were isolated in high yields instead of the expected nitroso compounds.<sup>74</sup> The direction of substitution is determined by the aniline nitrogen atom — the nitro group enters the *para*-position with respect to this atom. The researchers suggested that nitration gives a radical cation as an intermediate. It is of interest that the use of traditional nitrating agents (HNO<sub>3</sub>, HNO<sub>3</sub>–H<sub>2</sub>SO<sub>4</sub> or NO<sub>2</sub>BF<sub>4</sub>) results in very low yields of nitration products in this reaction.

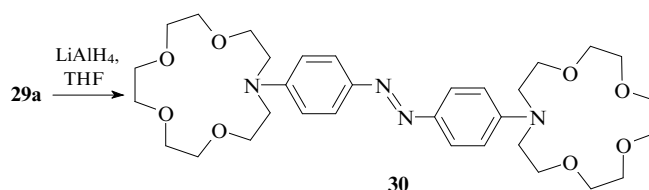


4'-Nitroso-*N*-phenylaza-15-crown 5-ethers **29** were prepared by nitrosation of *N*-phenylaza-15-crown-5 ethers with sodium nitrite in hydrochloric acid.<sup>20, 69</sup>

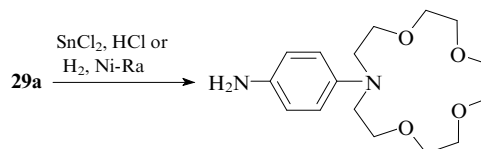


*N*-(4'-Nitrosophenyl)azacrown ethers condense with malononitrile and dicyanovinyl derivatives to give chromoionophoric compounds.<sup>69, 75</sup>

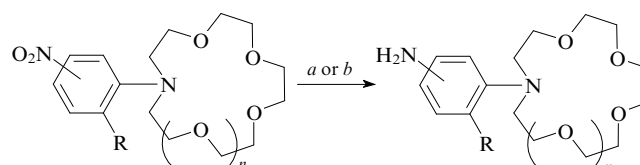
The reduction of nitroso derivative **29a** with lithium trihydridoaluminate gives azo compound **30** and its *N*-oxide (in a 1 : 3 ratio) in a total yield of 65%.<sup>20</sup>



A major route of modification of the nitroso group in *N*-phenylazacrown ethers is reduction to the amino group. The nitroso group in **29a** was reduced with tin(II) chloride in HCl with heating (yield 87%)<sup>20</sup> or with hydrogen in the presence of Raney nickel (Ni-Ra) at room temperature and atmospheric pressure (the yield was not reported).<sup>76</sup>



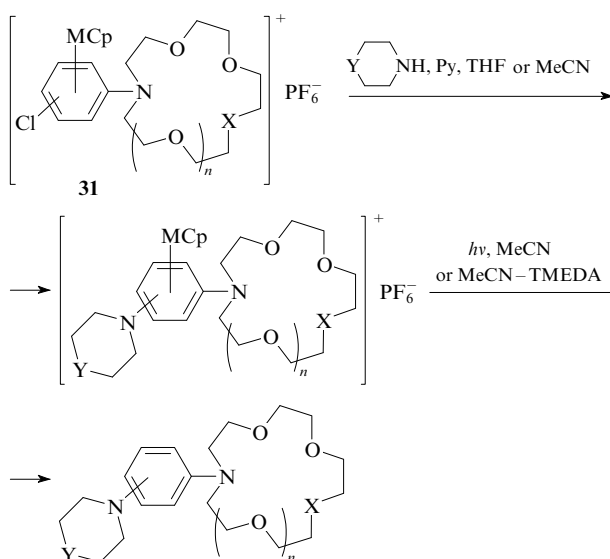
Amino derivatives of *N*-phenylazacrown ethers can also be prepared by palladium-catalysed reduction of nitro compounds with hydrogen<sup>30, 61, 74</sup> or by reduction with tin(II) chloride.<sup>24</sup>



(a) H<sub>2</sub>, Pd/C, EtOH; (b) SnCl<sub>2</sub> · 2 H<sub>2</sub>O, HCl, EtOAc.

| Position of NO <sub>2</sub> | R                 | <i>n</i> | Reaction conditions | Yield (%) | Ref. |
|-----------------------------|-------------------|----------|---------------------|-----------|------|
| 4                           | H                 | 0        | <i>b</i>            | 89        | 24   |
| 4                           | H                 | 1        | <i>b</i>            | 85        | 24   |
| 4                           | CO <sub>2</sub> H | 1        | <i>a</i>            | 94        | 61   |
| 4                           | OMe               | 1        | <i>a</i>            | 98        | 74   |
| 4                           | OMe               | 2        | <i>a</i>            | 68        | 74   |
| 3                           | H                 | 1        | <i>a</i>            | 85        | 30   |

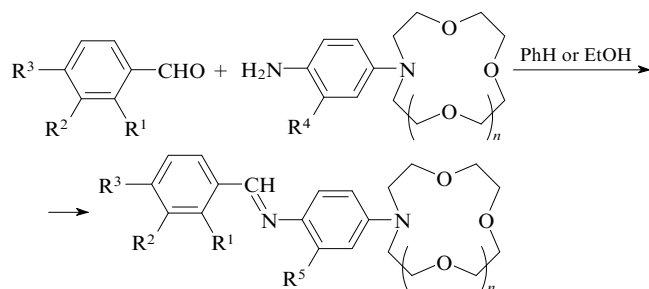
A number of *para*- or *ortho*-substituted *N*-(aminophenyl)aza- and -diazacrown ethers were synthesised by nucleophilic aromatic substitution of chlorine in complexes **31**, followed by demetallation on exposure to UV light.<sup>67, 77</sup> The total yields of amino derivatives in relation to the starting dichlorobenzene complex with [CpM]<sup>+</sup>PF<sub>6</sub><sup>−</sup> were 26%–37% (for M = Ru) and 50%–96% (for M = Fe).



M = Ru: *n* = 1, 2; X = O; Y = CH<sub>2</sub>; M = Fe: *n* = 1, 2; X = O, NH, NAc, NBz, NBn; Y = CH<sub>2</sub>, CHOH, NH.

The obtained 4-amino- and 3,4-diamino derivatives of *N*-phenylazacrown ethers were used in condensations with various

substituted benzaldehydes, giving rise to chromoionophoric Schiff's bases.<sup>21, 50</sup>

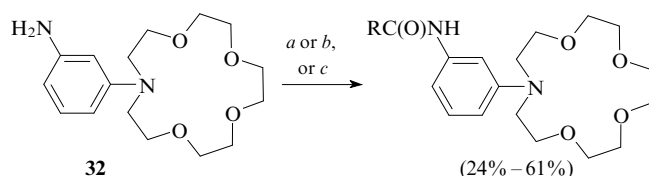


$n = 1$ :  $R^1 = \text{OH}$ ,  $R^2 = R^3 = R^4 = R^5 = \text{H}$  (84%);  $R^1 = \text{OH}$ ,

$R^2 = R^3 = \text{H}$ ,  $R^4 = \text{H}_2\text{N}$ ,  $R^5 = \text{N}=\text{CH}-\text{C}_6\text{H}_4-\text{OH}$  (80%);

$n = 2$ :  $R^1 = \text{H}$ ,  $\text{OH}$ ;  $R^2 = \text{H}$ ,  $\text{OMe}$ ;  $R^3 = \text{H}$ ,  $\text{OMe}$ ,  $\text{NO}_2$ ,  $\text{NMe}_2$ ;  $R^4 = R^5 = \text{H}$  (20%–84%).

Acylation of *m*-amino-*N*-phenylaza-15-crown-5 ether **32** with acyl chlorides or acid anhydrides provided the synthesis of a series of amphiphilic azacrown ethers able to form bilayer membranes.<sup>30, 78</sup>



$R = \text{Me}$ ,  $\text{Et}$ ,  $\text{Pr}^n$ ,  $\text{Pr}^i$ ,  $n\text{-C}_n\text{H}_{2n+1}$  ( $n = 5, 11, 13, 15, 17$ );

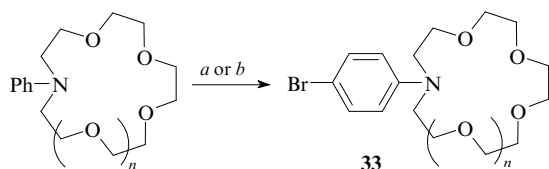
(a)  $\text{RCOCl}$ ,  $\text{KOH}$ ,  $\text{PhH}$ ; (b)  $\text{Ac}_2\text{O}$ ; (c)  $(\text{EtCO})_2\text{O}$ .

*N*-(4'-Aminophenyl)azacrown ethers can add to naphthoquinones<sup>54</sup> and dicyanovinyl-containing heterocycles<sup>79</sup> to afford chromoionophoric compounds.

## 2. Halogen derivatives of *N*-phenylazacrown compounds

Examples of the synthesis of bromo derivatives of *N*-phenylazacrown compounds *via* electrophilic substitution are documented. Different brominating agents were used and the product yields were often high.

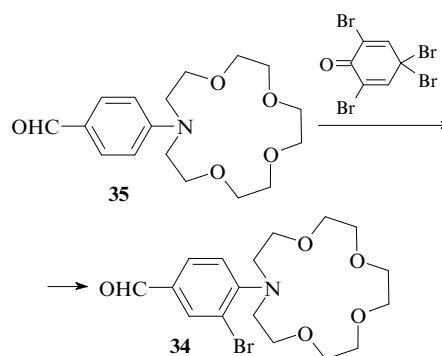
For example, bromination of *N*-phenylaza-15(18)-crown-5(6) ethers with tetrabutylammonium tribromide in dichloromethane<sup>80</sup> or with *N*-bromosuccinimide (NBS) in tetrachloromethane<sup>81</sup> furnishes the corresponding 4-bromophenyl derivatives **33**.



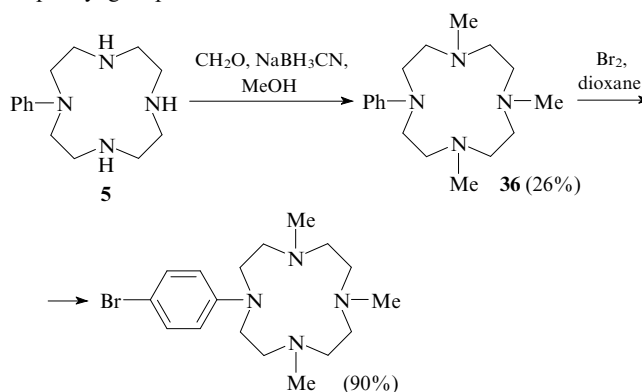
(a)  $\text{Bu}_4\text{NBr}_3$ ,  $\text{CH}_2\text{Cl}_2$ ; (b)  $\text{NBS}$ ,  $\text{CCl}_4$ .

| $n$ | Reaction conditions | Yield (%) |
|-----|---------------------|-----------|
| 1   | <i>b</i>            | —         |
| 1   | <i>a</i>            | 82        |
| 2   | <i>a</i>            | 76        |

The *o*-bromo derivative of *N*-(formylphenyl)aza-15-crown-5 ether **34** was prepared from aldehyde **35** using tetrabromocyclohexadienone as the brominating agent.<sup>82</sup>

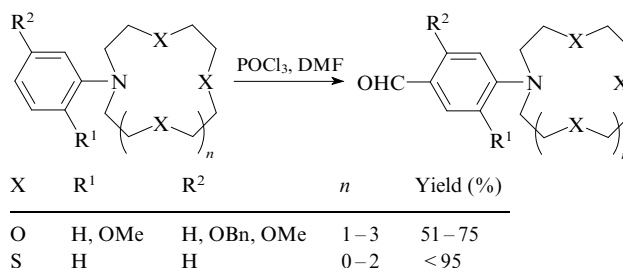


Cyclen **36**, prepared by reductive methylation of compound **5**, reacts with bromine in dioxane to give the product in a high yield.<sup>33</sup> In this case, bromination occurs at the *para*-position of the *N*-phenyl group.

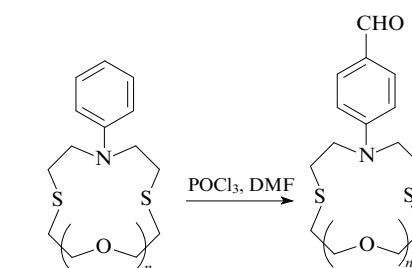


## 3. Formyl derivatives of *N*-phenylazacrown compounds

Numerous publications have been devoted to the introduction of a formyl group into *N*-phenylazacrown compounds. The formylation of *N*-phenylazacrown ethers<sup>19, 20, 27–29, 49</sup> and *N*-phenylpolythiaazacrown compounds<sup>83, 84</sup> has been accomplished by the Vilsmeier reaction.



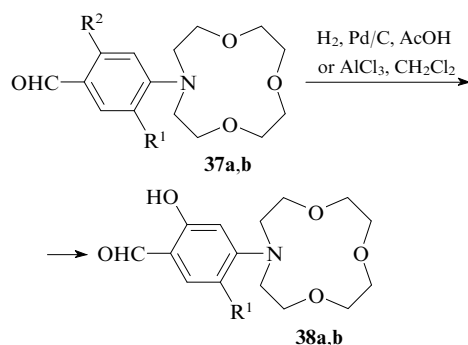
The formyl derivatives of mixed oxathiaazacrown compounds have been synthesised in a similar way.<sup>34</sup>



$n = 1, 2$ .

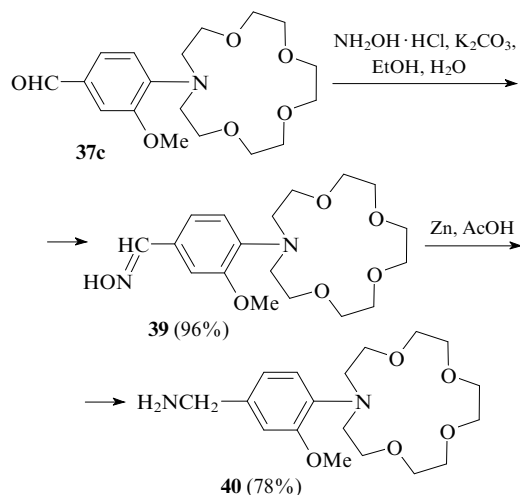
Hydrogenolysis of benzyl ether **37a** at room temperature and a pressure of 1 atm resulted in salicylaldehyde derivative **38a**.

Treatment of dimethoxy derivative **37b** with aluminium chloride in dichloromethane induces the selective demethylation of the methoxy group located in the *ortho*-position relative to the formyl group to give compound **38b**.<sup>49</sup> Hydroxyaldehydes **38** were used to prepare fluorophores, in particular, azacrown-containing coumarins.<sup>49</sup>

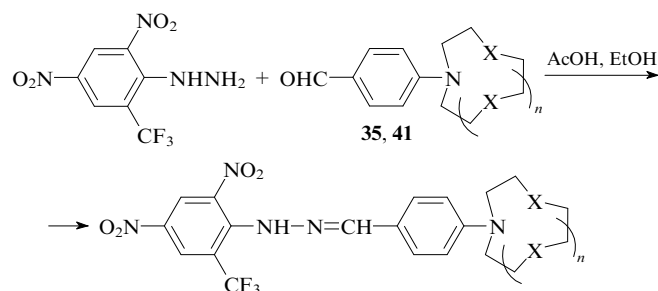


$R^1 = \text{H}, R^2 = \text{OBn}$  (a);  $R^1 = R^2 = \text{OMe}$  (b).

The introduction of the reactive formyl group in the molecule opens the way for the preparation of other derivatives of azacrown compounds. Indeed, the reaction of aldehyde **37c** with hydroxylamine in aqueous ethanol affords oxime **39**, which is reduced by zinc in acetic acid to yield aminomethylated *N*-phenylaza-15-crown-5 ether **40**.<sup>28, 29</sup>

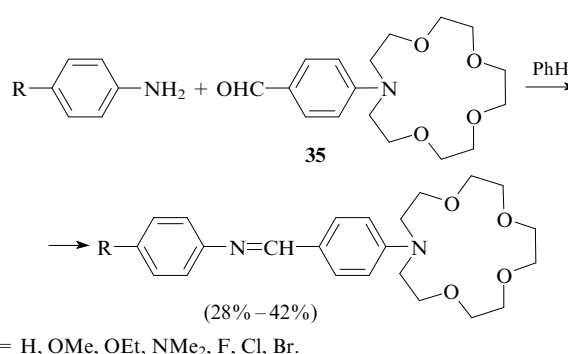


By the reaction of 2,4-dinitro-6-trifluoromethylphenylhydrazine with the formyl derivatives **35** ( $X = \text{O}, n = 3$ ) and **41** ( $X = \text{S}, n = 1, 3$ ), the corresponding hydrazones have been obtained.<sup>83, 85</sup> These were used for the extraction of heavy and transition metal ions<sup>83, 85, 86</sup> and for  $\text{Ag}^+$  transport through liquid membranes.<sup>87</sup>



$X = \text{O}; n = 3$  (49%);  $X = \text{S}; n = 1$  (39%), 3 (52%).

The condensation of aldehyde **35** with *para*-substituted anilines provided the route to chromoionophoric Schiff's bases.<sup>21</sup>

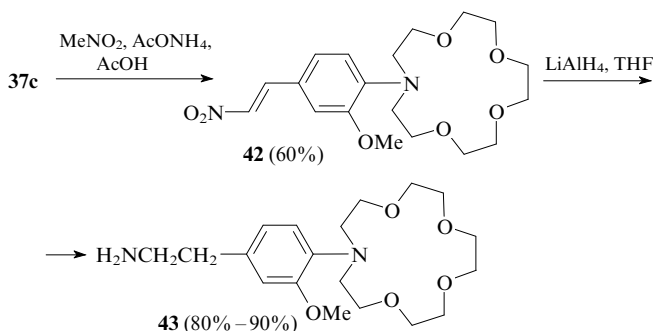


$R = \text{H}, \text{OMe}, \text{OEt}, \text{NMe}_2, \text{F}, \text{Cl}, \text{Br}$ .

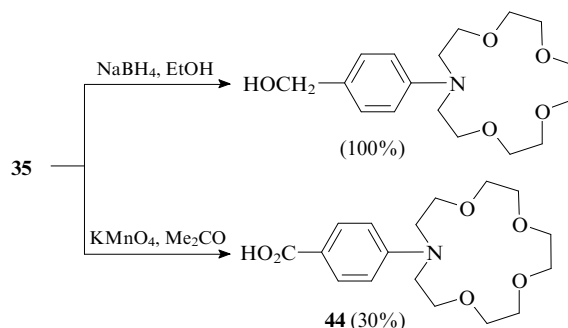
The aldehyde functional group in azacrown compounds can also be modified *via* reactions with C-nucleophiles. 4'-Formyl-*N*-phenylaza-15-crown-5 ether **35** reacts with acetone in an alkaline medium to give bis(crown ether) dibenzylideneacetone, which exhibits fluoroionophoric properties.<sup>88</sup>

Compounds containing an active methylene group can undergo Knoevenagel condensation with the formyl derivatives of *N*-phenylazacrown ethers. Under these conditions, 4'-formyl-*N*-phenylaza-18(15)-crown-6(5) ethers react with malononitrile to yield crown-containing benzylidenemalononitriles.<sup>75</sup>

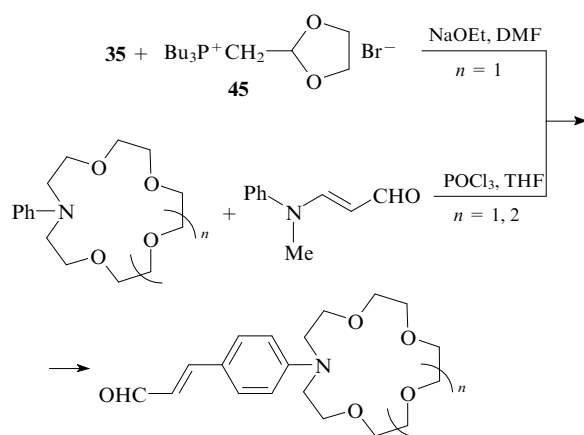
The nitroethylene derivative **42** has been prepared by the reaction of aldehyde **37c** with nitromethane in an acetic acid–ammonium acetate mixture. The reduction of this product gives azacrown ether **43**,<sup>28, 29</sup> which has found application as an intermediate *en route* to fluorescent indicators of sodium ions.



The reduction<sup>76</sup> of the formyl group in *N*-phenylaza-15-crown-5 ether **35** on treatment with sodium borohydride affords the corresponding alcohol, while the oxidation of this group<sup>89</sup> with sodium permanganate in acetone affords crown-containing benzoic acid **44**.



Cinnamaldehydes based on *N*-phenylazacrown ethers were prepared by two routes. One employs the Wittig reaction of aldehyde **35** with phosphonium salt **45**.<sup>82</sup> In the alternative procedure,<sup>90</sup> the modified Vilsmeier reaction of *N*-phenylazacrown ethers with *N*-methyl-*N*-phenyl-3-aminoacrolein is used; the products are formed under mild conditions in 35% ( $n = 1$ ) and 37% ( $n = 2$ ) yields.

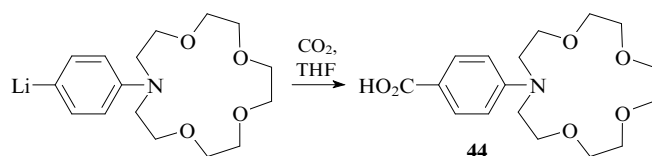


The formyl derivatives of *N*-phenylazacrown ethers are widely used in the synthesis of crown-containing stilbenes,<sup>20, 82, 91</sup> diphenylbutadienes,<sup>82</sup> hetarylphenylethylenes<sup>92–95</sup> and styryl,<sup>20, 92, 93, 96–101</sup> merocyanine<sup>20, 93, 102–104</sup> and butadienyl dyes.<sup>90</sup> These compounds have chromo- and fluoroionophore properties and are distinguished by high sensitivity and selectivity with respect to alkali and alkaline earth metal cations.<sup>20, 82, 90–117</sup>

#### 4. Azacrown-containing benzoic acids

The preparation and chemical properties of azacrown compounds containing an *N*-(4-carboxy)phenyl group are considered only in two papers.<sup>81, 89</sup>

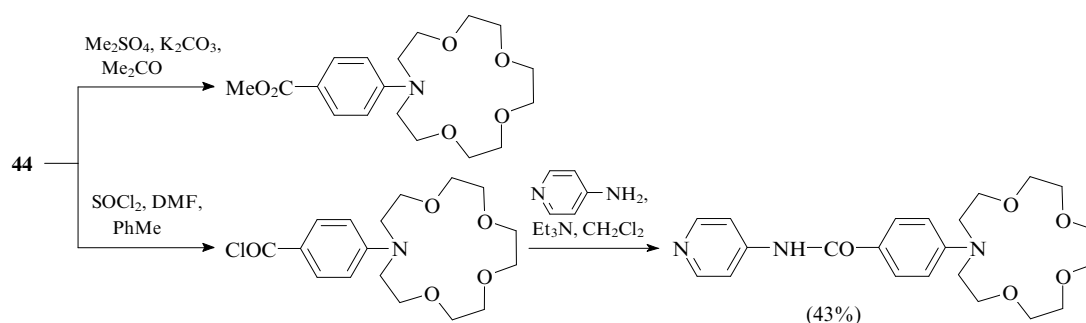
The synthesis of azacrown-containing benzoic acid **44** from the formyl derivative<sup>89</sup> has been described above (see Section III.3). The same compound is produced when carbon dioxide is passed into a tetrahydrofuran solution of the lithium derivative of *N*-(*p*-bromophenyl)aza-15-crown-5 ether.<sup>81</sup>



Acid **44** has been converted to give diverse derivatives, namely, the methyl ester (by the reaction with dimethyl sulfate in the presence of potassium carbonate in acetone),<sup>81</sup> the chloride (on treatment with SOCl<sub>2</sub> in a DMF–toluene mixture) and the amide (by the reaction of the chloride with 4-aminopyridine) (Scheme 2).<sup>89</sup>

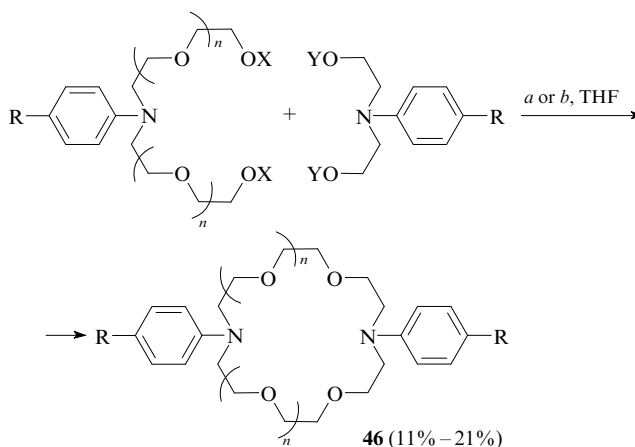
#### IV. *N,N'*-Diphenyldiazacrown compounds

Generally, the routes to *N,N'*-diphenyldiazacrown compounds differ little from the above methods used to prepare their analogues with one nitrogen atom in the macrocycle. Diphenyldiaza derivatives are obtained most often by condensation of two fragments and by *N*-arylation of diazacrown ethers.



#### 1. Routes based on the condensation of two fragments

The two versions of this type of condensation (the reactions of toluenesulfonates with alcohols under the action of bases) are presented below. The reaction of *N*-phenyldiethanolamine ditoluenesulfonates with *N*-phenyldiethanolamine or *N*-phenylazatetraethylene glycol derivatives in the presence of sodium hydride resulted in *para*-substituted *N,N'*-diphenyldiaza-12(18)-crown-4(6) ethers **46**.<sup>118</sup>



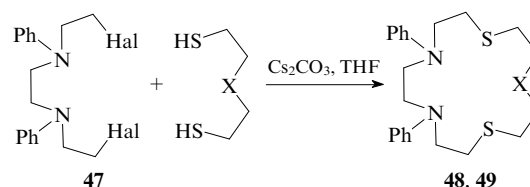
X = H, Y = Ts; *n* = 0, 1; R = H, Me, OMe, Cl;

X = Ts, Y = H; *n* = 1; R = H (18%);

(a) NaH; (b) Bu<sup>t</sup>OK.

In a similar method, *N*-phenylazatetraethylene glycol ditoluenesulfonate reacts with *N*-phenyldiethanolamine, which also gives *N,N'*-diphenyldiaza-18-crown-6 ether **46** (*n* = 1).<sup>38</sup> In this case, potassium *tert*-butoxide was used as the base.

The condensation of dihalide **47** with various dithiols<sup>34, 38</sup> affords *N,N'*-diphenyltetraethiadiaza-18-crown-6 ether **48** and *N,N'*-diphenyldiaza-15-crown-5 compound **49** containing two S atoms and one O atom in the macrocycle.



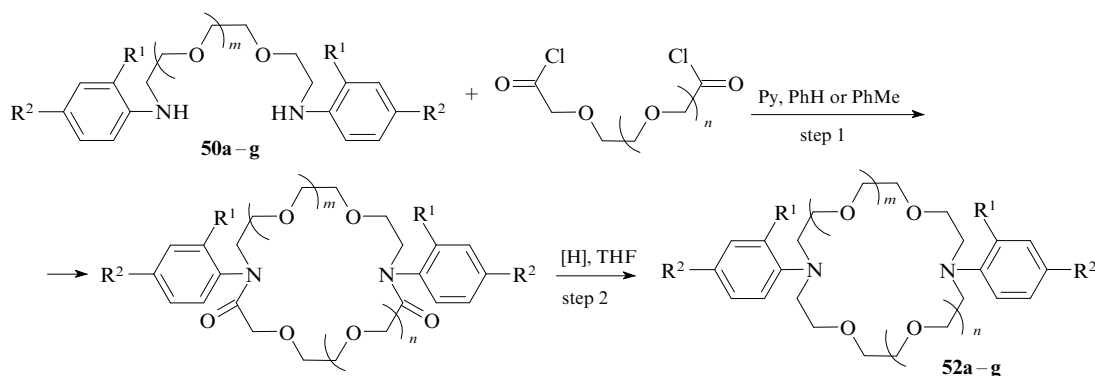
Hal = Br, X = S(CH<sub>2</sub>)<sub>2</sub>S (**48**, 11%); X = O (**49**).

As noted above (see Section II.1), the *N,N'*-diphenyltetraethiadiaza-18-crown-6 compound **11**, in which the nitrogen atoms in the macrocycle are separated by three ethylene units, has been isolated as a side product in 2% yield in the synthesis of *N*-phenyldithiaaza-9-crown-3 compound **10** (see Section II.1).<sup>38</sup>

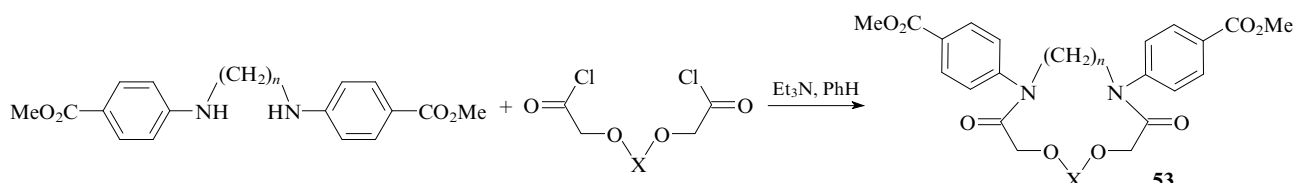
The condensation of diphenyldiamines **50a–g** and **51** (prepared from the corresponding anilines) (Scheme 3) with the dichlorides of dibasic carboxylic acids<sup>74, 119–125</sup> followed by the reduction of the obtained diamides is another method for the

Scheme 2

Scheme 3



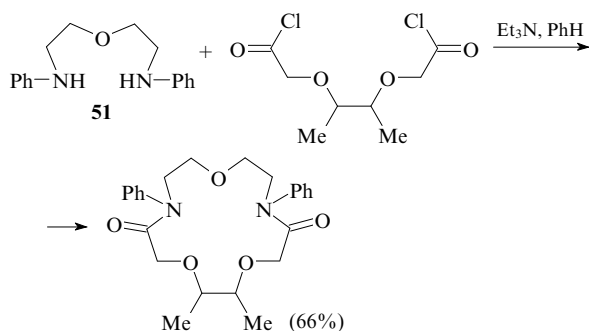
Scheme 4



X =  $\text{CMe}_2\text{CMe}_2$ ;  $n = 6, 10, 12, 14$  (61%–85%); X =  $\text{CH}_2\text{CMe}_2\text{CH}_2$ ;  $n = 10$  (62%), 12 (58%).

synthesis of *N,N'*-diphenyldiazacrown derivatives. The reactions of compounds **50a–g** were carried out in the presence of pyridine in benzene or toluene under high dilution conditions (Table 3). The reducing agents used included boron compounds ( $\text{B}_2\text{H}_6$ ,  $\text{BH}_3$  complexes with  $\text{Me}_2\text{S}$  or THF,  $\text{NaBH}_4$ ) and lithium tetrahydroaluminate. *N,N'*-Diphenyldiaza-24-crown-8 ethers **52d** ( $n = 2$ ,  $m = 2$ ) and **52g** ( $\text{R}^1 = \text{H}$ ;  $\text{R}^2 = \text{Me}$ ,  $\text{MeO}$ ,  $\text{Br}$ ;  $n = 2$ ;  $m = 2$ ) were prepared in 18%–33% total yields relative to the starting 4-substituted aniline.<sup>124</sup>

A similar reaction of dianiline **51** was carried out in benzene under the action of triethylamine.<sup>123</sup>



The removal of the tosyl protective groups from the nitrogen atoms in diazacrown compound **52c** was induced by sodium naphthalenide in tetrahydrofuran under mild conditions (yield 70%).<sup>120</sup> Diaza-15(18)-crown-5(6) ethers **52e,f** were used to prepare azo dyes.<sup>126</sup>

A series of macrocyclic *N,N'*-diaryldiaza(oligomethylene)diamides **53** has been obtained by condensation of diaryldiamines containing different numbers of methylene groups with dicarboxylic acid dichlorides on treatment with triethylamine in benzene under high dilution conditions (Scheme 4).<sup>127,128</sup> Compounds **53**, when introduced into polyvinyl chloride membranes, have shown high selectivity for  $\text{Li}^+$  ions.

## 2. Aromatic nucleophilic substitution reactions

Like azacrown ethers, diaza derivatives can be prepared by aromatic nucleophilic substitution in which the amino group of the crown compound attacks the carbon atom bonded to a halogen in an activated aryl halide.

*N,N'*-Diphenyldiazacrown compounds **54a–j**, containing electron-withdrawing substituents in the *para*- and *ortho*-positions of the benzene ring, have been synthesised by *N,N'*-diarylated diazacrown ethers.<sup>60,61,122,129–131</sup> The conditions of this reaction (the type of base and solvent) were mainly determined by the nature of the arylating agent. For example, the reaction of diaza-18-crown-6 ether with 2-chloro-3,5-dinitrobenzophenone

Table 3. Diphenyldiazacrown ether derivatives **52**.

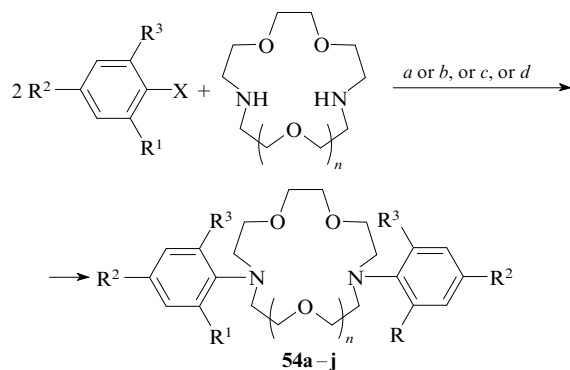
| Compounds<br><b>50, 52</b> | $\text{R}^1$ | $\text{R}^2$ | $m$  | $n$ | Yield (%) |                    | [H]                                     | Ref.     |
|----------------------------|--------------|--------------|------|-----|-----------|--------------------|-----------------------------------------|----------|
|                            |              |              |      |     | step 1    | step 2             |                                         |          |
| <b>a</b>                   | H            | Br           | 1    | 0   | 74        | 84                 | $\text{BH}_3 \cdot \text{Me}_2\text{S}$ | 122      |
| <b>b</b>                   | H            | Br           | 1    | 1   | 69        | 71                 | $\text{BH}_3 \cdot \text{Me}_2\text{S}$ | 122      |
| <b>c</b>                   | NHTs         | H            | 1    | 1   | 62        | 61                 | $\text{LiAlH}_4$                        | 119, 120 |
| <b>d</b>                   | H            | H            | 1    | 1   | 73        | 71                 | $\text{B}_2\text{H}_6$                  | 119, 120 |
|                            | H            | H            | 1, 2 | 0–2 | 33–71     | 41–50              | $\text{BH}_3 \cdot \text{THF}$          | 125      |
|                            | H            | H            | 2    | 2   | —         | 18–33 <sup>a</sup> | $\text{BH}_3 \cdot \text{THF}$          | 124      |
| <b>e</b>                   | OMe          | H            | 1    | 0   | 67        | 98                 | $\text{NaBH}_4$                         | 74       |
|                            | OMe          | H            | 1    | 0   | —         | —                  | $\text{B}_2\text{H}_6$                  | 121      |
| <b>f</b>                   | OMe          | H            | 1    | 1   | 73        | 92                 | $\text{NaBH}_4$                         | 74       |
| <b>g</b>                   | H            | Me, MeO, Br  | 2    | 2   | —         | 18–33 <sup>a</sup> | $\text{BH}_3 \cdot \text{THF}$          | 124      |

<sup>a</sup> The yield is given in relation to the starting 4-substituted aniline.



or with methyl 4-chloro-3,5-dinitrobenzoate in the presence of triethylamine in benzene gives compounds **54a,b** in high yields.<sup>60</sup> Compounds **54c,d** were prepared in a similar way.<sup>60</sup>

*N,N'*-Diphenyldiazacrown ethers **54e,f**, containing *ortho*-nitro- and *para*-trifluoromethyl groups, were prepared by the reaction of diazacrown ethers with the corresponding aryl chloride in the presence of triethylamine in THF under rigorous conditions (8 kbar pressure).<sup>129, 130</sup> Diaza-15-crown-5 ether reacts with 2-fluoro-5-nitroanisole<sup>61</sup> and diaza-18-crown-6 ether reacts with 4-fluoronitrobenzene<sup>131</sup> in pyridine, giving rise to *N,N'*-bis(nitrophenyl)diazacrown ethers **54g,h**. The diacyl derivatives **54i,j** were produced upon condensation of diaza-18(15)-crown-6(5) ethers with 4-fluoropropiophenone in the presence of tetra-butylammonium fluoride at 150 °C.<sup>122</sup>

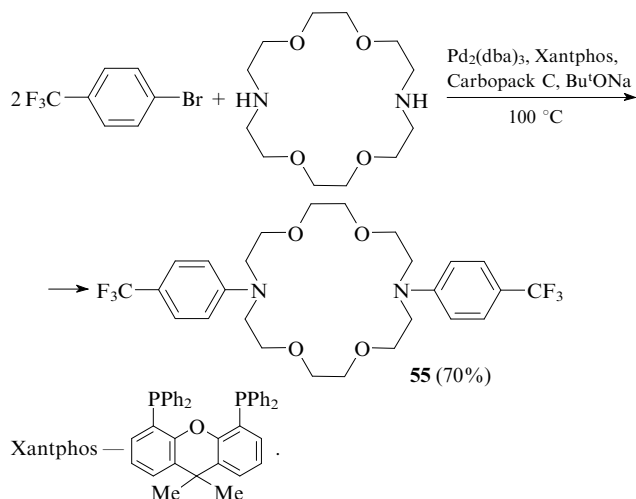


(a) Et<sub>3</sub>N, PhH; (b) Et<sub>3</sub>N, THF, 8 kbar; (c) Py; (d) Bu<sub>4</sub>N<sup>+</sup>F<sup>-</sup>·2H<sub>2</sub>O, 150 °C.

| Compound  | X  | R <sup>1</sup>     | R <sup>2</sup>     | R <sup>3</sup>  | n | Reaction conditions | Yield (%) | Ref.     |
|-----------|----|--------------------|--------------------|-----------------|---|---------------------|-----------|----------|
| <b>54</b> |    |                    |                    |                 |   |                     |           |          |
| <b>a</b>  | Cl | Bz                 | NO <sub>2</sub>    | NO <sub>2</sub> | 2 | <i>a</i>            | 76        | 60       |
| <b>b</b>  | Cl | NO <sub>2</sub>    | CO <sub>2</sub> Me | NO <sub>2</sub> | 2 | <i>a</i>            | 92        | 60       |
| <b>c</b>  | Cl | NO <sub>2</sub>    | CO <sub>2</sub> H  | NO <sub>2</sub> | 2 | <i>a</i>            | 80        | 60       |
| <b>d</b>  | Cl | CO <sub>2</sub> Me | NO <sub>2</sub>    | NO <sub>2</sub> | 2 | <i>a</i>            | 88        | 60       |
| <b>e</b>  | Cl | NO <sub>2</sub>    | CF <sub>3</sub>    | H               | 1 | <i>b</i>            | 79        | 129, 130 |
| <b>f</b>  | Cl | NO <sub>2</sub>    | CF <sub>3</sub>    | H               | 2 | <i>b</i>            | 92        | 129, 130 |
| <b>g</b>  | F  | OMe                | NO <sub>2</sub>    | H               | 1 | <i>c</i>            | 23        | 61       |
| <b>h</b>  | F  | H                  | NO <sub>2</sub>    | H               | 2 | <i>c</i>            | 24        | 131      |
| <b>i</b>  | F  | H                  | C(O)Et             | H               | 1 | <i>d</i>            | 25        | 122      |
| <b>j</b>  | F  | H                  | C(O)Et             | H               | 2 | <i>d</i>            | 28        | 122      |

### 3. Cross-coupling reactions

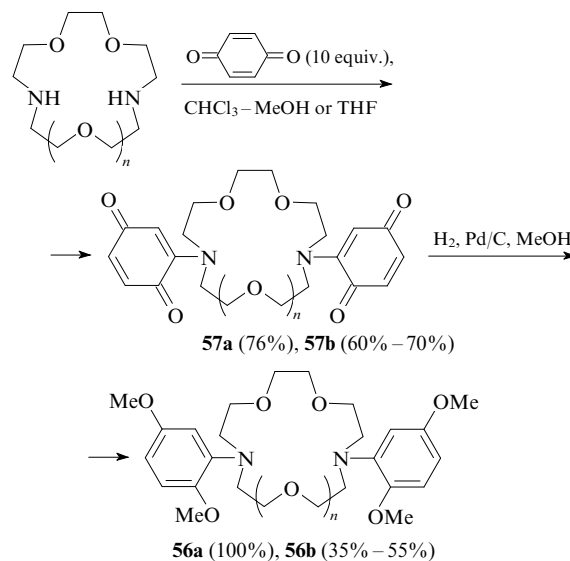
The preparation of *N,N'*-diphenyldiazacrown compounds *via* cross-coupling has been reported.<sup>132</sup> The arylation of diaza-18-crown-6 ether with *p*-bromobenzotrifluoride catalysed by Pd<sub>2</sub>(dba)<sub>3</sub>–Xantphos in the presence of the Carboxypack C graphite without a solvent resulted in compound **55**.



### 4. The substitution of hydrogen by diazacrown compounds

This method for the synthesis of *N,N'*-diphenyldiazacrown ethers, which is seldom encountered in the literature, is based on the addition of diazacrown ethers to an activated double bond followed by oxidation of the resulting adduct with excess reagent.

*N,N'*-Diphenyldiazacrown ethers **56a,b**, containing *ortho*- and *meta*-methoxy groups in the benzene rings have been prepared by hydrogenation of crown-containing *p*-benzoquinones **57a,b**. The reaction takes place in MeOH under atmospheric pressure at room temperature in the presence of palladium.<sup>61, 133, 134</sup> Macrocycles **57** were synthesised by the reaction of *p*-benzoquinone with diazacrown ethers. Apparently, benzoquinone itself, which is used in a large excess with respect to the crown ether, acts as the oxidant in this reaction.



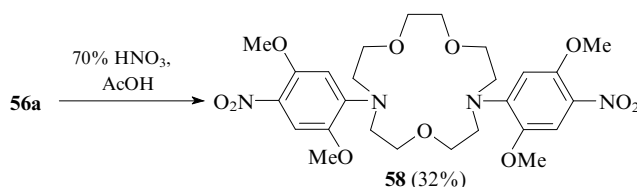
*n* = 1 (**a**), 2 (**b**).

## V. Functional derivatives of *N,N'*-diphenyldiazacrown compounds

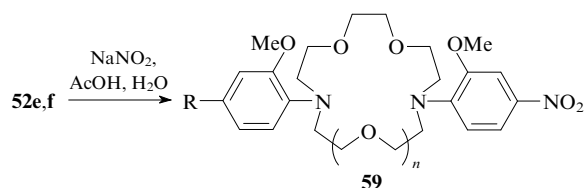
The transition from unsubstituted *N,N'*-diphenyldiazacrown compounds to their functional derivatives is similar to the reactions of *N*-phenylazacrown compounds.

### 1. Nitro and amino derivatives of *N,N'*-diphenyldiazacrown compounds

*N,N'*-Bis(nitrophenyl)diazacrown compounds can be prepared by the nitration of the aromatic ring. Treatment of *N,N'*-diaryl-diaza-15-crown-5 ether **56a** with an HNO<sub>3</sub>–AcOH mixture results in 4,4'-dinitro derivative **58**.<sup>131</sup>

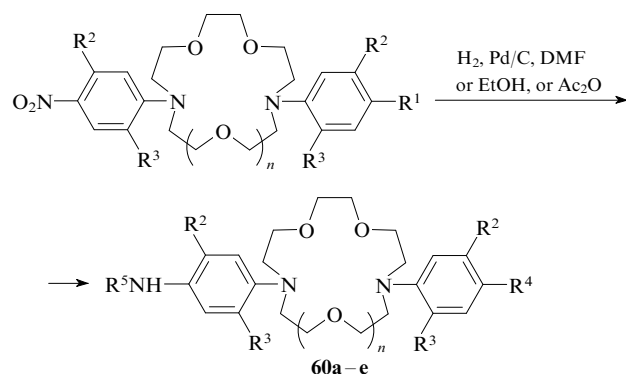


*N,N'*-Bis(*o*-methoxyphenyl)diaza-15(18)-crown-5(6) ethers **52e,f** react with sodium nitrite in aqueous AcOH (see also Section III.1) to give compounds **59** containing one or two nitro groups, whose ratio depends on the macrocycle size.<sup>74</sup> The researchers noted that the use of traditional nitrating agents (HNO<sub>3</sub>, HNO<sub>3</sub>–H<sub>2</sub>SO<sub>4</sub> or NO<sub>2</sub><sup>+</sup>BF<sub>4</sub><sup>–</sup>) results in a total yield of both mono- and dinitration products of only 5%–10%.



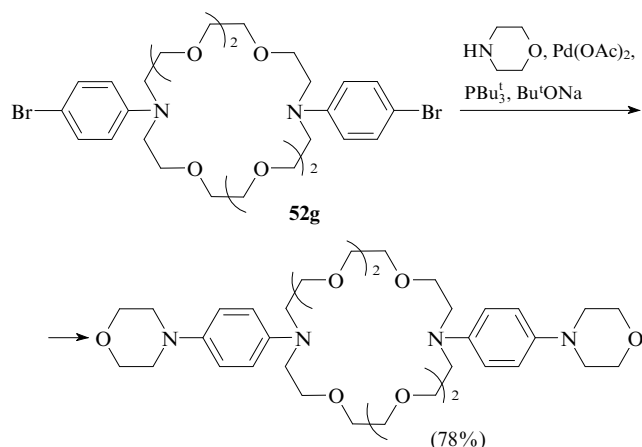
$n = 1$ : R = H (48%), NO<sub>2</sub> (17%);  $n = 2$ : R = H (43%), NO<sub>2</sub> (36%).

Amines **60a–d** have been prepared by the reduction of nitro derivatives of *N,N'*-diaryldiazacrown ethers with hydrogen in the presence of a palladium catalyst in dimethylformamide or ethanol.<sup>74, 131</sup> Conducting the reaction in acetic anhydride gave 4,4'-diacetamide derivative **60e**.<sup>61</sup>

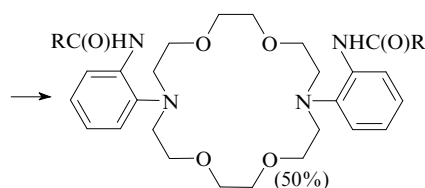
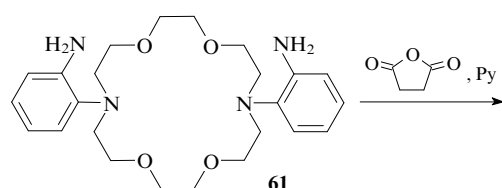


| Compound <b>60</b> | R <sup>1</sup>  | R <sup>2</sup> | R <sup>3</sup> | R <sup>4</sup>  | R <sup>5</sup> | $n$ | Yield (%) |
|--------------------|-----------------|----------------|----------------|-----------------|----------------|-----|-----------|
| <b>a</b>           | NO <sub>2</sub> | H              | H              | NH <sub>2</sub> | H              | 2   | —         |
| <b>b</b>           | NO <sub>2</sub> | OMe            | OMe            | NH <sub>2</sub> | H              | 1   | > 95      |
| <b>c</b>           | H               | H              | OMe            | H               | H              | 1   | 59        |
| <b>d</b>           | H               | H              | OMe            | H               | H              | 2   | 75        |
| <b>e</b>           | NO <sub>2</sub> | H              | H              | NHAc            | Ac             | 1   | 82        |

The bromine atom in compound **52g** is easily replaced by the morpholine residue in the presence of a palladium catalyst.<sup>124</sup>

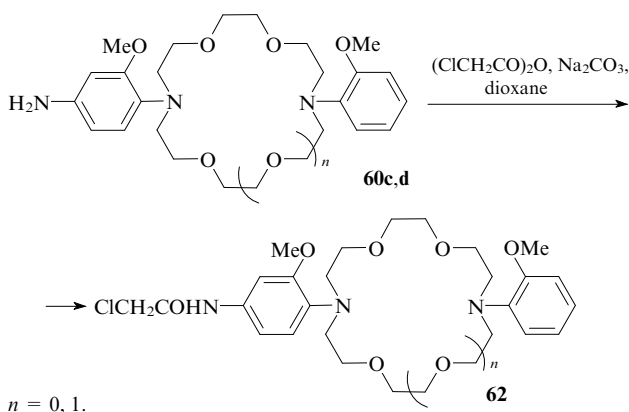


The acylation of diamine **61** with succinic anhydride in pyridine gave the corresponding disuccinic acid.<sup>120</sup>



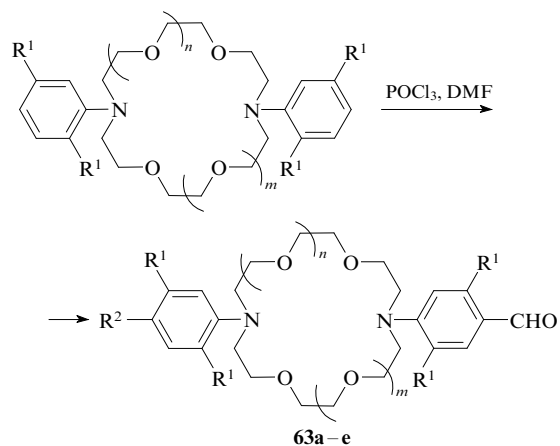
R = CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H.

Chloroacetamides **62** were synthesised in 62% yield by the reaction of amines **60c,d** with chloroacetic anhydride under the action of sodium carbonate in 1,4-dioxane.<sup>135</sup>

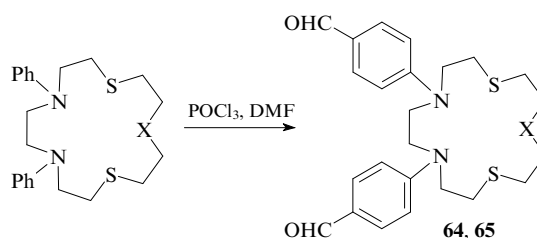


## 2. Formyl derivatives of *N,N'*-diphenyldiazacrown compounds

The formyl derivatives of *N,N'*-diphenyldiazacrown ethers **63a–e**<sup>61, 83, 125, 133, 134</sup> and *N,N'*-diphenylthiadiazacrown compounds **64**<sup>83</sup> and **65**<sup>34</sup> were obtained by the Vilsmeier reaction.

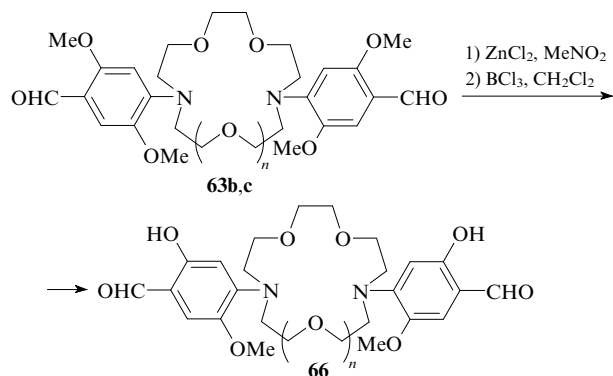


| Compound <b>63</b> | R <sup>1</sup> | R <sup>2</sup> | $m$ | $n$ | Yield (%) |
|--------------------|----------------|----------------|-----|-----|-----------|
| <b>a</b>           | H              | CHO            | 1   | 1   | 68        |
| <b>b</b>           | OMe            | CHO            | 0   | 1   | 75        |
| <b>c</b>           | OMe            | CHO            | 1   | 1   | 68        |
| <b>d</b>           | H              | H              | 3   | 3   | 47        |
| <b>e</b>           | H              | CHO            | 3   | 3   | 41        |



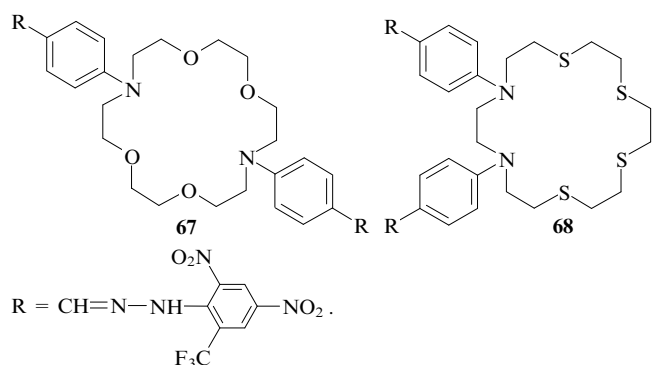
X = S(CH<sub>2</sub>)<sub>2</sub>S (**64**), O (**65**).

On treatment with boron trichloride, compounds **63b,c** undergo selective demethylation of the methoxy groups that occupy the *ortho* positions with respect to the formyl functions. Dialdehyde **66** thus formed was used to prepare fluorescent reagents for  $\text{Na}^+$  and  $\text{K}^+$  ions.<sup>61, 133, 134</sup>



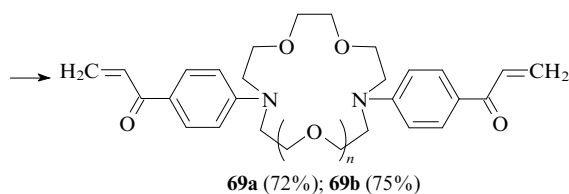
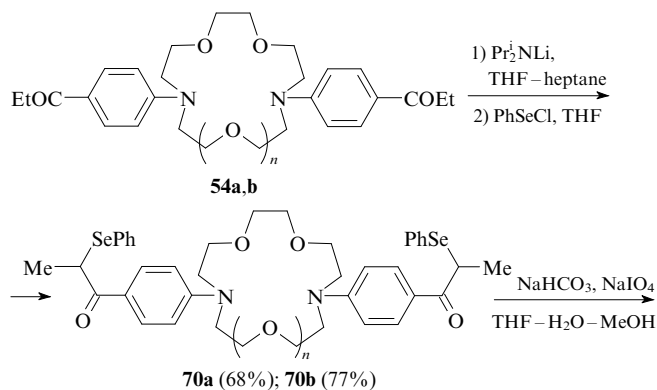
$n = 1$  (78%),  $2$  (45%).

The condensation of diformyl derivatives of *N,N'*-diphenyldiaza-18-crown-6 ether **63c** and *N,N'*-diphenyltetraethiadiaza-18-crown-6 compound **64** with dinitrotrifluoromethylphenylhydrazine affords hydrazones **67** and **68** in 68% and 52% yields, respectively.<sup>83</sup>



### 3. Acyl derivatives of *N,N'*-diphenyldiazacrown compounds

Diazacrown-containing  $\alpha,\beta$ -unsaturated ketones **69a,b** were prepared by converting the methyl groups of the propionyl substituent of compounds **54a,b** into methylene groups (see Section IV.2).<sup>122</sup> The reaction took place *via* selenium derivatives **70a,b**. The enolates, obtained by deprotonation of ketones **54** under the action of lithium diisopropylamide, reacted with phenylselenenyl chloride under mild conditions. The oxidation of diselenides **70** with sodium periodate was accompanied by elimination of organoselenium residues. Compounds **69a,b** thus formed react with arylhydrazines to give pyrazolines that are used as fluorescent indicators for the  $\text{Na}^+$  and  $\text{K}^+$  ions.



**69a** (72%); **69b** (75%)

$n = 1$  (**a**),  $2$  (**b**).

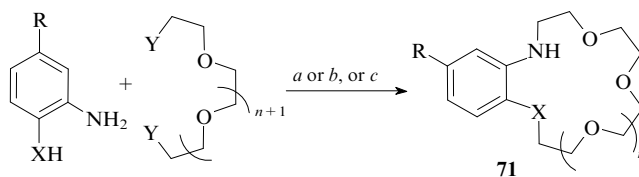
## VI. Benzoazacrown compounds

Benzoazacrown compounds that contain one or two nitrogen atoms conjugated with the benzene ring are obtained most often by [1 + 1]-condensation. In some cases, intramolecular cyclisation of podands (open-chain analogues of crown ethers) is used.

### 1. Condensation of two fragments

One method of synthesis of benzoaza- and benzodiazacrown compounds is the reaction of 2-aminophenols or *o*-phenylenediamines with oligoethylene glycol derivatives.<sup>41, 136–143</sup>

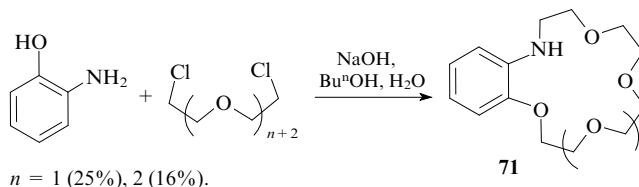
Thus by condensation of 2-aminophenols and *o*-phenylenediamine with the dichlorides, obtained from oligoethylene glycols, in DMF or water, Lockhart *et al.*<sup>41, 136, 137</sup> performed the first synthesis of azacrown compounds **71** with different macrocycle sizes (the yields were not reported). More recently, the same researchers described the synthesis<sup>138</sup> of benzodiazacrown compounds **71** by the condensation of *o*-phenylenediamine with tetraethylene glycol ditoluenesulfonate under the action of potassium carbonate in dimethylformamide on heating; however, the product yield was low.



(a) DMF; (b)  $\text{H}_2\text{O}$ ; (c)  $\text{K}_2\text{CO}_3$ , DMF.

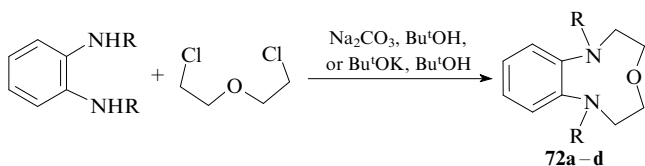
| Y   | X  | $n$  | R  |
|-----|----|------|----|
| Cl  | O  | 0–5  | H  |
| Cl  | NH | 0, 1 | H  |
| Cl  | NH | 1    | Me |
| OTs | NH | 1    | H  |

By the reaction of 2-aminophenol with the dichlorides prepared from tri- and tetraethylene glycol in aqueous butanol in the presence of sodium hydroxide, Pedersen and Bromels<sup>139</sup> have synthesised benzoaza-15(18)-crown-5(6) ethers **71** in moderate yields (25% and 16%, respectively). The same method<sup>140</sup> resulted in isolation of benzoaza-15-crown-5-ether in only 8% yield.



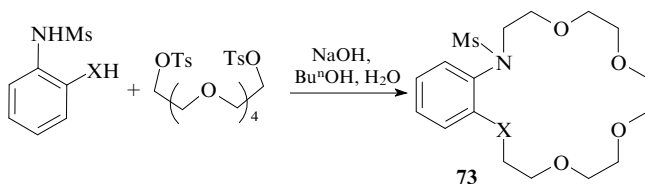
$n = 1$  (25%),  $2$  (16%).

Benzodiazacrown compounds **72a–d** have been prepared by condensation of *N,N'*-disubstituted *o*-phenylenediamines with chlorex.<sup>141, 142</sup> The tosyl groups in compound **72c** are removed by heating in concentrated  $\text{H}_2\text{SO}_4$  (yield 48%).



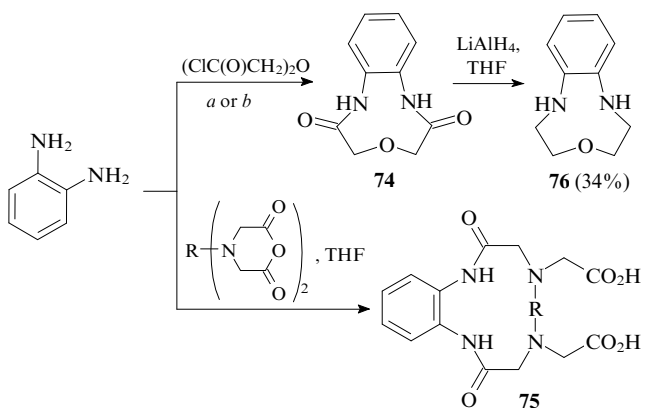
R = Me (**a**), Et (**b**), Ts (**c**), Ac (**d**).

Mesyl protection has also been used for the synthesis of nitrogen-containing benzocrown compounds **73**.<sup>143</sup> Mesylamides form crown compounds in higher yields than the corresponding tosylamides; however, it is difficult to prepare *N*-unsubstituted products from them. No data on the successful removal of mesyl groups from compounds **73** can be found in the literature.



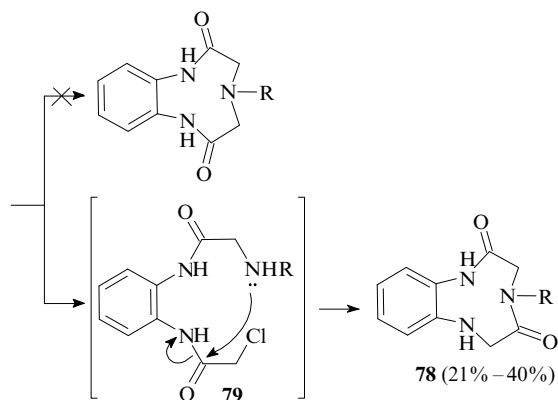
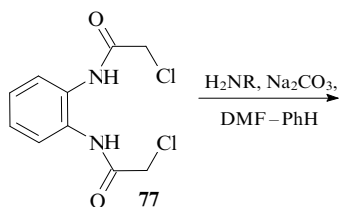
X = O (32%), NMs (5%).

The acylation of *o*-phenylenediamine with dicarboxylic acid dichlorides<sup>142, 144</sup> or tetracarboxylic acid dianhydrides<sup>145</sup> yielded macrocyclic diamides **74** and **75**. The reduction of compound **74** with lithium tetrahydroaluminate resulted in benzodiazacrown-3 compound **76**,<sup>142</sup> whose acylation with acetic anhydride afforded the corresponding *N,N'*-diacyl derivative in 25% yield.



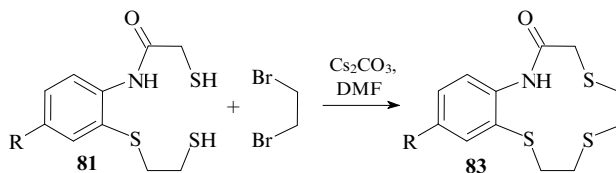
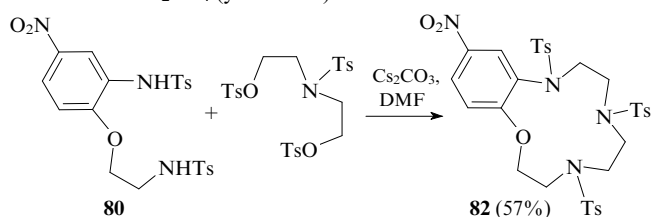
R = CH<sub>2</sub>CH<sub>2</sub> (95%), CH<sub>2</sub>(CH<sub>2</sub>OCH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub> (77%);  
(a) Na<sub>2</sub>CO<sub>3</sub>, xylene (62%); (b) Et<sub>3</sub>N, MeCN (30%).

Bis(chloroacetamide) **77** reacts with primary amines to give macrocyclic amides **78**. The mechanism includes an intramolecular rearrangement of the intermediate adduct **79**.<sup>146</sup>



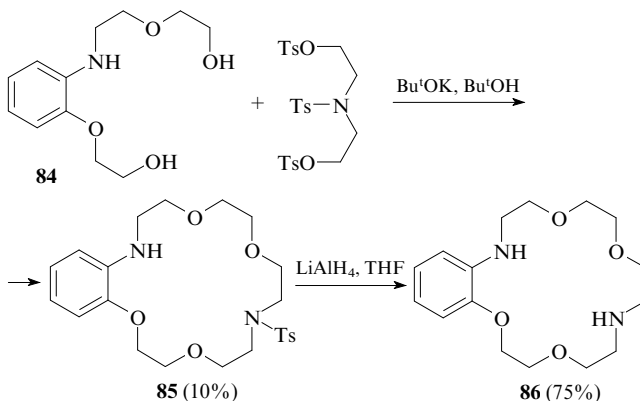
R = Bn, 4-MeC<sub>6</sub>H<sub>4</sub>, 2,4-Me<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, 4-EtOC<sub>6</sub>H<sub>4</sub>,  
3-Br-2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>3</sub>NHCOCH<sub>2</sub>.

Several examples of the synthesis of benzoazacrown compounds based on their linear analogues have been reported. Thus podands **80** and **81**, containing two terminal NH or SH groups, have been converted into benzopolyaza- and benzopolythiaza-crown compounds **82** and **83**.<sup>147, 148</sup> The removal of the tosyl groups in compound **82** was accomplished under acidic conditions as for sulfonamide **72c**, namely, by heating the compound in concentrated H<sub>2</sub>SO<sub>4</sub> (yield 94%).

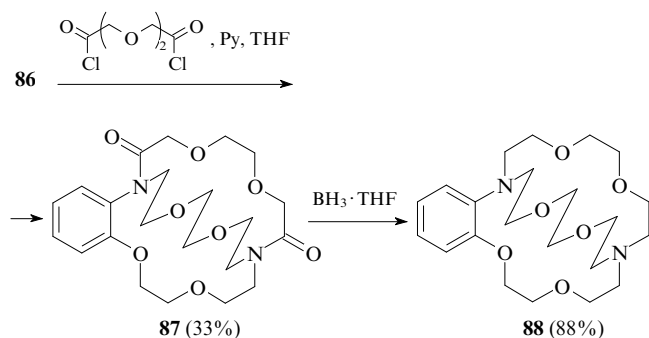


R = H (31%), OMe (17%).

The condensation of podand **84** with diethanolamine tritoluenesulfonate induced by potassium *tert*-butoxide in *tert*-butyl alcohol furnished the tosyl derivative of benzodiazacrown-6 ether **85**.<sup>149</sup> In this case, the *N*-tosyl group was removed by treatment with lithium tetrahydroaluminate.



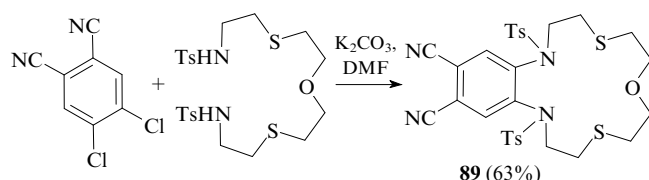
Acylation of benzodiazacrown-6 ether **86** with *O,O'*-ethylenediglycolic acid dichloride in THF in the presence of pyridine, followed by the reduction of the resulting diamide **87** with the borane complex with THF, afforded the corresponding benzocryptand **88**.<sup>149</sup>



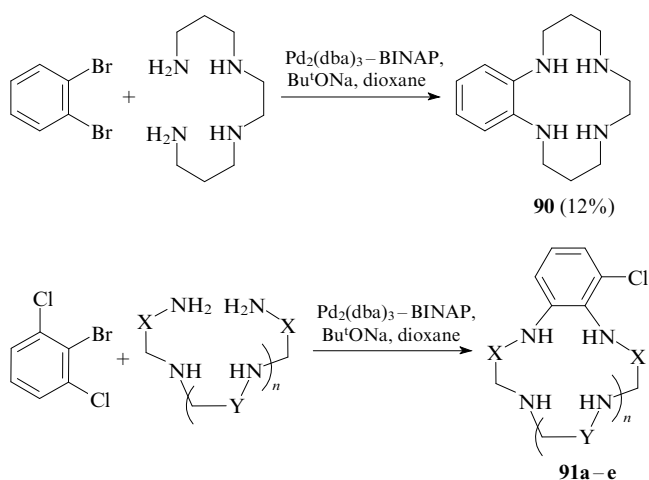
## 2. Arylation of $\alpha,\omega$ -diamino compounds with 1,2-dihalobenzenes

The reactions of *o*-dihalobenzenes with diamines deserve a separate section. In these cases, the bonds between the nitrogen atoms and the benzene ring are formed as a result of nucleophilic aromatic replacement of halogen atoms in activated aryl halides or as a result of C–N cross-coupling.

The benzodithiadiazacrown compound **89**, containing two nitrile groups on the benzene ring, has been prepared by the reaction of 4,5-dichlorophthalonitrile with an acyclic dithioamide under the action of potassium carbonate in DMF.<sup>150</sup>



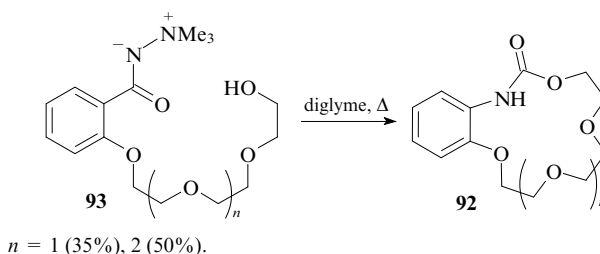
Benzocyclam **90** and benzopolyazacrown compounds **91a–e** with different macrocycle sizes were prepared by amination of 1,2-di- or 1,2,3-trihalobenzenes with linear polyamines in the presence of the Pd(dba)<sub>3</sub>–BINAP catalyst system.<sup>151</sup> In addition to the macrocycles, linear products were also isolated in these reactions. The attempts to prepare benzodiazacrown-15-crown-5 ether derivatives from 2,6-dichlorobromobenzene and the corresponding trioxadiazacrown-15-crown-5 ether derivatives with the same catalyst system have not met with success. Only the linear product was isolated in this case.



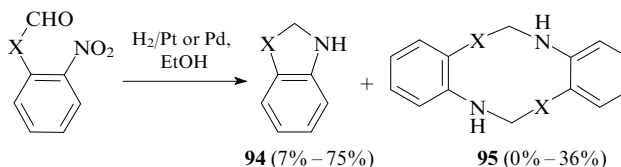
| Compound 91 | X                               | Y                               | n | Yield (%) |
|-------------|---------------------------------|---------------------------------|---|-----------|
| a           | CH <sub>2</sub> CH <sub>2</sub> | CH <sub>2</sub>                 | 1 | 47        |
| b           | CH <sub>2</sub>                 | CH <sub>2</sub>                 | 1 | 27        |
| c           | CH <sub>2</sub>                 | CH <sub>2</sub> CH <sub>2</sub> | 1 | 17        |
| d           | CH <sub>2</sub>                 | CH <sub>2</sub>                 | 2 | 12        |
| e           | CH <sub>2</sub>                 | CH <sub>2</sub>                 | 3 | 10        |

## 3. Intramolecular cyclisation of podands

This method of synthesis is based on the transformation of a linear molecule into a macrocycle with an annulated benzene ring. Urethane-type benzoazacrown compounds **92** are obtained from betaines **93**.<sup>152</sup> Under drastic conditions, these products rearrange into intermediate, readily cyclisable *N*-aryl isocyanates. The addition of template salts (NaBF<sub>4</sub>, KBF<sub>4</sub>) was found to affect only slightly the yields of these crown compounds.



Hydrogenation of nitrobenzenes containing an aldehyde function in the peripheral substituent, over a platinum or a palladium catalyst in ethanol, furnished a large series of benzoazacrown compounds **94a–g**.<sup>153</sup> Apart from compounds **94**, the reaction mixture contained in some cases dibenzodiazacrown compounds **95b,e–g** and polymerisation products. It was shown that the formation of nine- or ten-membered macrocycles is less favourable than the formation of dimers **95** with a macrocycle comprising 18–20 units (see below, Section VIII.2.a, synthesis of compounds **95h–o**). After the introduction of an *N*-benzoyl group into the nitroaldehyde molecule, this reaction gives only the nine-membered compound **94a**. Monomers **94f,g** with a macrocycle size of 15 and 16 units are formed more readily than the corresponding dimers **95f,g** (30- and 32-membered rings). In these cases, the **94**:**95** ratio in the products varies from 1.5:1 to 3:1. It is noteworthy that 11-, 13- and 14-membered benzoazacrown compounds **94c–e** were synthesised in high yields without dimer formation (except for slight amounts of **95e**).

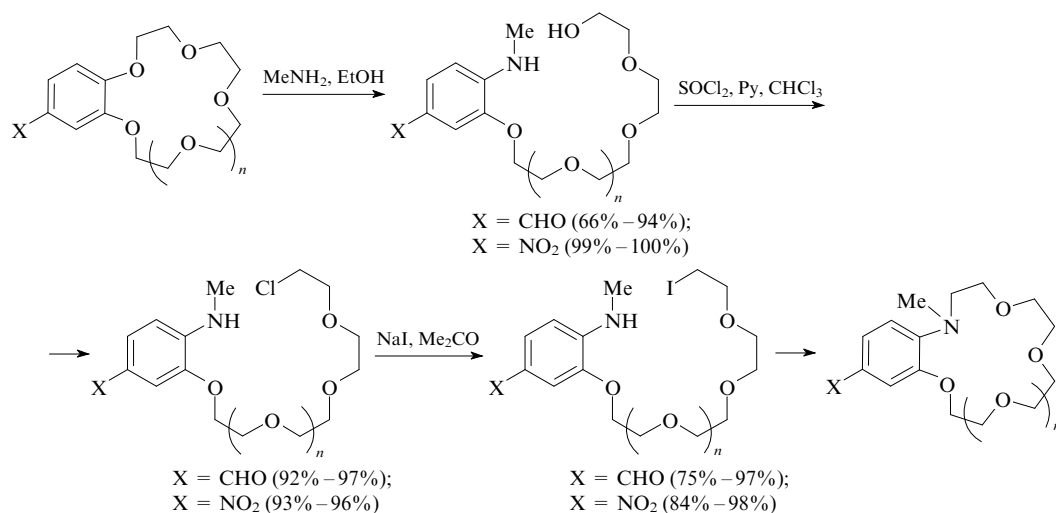


| Compounds 94, 95 | X                                                                                     | Catalyst | Yield (%) |    |
|------------------|---------------------------------------------------------------------------------------|----------|-----------|----|
|                  |                                                                                       |          | 94        | 95 |
| a                | NBz(CH <sub>2</sub> ) <sub>4</sub>                                                    | Pd       | 22        | —  |
| b                | O(CH <sub>2</sub> ) <sub>2</sub> O(CH <sub>2</sub> ) <sub>3</sub>                     | Pd       | 19        | 36 |
|                  | O(CH <sub>2</sub> ) <sub>2</sub> O(CH <sub>2</sub> ) <sub>3</sub>                     | Pt       | 22        | 18 |
| c                | O(CH <sub>2</sub> ) <sub>2</sub> N(SO <sub>2</sub> Me)(CH <sub>2</sub> ) <sub>3</sub> | Pt       | 36        | —  |
| d                | O[(CH <sub>2</sub> ) <sub>2</sub> O] <sub>2</sub> CH <sub>2</sub> CHMe                | Pd       | 56        | —  |
| e                | O[(CH <sub>2</sub> ) <sub>2</sub> O] <sub>2</sub> (CH <sub>2</sub> ) <sub>3</sub>     | Pd       | 75        | 6  |
|                  | O[(CH <sub>2</sub> ) <sub>2</sub> O] <sub>2</sub> (CH <sub>2</sub> ) <sub>3</sub>     | Pt       | 58        | —  |
| f                | O(CH <sub>2</sub> ) <sub>9</sub> CHMe                                                 | Pt       | 29        | 18 |
|                  | O(CH <sub>2</sub> ) <sub>9</sub> CHMe                                                 | Pd       | 27        | 19 |
| g                | O(CH <sub>2</sub> ) <sub>11</sub>                                                     | Pt       | 36        | 11 |

## 4. Synthesis of benzoazacrown ethers by the transformation of the benzocrown macrocycle

We proposed a new methodology for the synthesis of benzoazacrown ethers based on a stepwise ring transformation of benzocrown ethers. A distinctive feature of this method is macrocycle opening upon cleavage of the Ar–O bond followed by ring closure to give the corresponding aza analogues. The starting compounds used were benzocrown ethers whose benzene ring contained an electron-withdrawing group (nitro or formyl group), which activated the regioselective macrocycle opening induced by amines.<sup>155–158</sup> For successful recyclisation, the hydroxyl group present in the nitrogen-containing podands thus formed was

Scheme 5

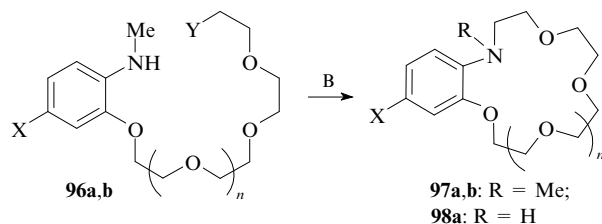


$X = \text{CHO}, \text{NO}_2$ ;  $n = 0-2$ .

replaced by a better leaving group such as a chlorine or an iodine atom.<sup>159–164</sup> The general pattern of the stepwise ring transformation in benzocrown ethers can be represented by Scheme 5.

The key step of this reaction sequence is ring closure in the podands to give the azamacrocyclic. Several procedures differing in the reaction conditions were developed. Ring closure in the halogen derivatives of azapodands can take place both under the action of bases and without bases. Most often, iodine derivatives of azapodands are used to prepare benzoazacrown ethers.

Heating of formyl-containing iodides **96a** in the presence of alkali metal carbonates affords *N*-methylbenzoazacrown ethers **97a**<sup>159–161</sup> together with *N*-demethylated benzoazacrown ethers **98a** as side products (yields 11%–18%). However, in the absence of bases, the reaction gives mainly (in some cases, only) *N*-demethylated benzoazacrown ethers. A drawback of the two methods of ring closure is the very long duration: the reaction does not go to completion even after 150 h. An increase in the time of heating results in a pronounced decrease in the yield of products **97a** (especially in the case of a 18-membered macrocycle) due to substantial resinification of the reaction mixture. Nitro-substituted iodopodand **96b** was converted into *N*-methylbenzoaza-15-crown-5 ether **97b**, whose yields in the presence and in the absence of potassium carbonate were 54% and 22%, respectively.<sup>165</sup>



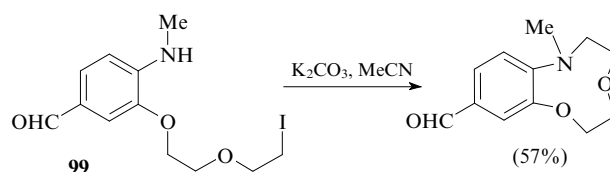
$X = \text{CHO}, n = 0-2$  (**a**);  $X = \text{NO}_2, n = 1$  (**b**);  
 $Y = \text{I}, \text{Cl}$ ; B is a base.

The use of alkali metal hydroxides or NaH, which are stronger bases than alkali metal carbonates, allows selective preparation of *N*-methylated benzoazacrown ethers **97** over much shorter periods of time.<sup>162–166</sup> Indeed, sodium hydride-induced ring closure in iodopodands **96** takes place on heating for 0.5–2 h. The yields of the products are much higher with NaH than with hydroxides; in some cases, not only iodo but also less reactive chloro derivatives can be used. Table 4 summarises all the preparative procedures for ring closure in halopodands **96**.

Heating of iodide **99** in the presence of  $\text{K}_2\text{CO}_3$  resulted in *N*-methylbenzoaza-9-crown-3 ether in 57% yield in relation to the converted iodide (the degree of conversion was only 23%).<sup>166</sup>

**Table 4.** Methods for the preparation of azacrown ethers **97** from halopodands.

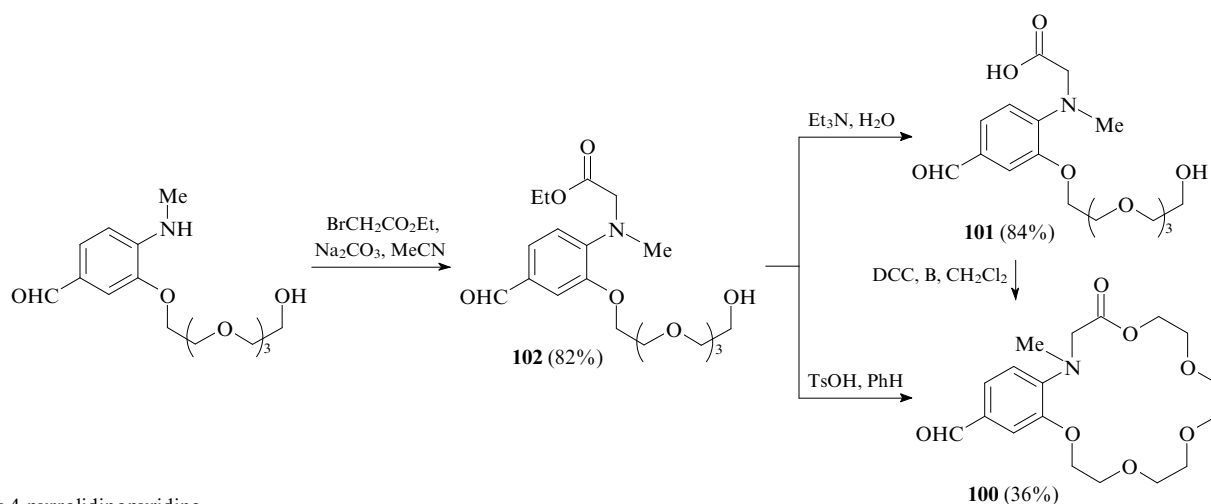
| Compo-<br>unds <b>96, 97</b>   | <i>n</i> | Y  | Reaction conditions                                              | Yield of<br><b>97</b> (%) | Ref.     |
|--------------------------------|----------|----|------------------------------------------------------------------|---------------------------|----------|
| <b>a</b> ( $X = \text{CHO}$ )  | 0        | I  | $\text{M}_2\text{CO}_3$ ( $M = \text{Li, Na, K, Rb, Cs}$ ), MeCN | 53–67                     | 159–161  |
|                                | 0        | I  | NaH, THF                                                         | 61–68                     | 166      |
|                                | 1        | Cl | NaH, THF                                                         | 59                        | 166      |
|                                | 1        | I  | $\text{M}_2\text{CO}_3$ ( $M = \text{Li, Na, K, Rb}$ ), MeCN     | 53–61                     | 159–161  |
|                                | 1        | I  | NaH, THF                                                         | 61–63                     | 166      |
|                                | 2        | I  | $\text{M}_2\text{CO}_3$ ( $M = \text{Li, Na, K, Rb}$ ), MeCN     | 52–53                     | 159–161  |
| <b>b</b> ( $X = \text{NO}_2$ ) | 2        | I  | NaH, THF                                                         | 51–57                     | 166      |
|                                | 0        | I  | NaH, THF                                                         | 36                        | 162–165  |
|                                | 1        | I  | $\text{Na}_2\text{CO}_3$ , MeCN                                  | 54                        | 165      |
|                                | 1        | I  | NaH, THF                                                         | 74–80                     | 162–165  |
|                                | 2        | I  | NaOH, dioxane                                                    | 56                        | 162, 165 |
|                                | 2        | I  | NaH, THF                                                         | 71                        | 162–165  |



As an example of another application of podands in the synthesis of benzoazacrown ethers, one can consider the synthesis of compound **100**, which contains an ester group in the macrocycle. This azacrown ether was prepared in two ways: by intramolecular esterification of acid **101** under the action of *N,N'*-dicyclohexylcarbodiimide (DCC) and by transesterification of podand **102** in the presence of *p*-toluenesulfonic acid as the catalyst (Scheme 6).<sup>167</sup>

The resulting *N*-methylated benzoazacrown ethers form complexes with metal cations characterised by high stability constants, due to the specific features of their conformations. The complexing properties of these compounds substantially exceed those of widely used *N*-phenylazacrown ethers (and in many cases, benzocrown ethers, too) with the same macrocycle size.<sup>161, 165, 168</sup> Owing to the presence of a nitro or a formyl group in the products obtained, it is possible to convert them into diverse derivatives containing benzoazacrown ether fragments. These can be used as selective ligands for metal cations, for the extraction of metal ions

Scheme 6



**B** is 4-pyrrolidinopyridine.

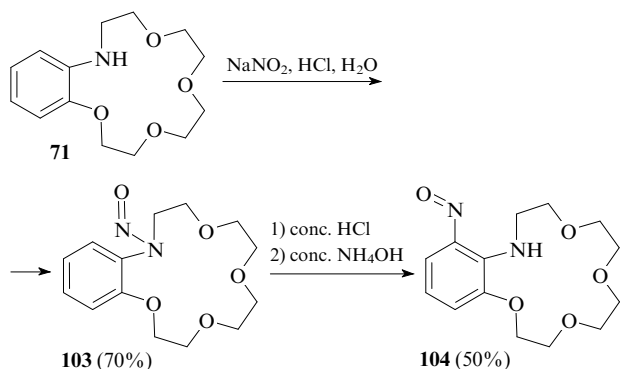
from water and for membrane transport of metal ions, as ion selective dyes and fluoroionophores, in ion selective electrodes, and as parts of polymer films and Langmuir–Blodgett films.

## VII. Functional derivatives of benzoazacrown compounds

### 1. Synthesis of benzoazacrown compounds with substituents in the benzene ring

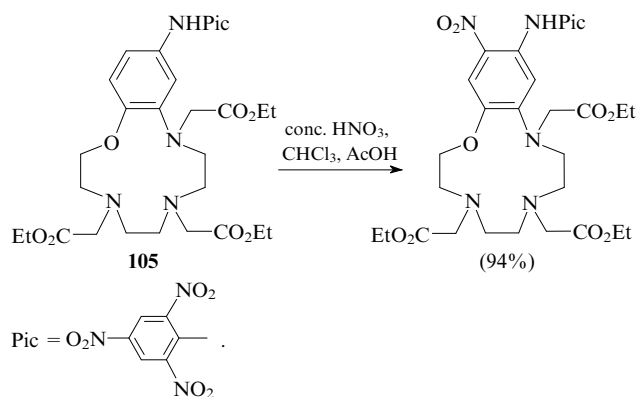
Only a few examples of the synthesis of benzoazacrown derivatives by electrophilic substitution in the benzene ring have been reported.

On treatment with sodium nitrite in hydrochloric acid under mild conditions, benzoaza-15-crown-5 ether **71** is converted into *N*-nitroso derivative **103**, which isomerises in the presence of cold concentrated  $\text{HCl}$  to give 3'-nitrosobenzo derivative **104**.<sup>139</sup>

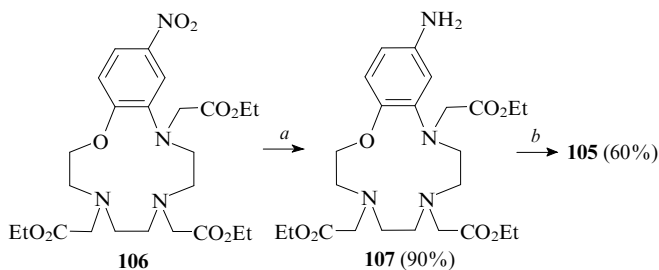


Azo coupling of benzoaza-12-crown-4 with *p*-nitrophenyldiazonium chloride leads to crown-containing azobenzene in which the substituent is in the *para*-position relative to the macrocycle nitrogen atom.<sup>169</sup>

Compound **105** undergoes selective nitration, under mild conditions, of the 5-position of the benzene ring annelated to the macrocycle.<sup>147</sup>

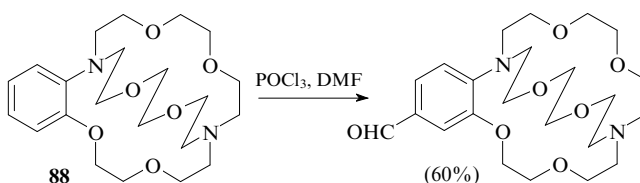


4'-Nitrobenzotriazacrown compound **106** (see below, Section VII.2) is reduced with hydrogen in the presence of a palladium catalyst to form aniline derivative **107**.<sup>147</sup> This product reacts with picryl chloride in the presence of potassium carbonate to afford benzotriazacrown compound **105**.<sup>147</sup>



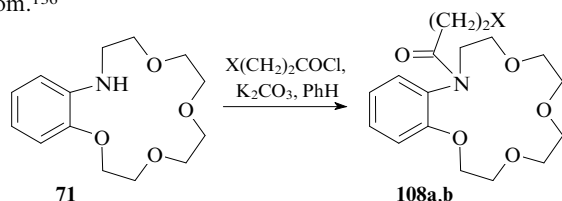
(a)  $\text{H}_2$ ,  $\text{Pd/C}$ ,  $\text{TsOH}$ , aq.  $\text{EtOH}$ ; (b)  $\text{PicCl}$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{MeOH}$ .

The formylation of benzocryptand **88** has been carried out by the Vilsmeier reaction.<sup>149</sup>



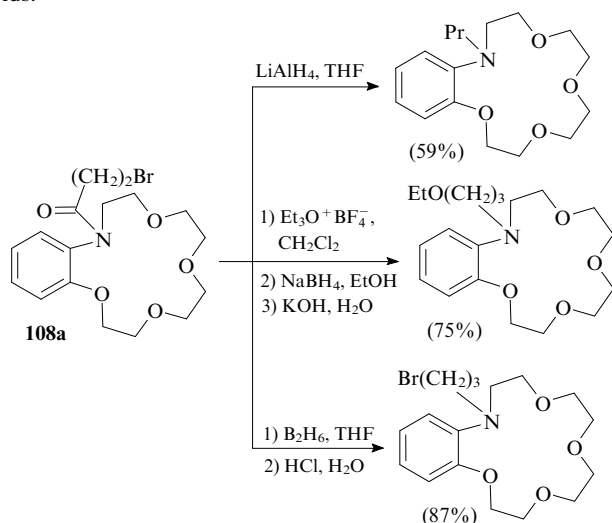
## 2. Benzoazacrown derivatives at the macrocycle nitrogen atom

The examples of synthesis of functional derivatives at the nitrogen atom refer to benzoaza-15-crown-5 ether **71**. This compound reacts with acyl chlorides with acylation of the secondary nitrogen atom.<sup>136</sup>

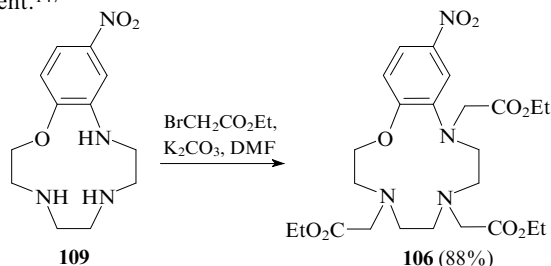


X = Br (**a**, 95%), CO<sub>2</sub>H (**b**, 59%).

The amide bond in compound **108a** was reduced with various reagents. This gave *N*-alkylbenzoaza-15-crown-5 ethers in good yields.<sup>136</sup>



Attempts at alkylation of benzotriazacrown compounds **109** with ClCH<sub>2</sub>CO<sub>2</sub>H have failed. However, this reaction readily proceeds when ethyl bromoacetate is used as the alkylating agent.<sup>147</sup>



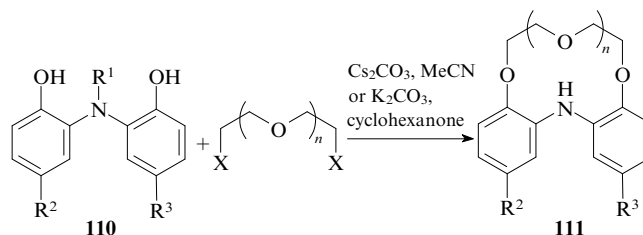
## VIII. Dibenzoazacrown compounds

### 1. Dibenzoazacrown derivatives

The dibenzomonoazacrown ethers described in the literature, in which the nitrogen atom of the macrocycle is conjugated with two benzene rings, have been synthesised by two routes.<sup>170, 171</sup>

The first route involves the condensation of bisphenol **110** with oligoethylene glycol derivatives under the action of bases. The reactions with oligoethylene glycol ditoluenesulfonates (*n* = 2, 4) were performed in the presence of caesium carbonate in acetonitrile,<sup>170</sup> while the reactions with dihalides and ditoluenesulfonate (*n* = 3) were performed in the presence of potassium carbonate (with addition of catalytic amounts of KI in the case of dichlorides) in various solvents. The highest product yields were attained in cyclohexanone.<sup>171</sup> The addition of LiBr as the template salt in the synthesis of dibenzomonoaza-12-crown-4 ether increased the yield from 8% to 30%. The cyclisation of compound

**110** (*R*<sup>1</sup> = CHO, Ac) is accompanied by deacylation giving rise to macrocycles **111**, which contain a secondary amino group. Subsequently, compound **111** (*n* = 3, *R*<sup>2</sup> = Cl, *R*<sup>3</sup> = H) was acylated. The reaction of **111** with formic acid and acetic anhydride furnished *N*-formylated and *N*-acetylated dibenzoazacrown ethers in 60% and 76% yields, respectively.

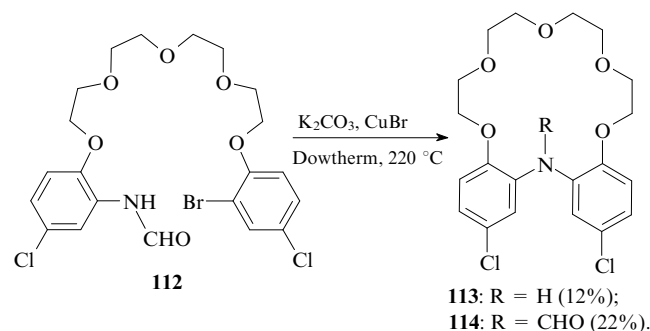


*R*<sup>1</sup> = *R*<sup>2</sup> = *R*<sup>3</sup> = H, X = OTs, *n* = 2–4 (22%–68%);

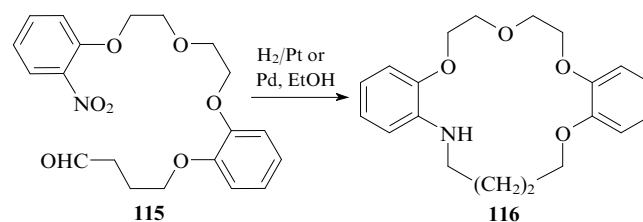
*R*<sup>1</sup> = H, CHO, Ac; *R*<sup>2</sup> = Cl; *R*<sup>3</sup> = H, Cl;

X = Cl, Br; *n* = 1–4 (24%–51%).

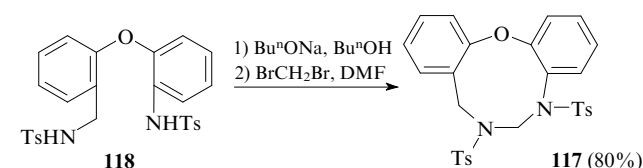
The second route to dibenzomonoazacrown ethers consists of the intramolecular cyclisation of podand **112** in the presence of potassium carbonate and copper(I) bromide under drastic conditions (Dowtherm, 220 °C).<sup>171</sup> Two products were isolated — compounds **113** and **114**. The latter can also be synthesised from the NH-unsubstituted derivative **113** by treatment with formic acid.



In some cases, podands containing two phenylene substituents are used as substrates in the synthesis of dibenzomonoazacrown ethers. Thus hydrogenation of nitroaldehyde **115** over a platinum or a palladium catalyst gives dibenzoazacrown ether **116** in 47% and 65% yield, respectively.<sup>153</sup>

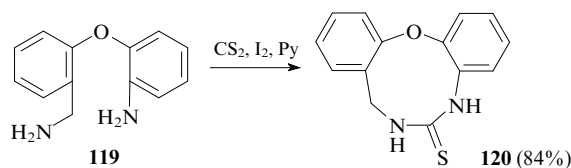


Examples of dibenzodiazacrown compounds in which one nitrogen atom is conjugated with the benzene ring, while the second nitrogen atom is separated from the aromatic ring by a methylene bridge are reasonably assigned to the same Section. Compound **117** was prepared by condensation of *N,N'*-ditosylamide **118** with dibromomethane, induced by sodium *n*-butoxide in DMF.<sup>172</sup> Attempts at detosylation by treatment with concentrated H<sub>2</sub>SO<sub>4</sub> failed.





The reaction of diamine **119** with carbon disulfide in pyridine using iodine as the catalyst resulted in the synthesis of dibenzoazacrown compound **120**, which is a thiourea derivative.<sup>173</sup>



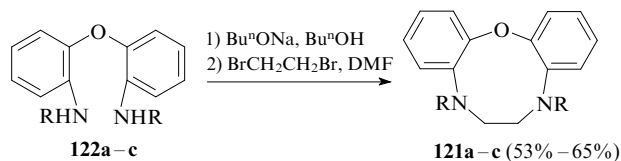
## 2. Dibenzodiazacrown and dibenzotetraazacrown compounds

The construction of the macrocycle in the dibenzoazacrown compounds containing two or four nitrogen atoms conjugated with benzene rings is based most often on the condensation of two fragments. Only a few examples of the synthesis of dibenzotetraazacrown compounds from four fragments have been reported.

### a. Syntheses based on the condensation of two fragments

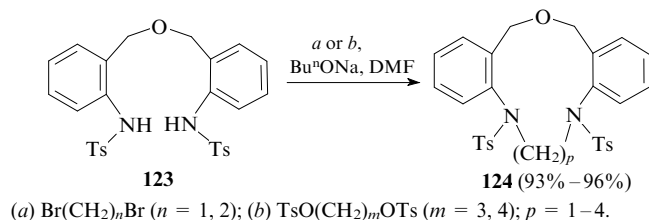
The alkylation of diamines or  $N,N'$ -disubstituted analogues under the action of bases is a widely used method for the synthesis of dibenzodiazacrown compounds. The alkylating agents used include  $\alpha,\omega$ -dihaloalkanes and derivatives of oligoethylene glycols and their aza analogues.<sup>143, 174–179</sup>

Dibenzodiazacrown compounds **121a–c** have been prepared in good yields by the reaction of  $N,N'$ -derivatives of diamines **122a–c** with dibromoethane in the presence of sodium *n*-butoxide.<sup>174</sup> The tosyl groups present in compound **121c** were removed by heating in concentrated  $\text{H}_2\text{SO}_4$  (yield 89%).



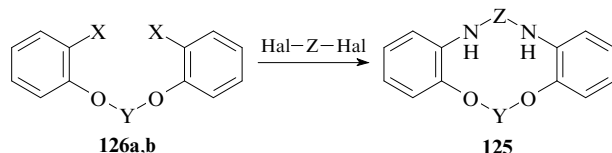
$\text{R} = \text{Me}$  (a),  $\text{Bz}$  (b),  $\text{Ts}$  (c).

Under the same conditions, dibenzyl ether **123** was converted to **124** using dibromomethane and 1,2-dibromoethane as well as analogous  $O,O'$ -ditoluenesulfonates with longer alkylene chains as the alkylating agents.<sup>175</sup>

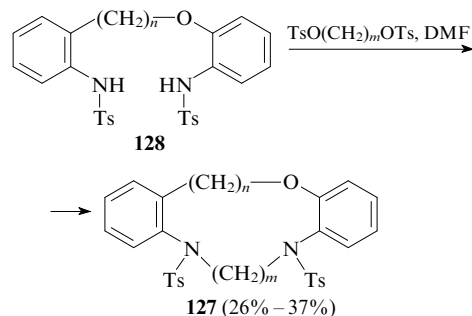


(a)  $\text{Br}(\text{CH}_2)_n\text{Br}$  ( $n = 1, 2$ ); (b)  $\text{TsO}(\text{CH}_2)_m\text{OTs}$  ( $m = 3, 4$ );  $p = 1–4$ .

Dibenzodiazacrown compounds **125** (Table 5) have been prepared in moderate yields by the alkylation of either the diamine as dihydrochloride (**126a**) or the  $N,N'$ -ditosyl derivative **126b** with the corresponding dihalides under the action of alkali metal carbonates.<sup>176</sup> In the latter case, the tosyl groups were removed after the reaction by treatment with sodium naphthalenide in dimethoxyethane.

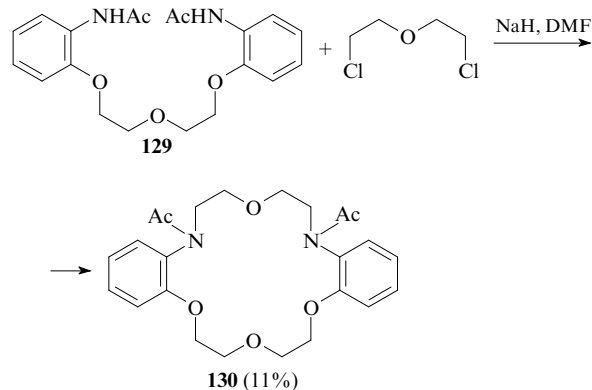


Dibenzodiazacrown compounds **127** were prepared by the reaction of the  $N,N'$ -ditosyl derivative of diamine **128** with ditoluenesulfonates of propylene or butylene glycols on heating in  $\text{DMF}$ .<sup>177</sup> Detosylation with concentrated  $\text{H}_2\text{SO}_4$  was successful only for compound **127** ( $n = 1, m = 4$ ).

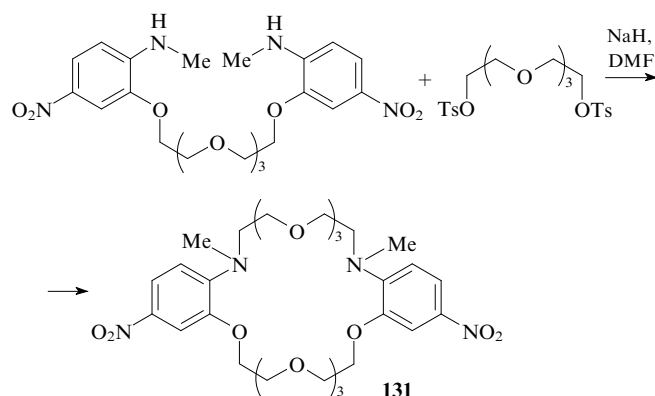


$n = 0, 1; m = 3, 4$ .

The sodium hydride-induced condensation of diamine **129**, containing  $N$ -acetyl protective groups, with the dichloride prepared from diethylene glycol affords dibenzodiazacrown-18-crown-6 compound **130**.<sup>178</sup>



Dinitrodibenzodiazacrown-30-crown-10 ether **131**, with  $N$ -methyl substituents, has been obtained under similar conditions using appropriate reagents.<sup>179</sup>



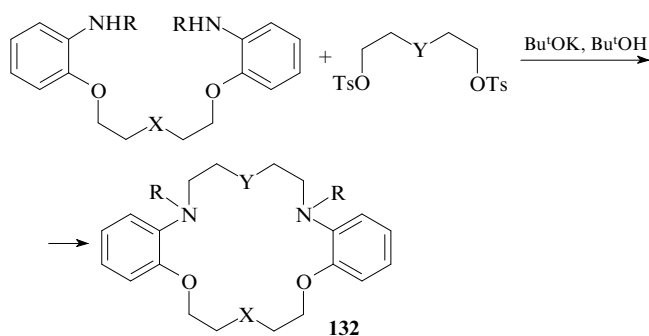
In an early study,<sup>143</sup> dibenzodiazacrown, triaza- and tetraaza-18-crown-6 compounds **132** were synthesised by condensation of  $N$ -tosyl- or  $N$ -mesyldiamines with appropriate ditoluenesulfonates. The reaction proceeds in the presence of potassium *tert*-butoxide in *tert*-butyl alcohol. The removal of the sulfonyl groups from the macrocycle nitrogen atoms is best accomplished by the heating of compounds **132** with an  $\text{AcOH}$  (glacial)– $\text{HBr}$ – $\text{PhOH}$  mixture (the yields of the  $\text{NH}$  derivatives were 30%–82%). Minor amounts of benzene ring bromination products were also isolated;

**Table 5.** Synthesis of dibenzodiazacrown compounds **125**.

| Compound <b>126</b> | X                    | Y                                                                                                                                   | Z                                                                                | Hal | Reaction conditions                                                                                 | Yield (%) |
|---------------------|----------------------|-------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----|-----------------------------------------------------------------------------------------------------|-----------|
| <b>a</b>            | NH <sub>2</sub> ·HCl | (CH <sub>2</sub> ) <sub>n</sub> , <i>n</i> = 2, 3; (CH <sub>2</sub> ) <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub>                 | (CH <sub>2</sub> ) <sub>n</sub> , <i>n</i> = 2, 3                                | Br  | K <sub>2</sub> CO <sub>3</sub> , DMF                                                                | 1–9       |
|                     | NH <sub>2</sub> ·HCl | (CH <sub>2</sub> ) <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub>                                                                    | CH <sub>2</sub> (CH <sub>2</sub> OCH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> | I   | K <sub>2</sub> CO <sub>3</sub> , DMF                                                                | 12        |
| <b>b</b>            | NHTs                 | (CH <sub>2</sub> ) <sub>n</sub> , <i>n</i> = 2, 3; CH <sub>2</sub> (CH <sub>2</sub> OCH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> | (CH <sub>2</sub> ) <sub>n</sub> , <i>n</i> = 2, 3                                | Br  | 1) Na <sub>2</sub> CO <sub>3</sub> , DMF;<br>2) C <sub>10</sub> H <sub>8</sub> Na, DME <sup>a</sup> | 4–8       |

<sup>a</sup> DME is 1,2-dimethoxyethane.

the bromine atoms were removed by treatment with hydrazine on a Pd catalyst.



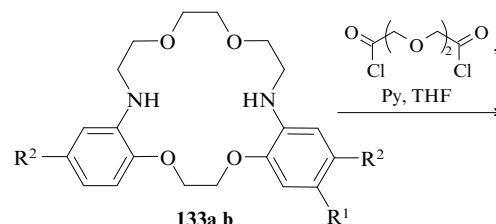
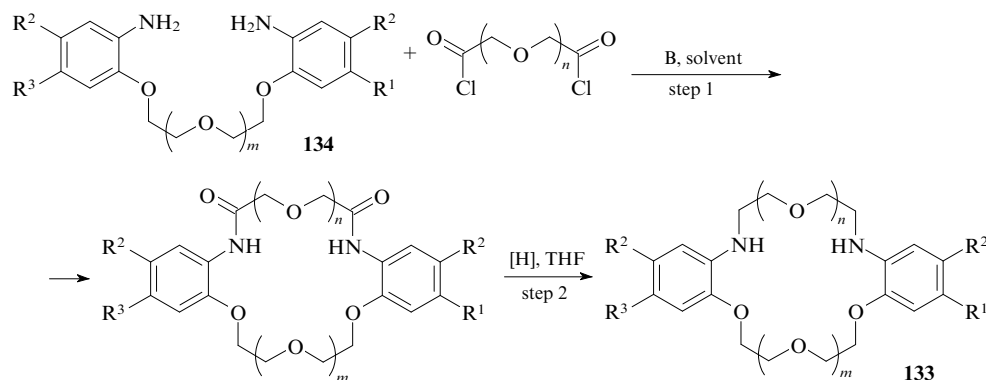
R = Ms: X = Y = O (40%);

R = Ts: X = NTs; Y = O (54%), NTs (20%).

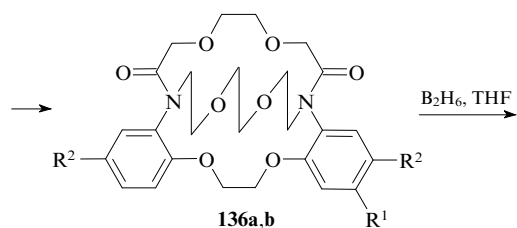
Yet another method used rather widely to prepare dibenzodiazacrown compounds is acylation of the corresponding bridged bis(anilines) with dicarboxylic acid derivatives. Most often, this process is induced by bases and is carried out under high dilution conditions.<sup>136, 144, 169, 178, 180–194</sup> The diamides formed are subsequently reduced by lithium tetrahydroaluminate or diborane.<sup>136, 169, 180–183, 185–193</sup>

Dibenzodiazacrown compounds with different macrocycle sizes **133** have been obtained by the acylation of diamines **134** with oxalic and di- or triglycolic acid dichlorides (Scheme 7, Table 6).<sup>136, 169, 180–183</sup> Compounds **133** with *m* = 1 were used in Pb<sup>2+</sup> extraction experiments and that with R<sup>2</sup> = Bu<sup>t</sup> was also employed to study Pb<sup>2+</sup> ion transport through plasticised cellulose triacetate membranes.<sup>181</sup>

Dibenzodiazacrown compounds **133a,b** were employed in the preparation of benzoannelated cryptands **135a,b**.<sup>180, 182</sup> The substrates **133a,b** were acylated with triglycolic acid dichloride under high dilution conditions, and the subsequent reduction of the resulting amides **136a,b** was carried out with a solution of diborane in THF. The yields were reported only for R<sup>1</sup> = H, R<sup>2</sup> = OBn: **136b**, 43%; **135b**, 88%.<sup>182</sup>

**Scheme 7****Table 6.** Synthesis of dibenzodiazacrown compounds **133**.

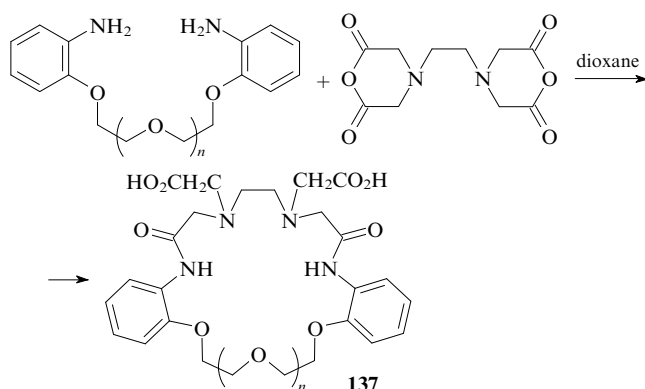
| R <sup>1</sup> | R <sup>2</sup>  | R <sup>3</sup> | <i>m</i> | <i>n</i> | Step 1            |                                 |           | Step 2                        |           | Ref. |
|----------------|-----------------|----------------|----------|----------|-------------------|---------------------------------|-----------|-------------------------------|-----------|------|
|                |                 |                |          |          | B                 | solvent                         | yield (%) | [H]                           | yield (%) |      |
| H              | H               | H              | 1        | 0        | Py                | benzene                         | 54        | LiAlH <sub>4</sub>            | 77        | 169  |
| H              | H               | H              | 1        | 0        | Et <sub>3</sub> N | toluene                         | 61        | LiAlH <sub>4</sub>            | 60        | 181  |
| H              | H               | H              | 1        | 1        | Et <sub>3</sub> N | toluene                         | 88        | LiAlH <sub>4</sub>            | 98        | 181  |
| H              | H               | H              | 1        | 1        | Py                | benzene                         | 40        | LiAlH <sub>4</sub>            | 71        | 169  |
| H              | H               | H              | 1        | 2        | excess <b>134</b> | benzene                         | 88        | LiAlH <sub>4</sub>            | 62        | 136  |
| H              | Bu <sup>t</sup> | H              | 1        | 1        | Et <sub>3</sub> N | toluene                         | 63        | LiAlH <sub>4</sub>            | 80        | 181  |
| H              | OBn             | H              | 0        | 2        | Et <sub>3</sub> N | THF                             | 60        | LiAlH <sub>4</sub>            | 77        | 182  |
| Me             | H               | H              | 0        | 2        | —                 | —                               | —         | LiAlH <sub>4</sub>            | —         | 180  |
| F              | H               | F              | 0        | 1        | Py                | CH <sub>2</sub> Cl <sub>2</sub> | 40        | B <sub>2</sub> H <sub>6</sub> | 92        | 183  |



135a,b

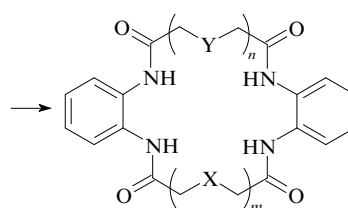
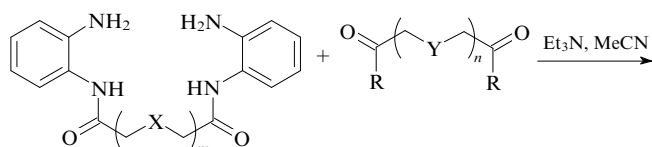
$R^1 = \text{Me}$ ,  $R^2 = \text{H}$  (a);  $R^1 = \text{H}$ ,  $R^2 = \text{OBn}$  (b).

*N,N'*-Dicarboxymethyldibenzotetraazacrown compounds **137** have been obtained from diamines and ethylenediaminetetraacetic acid dianhydride in dioxane.<sup>184</sup>



$n = 1$  (55%),  $2$  (42%).

Macrocyclic 18–24-membered dibenzotetraaza- (**138a**) and dibenzopolyazatetralactams (**138b**) are formed in the reaction of diamines with derivatives of dicarboxylic acids under the action of triethylamine. The reaction occurs in highly diluted solution in the case of oxygen-containing compounds **138a** ( $X = Y = \text{O}$ ) and without dilution in the case of polyazacrown compounds **138b** ( $X = \text{NBoc}$ ,  $\text{NCbz}$ ;  $Y = \text{NBoc}$ ).<sup>144</sup>

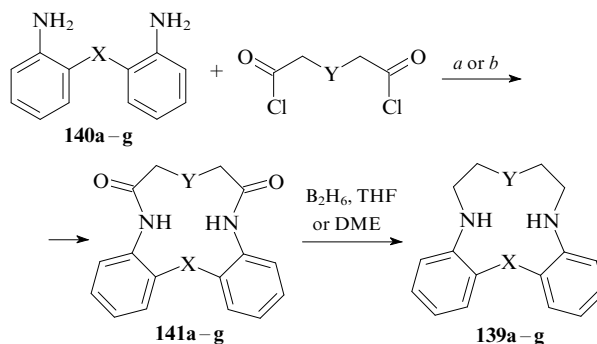


138a (63%–72%); 138b (30%–35%)

$n = m = 1, 2$ ;  $X = Y = \text{O}$ ;  $R = \text{Cl}$  (a);  
 $n = 2$ ;  $m = 1, 2$ ;  $X = \text{NBoc}$ ;  $Y = \text{NBoc}$ ,  $\text{NCbz}$ ;  $R = \text{PivO}$  (b);  
 Boc is *tert*-butoxycarbonyl, Cbz is benzyloxycarbonyl,  
 Piv is *tert*-butylcarbonyl

A series of 15- and 18-membered dibenzodiazacrown (**139a,b**) and dibenzodithiadiazacrown compounds (**139c–e**) (Table 7), containing one or two O, S or N atoms in the macroheterocycle in addition to the two N atoms, have been synthesised from diamines **140a–e** and dichlorides of dibasic acids (glutaric, diglycolic, thiodiglycolic and *N*-tosyliminodiacetic). Pyridine was used as the base and the condensation was carried out in a highly diluted benzene solution. The subsequent reduction of the carbonyl groups in the resulting diamides **141a–e** was performed by treatment with a solution of borane in THF or dimethoxyethane.<sup>185–193</sup>

Amides **141e** were prepared by condensation in dichloromethane in the presence of KF and catalytic amounts of  $\text{Bu}_4\text{NHSO}_4$ .<sup>194</sup> An attempt to reduce amides **141a–c** with lithium tetrahydroaluminate was successful only for **141a** with  $Y = \text{CH}_2$  (yield 77%).<sup>185</sup> The tosyl group in compounds **139b** ( $Z = \text{NTs}$ ;  $Y = \text{CH}_2$ , O, NTs) was removed by treatment with an  $\text{AcOH}-\text{HBr}-\text{PhOH}$  mixture (yields up to 60%), whereas in compound **139b** ( $Z = \text{O}$ ,  $Y = \text{NTs}$ ), the removal took place only on treatment with sodium in boiling *n*-butanol (yield 67%).<sup>186</sup>



(a) Py, PhH; (b) KF,  $\text{Bu}_4\text{N}^+\text{HSO}_4^-$ ,  $\text{CH}_2\text{Cl}_2$ .

A number of 16–18-membered dibenzodiazacrown compounds **139f**, containing polymethylene chains (3 to 5 units) and additional donor atoms (O, S and N) in the macrocycles, have been synthesised by acylation of the corresponding diamines with

**Table 7.** Synthesis of dibenzodithiadiazacrown compounds **139**.

| Compounds<br><b>139–141</b> | X                                                                                   | $n$ | Y                         | Reaction<br>conditions | Yield (%)  |            | Ref.     |
|-----------------------------|-------------------------------------------------------------------------------------|-----|---------------------------|------------------------|------------|------------|----------|
|                             |                                                                                     |     |                           |                        | <b>141</b> | <b>139</b> |          |
| <b>a</b>                    | $\text{OCH}_2\text{CH}_2\text{O}$                                                   | —   | $\text{CH}_2$ , O, S, NTs | <i>a</i>               | 50–87      | 75–84      | 185, 192 |
| <b>b</b>                    | $\text{O}(\text{CH}_2)_2\text{Z}(\text{CH}_2)_2\text{O}$ ; $Z = \text{O}$ , S, NTs  | —   | $\text{CH}_2$ , O, S, NTs | <i>a</i>               | 28–96      | 38–95      | 186–188  |
| <b>c</b>                    | $\text{SCH}_2\text{CH}_2\text{S}$                                                   | —   | $\text{CH}_2$ , O, S      | <i>a</i>               | 70–90      | 78–95      | 185      |
| <b>d</b>                    | $\text{S}(\text{CH}_2)_2\text{Z}(\text{CH}_2)_2\text{S}$ ; $Z = \text{CH}_2$ , O, S | —   | $\text{CH}_2$ , O, S, NTs | <i>a</i>               | 19–90      | 44–88      | 189–191  |
| <b>e</b>                    | $\text{SCH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2\text{S}$                        | 1–3 | S                         | <i>b</i>               | 68–80      | —          | 194      |
| <b>f</b>                    | $\text{O}(\text{CH}_2)_n\text{O}$                                                   | 3–5 | $\text{CH}_2$ , O, S, NTs | <i>a</i>               | 20–92      | 28–85      | 186, 195 |
| <b>g</b>                    | $\text{OCH}_2\text{CH}(\text{OAc})\text{CH}_2\text{O}^a$                            | —   | $\text{CH}_2$ , O, S, NTs | <i>a</i>               | 18–95      | 41–95      | 196      |

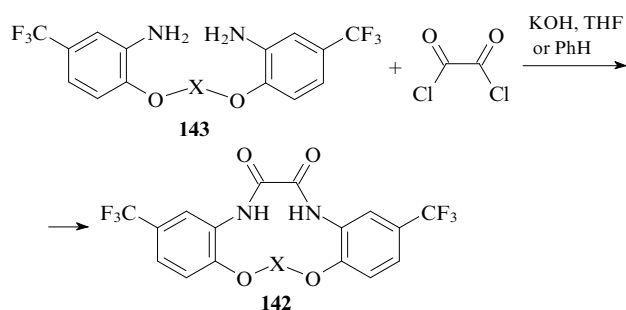
<sup>a</sup> For compound **139g**,  $X = \text{OCH}_2\text{CH}(\text{OH})\text{CH}_2\text{O}$ .

dicarboxylic acid dichlorides under similar conditions (see Table 7).<sup>186, 195</sup> The tosyl group from **139f** ( $n = 5$ ;  $Y = \text{NTs}$ ) was removed by treatment with an  $\text{AcOH-HBr-PhOH}$  mixture (yield 71%).

The macrocyclic 15-membered compounds **139a,c** and 16–20-membered compounds **139b** ( $Z = \text{O}$ , NTs;  $Y = \text{CH}_2$ , O, NTs), **139f** ( $n = 3-5$ ;  $Y = \text{S}$ ;  $n = 5$ ;  $Y = \text{CH}_2$ , O, NTs) and **139e** were used in experiments on extraction and membrane transport of heavy and transition metal ions.<sup>192–194, 197–199</sup>

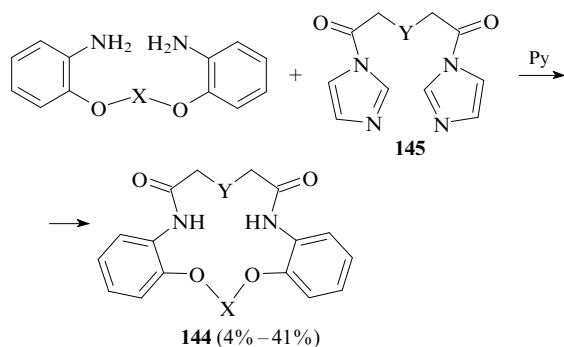
The acylation of acetoxy-substituted aromatic diamine **140g** with glutaric, diglycolic, thiodiglycolic and *N*-tosyliminodiacetic acid dichlorides in the presence of pyridine in benzene gave 16-membered acetoxy-substituted crown lactams (see Table 7). The reduction of these products with diborane in dimethoxyethane to give macrocyclic diamines **139g** is accompanied by elimination of the acetyl group.<sup>196</sup> On attempted reduction in THF, only extremely stable complexes of compounds **139g** with the solvent and, perhaps, with boron hydride were isolated.

Macrocyclic diamides **142**, containing trifluoromethyl groups, have been prepared by acylation of diamines **143** with oxalyl chlorides.<sup>200</sup>



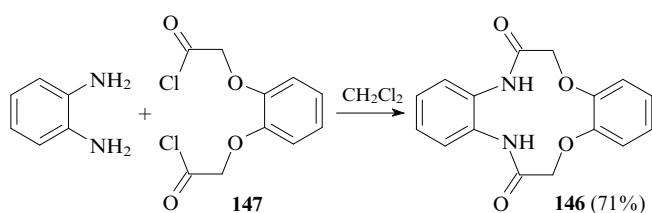
$X = \text{CH}_2\text{CH}_2$  (50%),  $(\text{CH}_2)_2\text{S}(\text{CH}_2)_2$  (79%).

In the synthesis of compounds **144**, diimidazolides **145** were used as acylating agents.<sup>178</sup> The reaction takes place on heating of the reactants in pyridine, but the product yields are relatively low.

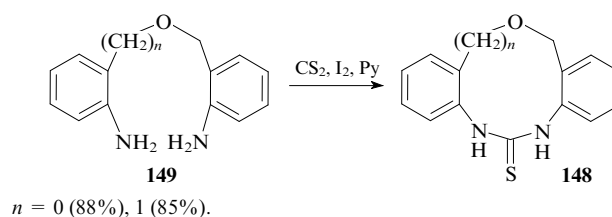


$X = (\text{CH}_2)_3$ ,  $\text{CH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2$  ( $n = 1, 2$ );  $Y = \text{O}$ , S, NMe.

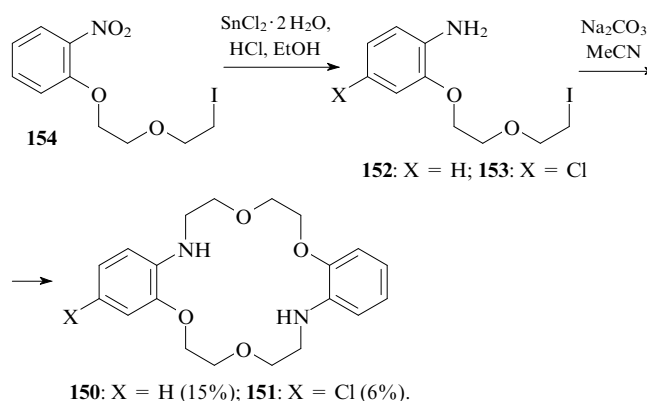
*o*-Phenylenediamine diamide **146** has been prepared by condensation of *o*-phenylenediamine with dichloride **147** at room temperature.<sup>201</sup>



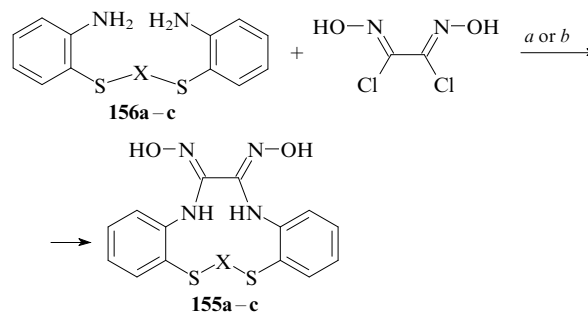
Macrocyclic derivatives of *N,N'*-diphenylthiourea **148** were obtained by the reaction of bis(anilines) **149** with carbon disulfide in pyridine in the presence of iodine as the catalyst.<sup>173</sup>



Dibenzodiazia-18-crown-6 ether **150** and its chloro derivative **151** are formed upon intramolecular alkylation of aromatic amines **152** and **153** in the presence of sodium carbonate.<sup>202</sup> Amines **152**, **153** were formed in a 10:1 ratio upon the reduction of nitro compound **154**. Due to their low stability, they were not separated but used in the condensation as a mixture. The yields of products **150** and **151** are given in relation to the starting nitro compound **154**.



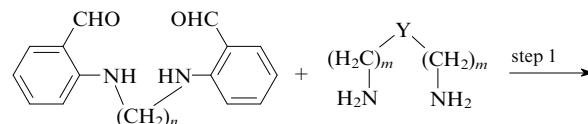
Dibenzodithiadiazacrown dioximes **155a,b** were synthesised from diamines **156a,b** and oxalylidihydroxymoyl chloride in an aqueous solution of sodium carbonate at low temperature.<sup>203, 204</sup> Dibenzodithiadiazia-12-crown-4 tetraoxime **155c** was prepared from dioxime **156c** in ethanol in the presence of sodium hydrogen carbonate.<sup>205</sup>

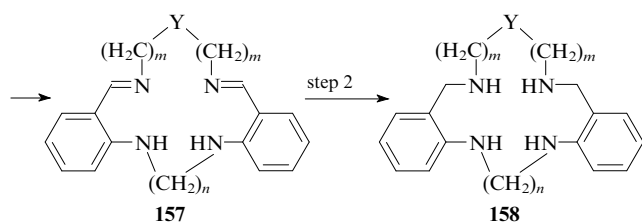


$X = \text{CH}_2\text{CH}_2$  (**a**, 27%),  $\text{CH}_2(\text{CH}_2\text{OCH}_2)_3\text{CH}_2$  (**b**, 63%);  
 $\text{C}(=\text{NOH})\text{C}(=\text{NOH})$  (**c**, 65%);  
 (a)  $\text{Na}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ ; (b)  $\text{NaHCO}_3$ ,  $\text{EtOH}$ .

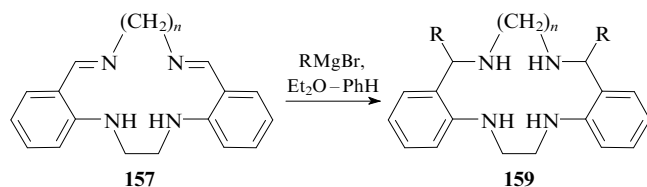
The macrocyclic diimines obtained by condensation of aliphatic diamines with the corresponding dialdehydes are important precursors of dibenzotetraazacrown compounds.<sup>206, 207</sup>

The reduction of diimines **157** yields dibenzotetraazacrown compounds **158** (Table 8).<sup>207–209</sup> Schiff's bases **157** ( $Y = \text{O}$ , S, NH) were synthesised in the presence of *p*-toluenesulfonic acid, which served as the catalyst.<sup>207</sup>



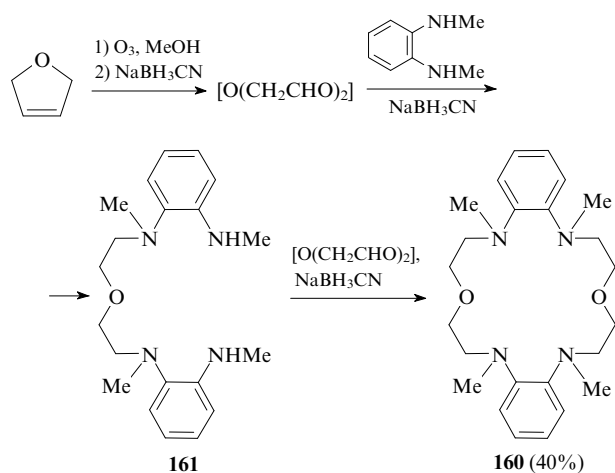


The reactions of diimines **157** ( $n = 2$ ;  $m = 1, 2$ ; Y is none or  $\text{CH}_2$ ) with Grignard reagents have produced tetraazacrown compounds with alkyl substituents in the macrocycle **159**.<sup>208, 210</sup>

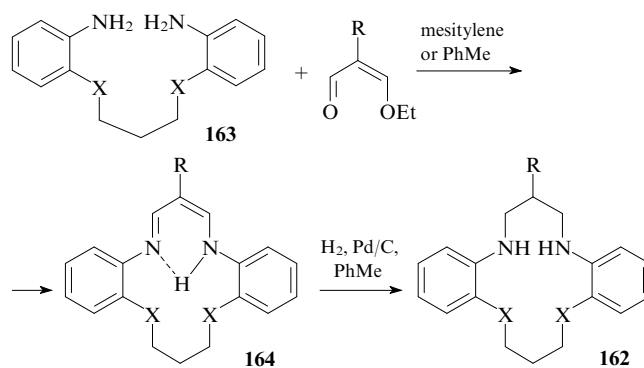


$n = 2-5$ , R = Et (87%–94%);  $n = 3$ , R = Pr<sup>n</sup> (80%), Bu<sup>n</sup> (71%).

An unusual procedure has been developed for the synthesis of symmetric dibenzotetraazacrown compounds **160**.<sup>211</sup> Dihydrofuran was used as the reagent; first, it was ozonised and then reduced with sodium cyanoborohydride to dialdehyde. The product was used, without isolation, in the reductive alkylation of *N,N'*-dimethyl-*o*-phenylenediamine. The resulting diamine **161** was converted into dibenzotetraazacrown compound **160** using a similar reaction sequence. The yield of product **160** is given in relation to *N,N'*-dimethyl-*o*-phenylenediamine.

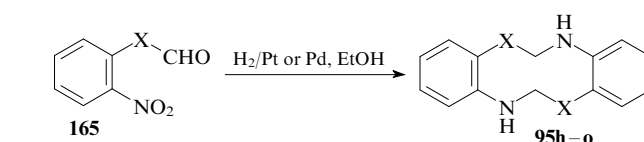


Dibenzodiaza- and tetraazacrown compounds **162** were prepared from diamines **163** and 2-alkyl-3-ethoxyacroleins.<sup>208, 212, 213</sup> The condensation products **164** thus formed, which contain C=C and C=N double bonds, were reduced with hydrogen over a Pd catalyst.<sup>208, 212</sup>



| X  | R  | Yield (%) |     |
|----|----|-----------|-----|
|    |    | 164       | 162 |
| O  | H  | 37        | 86  |
| O  | Me | 26–41     | 84  |
| NH | Me | 40        | 57  |

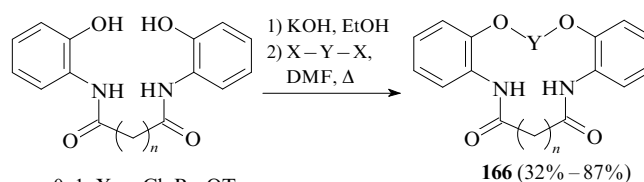
Hydrogenation of aldehydes **165** containing an *o*-nitrophenylene substituent has yielded a series of 16-, 18- and 20-membered dibenzodiazaacrown compounds **95h–o**.<sup>153</sup> It is noteworthy that no formation of monomers (benzoazacrown compounds) was observed in the synthesis of 18- and 20-membered macrocycles **95h,j–m,o** (see Section VI.3, the synthesis of compounds **94a–g**).



| Compounds <b>95</b>   | X                                                | Catalyst | Yield (%) |
|-----------------------|--------------------------------------------------|----------|-----------|
| <b>h</b>              | $\text{O}(\text{CH}_2)_2\text{CHMe}$             | Pd       | 30        |
| <b>i</b> <sup>a</sup> | $\text{O}(\text{CH}_2)_3$                        | Pd       | 8         |
| <b>j</b>              | $\text{O}(\text{CH}_2)_4$                        | Pd       | 64        |
|                       | $\text{O}(\text{CH}_2)_4$                        | Pt       | 75        |
| <b>k</b>              | $\text{O}(\text{CH}_2)_3\text{CHMe}$             | Pd       | 62        |
| <b>l</b>              | $\text{CH}_2\text{O}(\text{CH}_2)_3$             | Pd       | 23        |
| <b>m</b>              | $\text{O}(\text{CH}_2)_2\text{OCHMe}$            | Pd       | 58        |
|                       | $\text{O}(\text{CH}_2)_2\text{OCHMe}$            | Pt       | 47        |
| <b>n</b> <sup>b</sup> | $\text{O}(\text{CH}_2)_5$                        | Pd       | 20        |
| <b>o</b>              | $\text{O}(\text{CH}_2)_2\text{OCH}_2\text{CHMe}$ | Pd       | 37        |

<sup>a</sup> The major product is monomer **94i** (35%); <sup>b</sup> Monomer **94n** (7%) was also formed.

Thirteen- to sixteen-membered diamines **166** have been prepared from bis(phenols).<sup>214</sup> First, bis(phenols) were treated with an ethanolic solution of potassium hydroxide and the resulting phenolates were made to react with dihalides or ditoluenesulfonates on heating in DMF.



$n = 0, 1$ ; X = Cl, Br, OTs;

Y =  $(\text{CH}_2)_m$ ,  $m = 2-5$ ;  $\text{CH}_2\text{C}(\text{=CH}_2)\text{CH}_2$ ;  $(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$ .

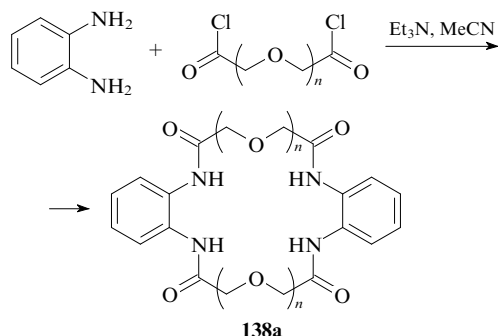
**Table 8.** Synthesis of dibenzotetraazacrown compounds **158**.

| $n$ | $m$ | Y                     | Step 1               |           | Step 2                                          |           |
|-----|-----|-----------------------|----------------------|-----------|-------------------------------------------------|-----------|
|     |     |                       | conditions           | yield (%) | conditions                                      | yield (%) |
| 2   | 1   | $(\text{CH}_2)_{0-2}$ | EtOH                 | 86–94     | $\text{NaBH}_4$ , EtOH                          | —         |
| 2   | 2   | O, S, NH              | <i>p</i> -TsOH, EtOH | 71–96     | $\text{LiAlH}_4$ , THF or $\text{Et}_2\text{O}$ | 20–58     |
| 3   | 3   | NH                    | <i>p</i> -TsOH, EtOH | 62        | $\text{LiAlH}_4$ , THF                          | 59        |

#### b. Condensation of four fragments

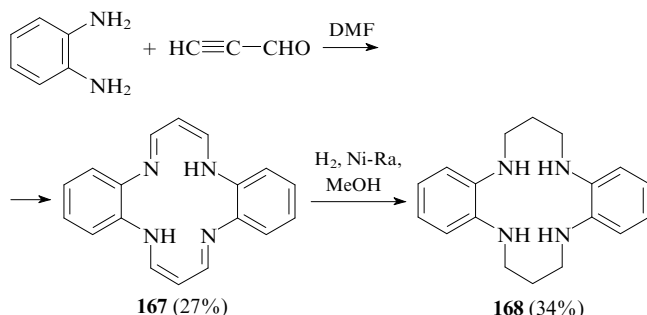
Macrocyclic dibenzotetramides **138a** are formed as side products (yields < 5%) in the reaction of *o*-phenylenediamine with di- and triglycolic acid chlorides in the presence of triethylamine under high dilution conditions in MeCN.<sup>144</sup> The reaction gave benzodi-

lactam monomers (yield 30% for benzodilactam **74** with  $n = 1$ , see Section VI.1) or oligomers as the major products.

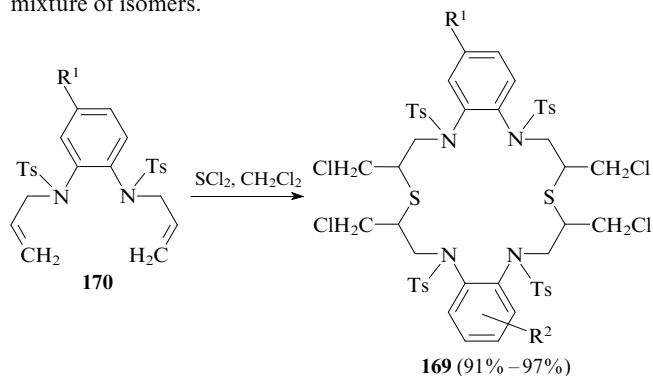


$n = 1, 2$ .

Tetraaza[14]annulene **167** has been prepared by the condensation of *o*-phenylenediamine with propionaldehyde; the catalytic reduction of this product with hydrogen in the presence of Raney nickel gives dibenzocyclam **168**.<sup>215</sup>



Dibenzodithiatetraazacrown compounds **169** were obtained in high yields by treatment of *N,N'*-diallyl-*N,N'*-ditosyl-*o*-phenylenediamines **170** with sulfur(II) chloride.<sup>216</sup> In the case of substituted *o*-phenylenediamine **170** ( $R^1 = \text{Me}$ ), this reaction gives a mixture of isomers.



$R^1 = R^2 = \text{H}$ ;  $R^1 = \text{Me}$ ;  $R^2 = 4\text{-Me}, 5\text{-Me}$ .

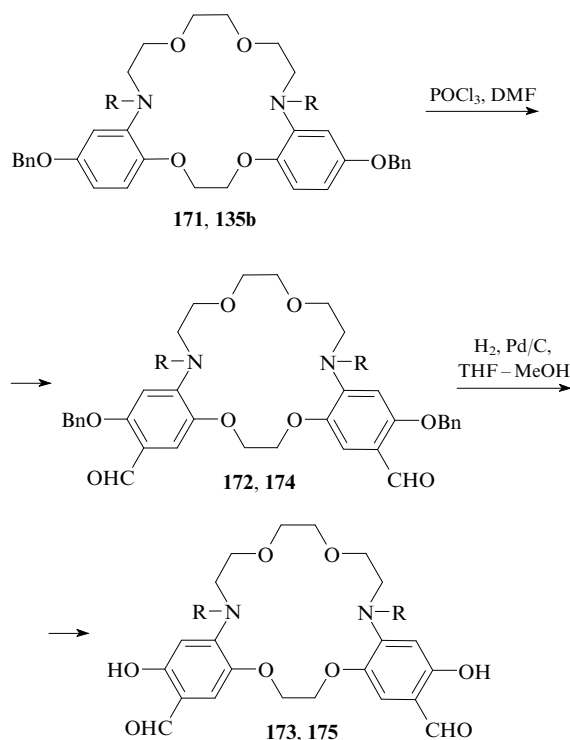
## IX. Functional derivatives of dibenzoazacrown compounds

### 1. Dibenzoazacrown derivatives at the benzene ring

The number of functional derivatives of dibenzoazacrown compounds at the benzene ring reported in the literature is relatively small. These compounds were mainly prepared during the dibenzoazacrown ring construction by condensation of reactants already containing the required substituents (see Section VIII.2). Some examples of the synthesis of functional derivatives of dibenzoazacrown compounds by electrophilic aromatic substitution have been reported.

For example, formylation of dibenzodiazacrown compound **171** by the Vilsmeier reagent gave dialdehyde **172** (yield 77%). The

removal of the benzyl protective groups in the aryl substituents by hydrogenolysis gave rise to the desired product **173** (yield 97%).<sup>182</sup>



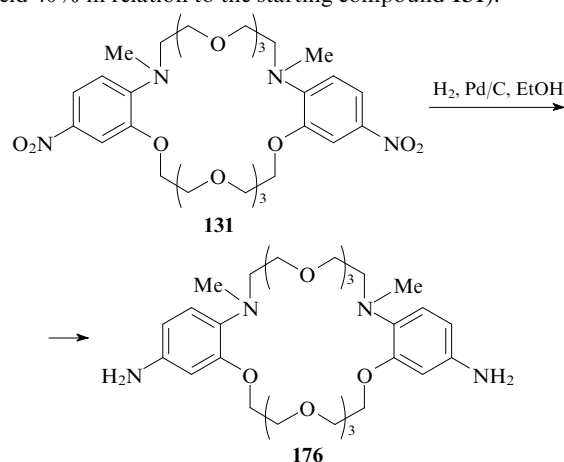
$R = \text{CH}_2\text{CO}_2\text{Me}$  (**171**, **172**, **173**);

$R-R = \text{CH}_2(\text{CH}_2\text{OCH}_2)_2\text{CH}_2$  (**135b**, **174**, **175**).

A similar formylation of benzoannulated cryptand **135b**, followed by reductive elimination of the benzyl groups in compound **174**, resulted in the formation of compound **175** in an overall yield of 71%.<sup>182</sup> Macrocycles **173** and **175** were used to prepare crown-containing coumarins, which are fluorescent reagents for alkali and alkaline earth metal ions.

Dibenzodiazacrown compounds easily enter into azo coupling with *p*-nitrophenyldiazonium chloride.<sup>169</sup>

Reduction of the dinitro derivative of *N,N'*-dimethyldibenzo-diaza-30-crown-10 compound **131** with hydrogen over a palladium catalyst gave diamine **176**. This product reacts with methyl isothiocyanate to give a crown-containing thiourea derivative (yield 40% in relation to the starting compound **131**).<sup>179</sup>

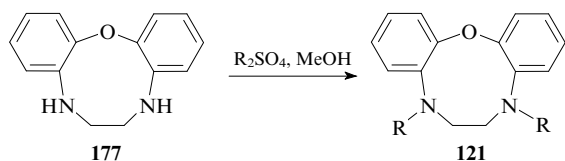


### 2. Derivatives of dibenzoazacrown compounds at the macrocycle nitrogen atom

*N*-Substituted dibenzoazacrown compounds are often formed upon cyclisation or condensation of fragments (see Section

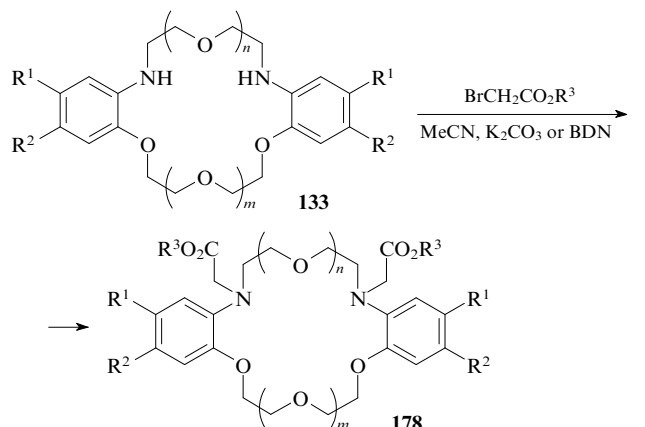
VIII.2). In addition, these compounds can be obtained by direct alkylation of pre-formed macrocycles; however, only a few such examples are known.

The reaction of compound **177** with dialkyl sulfate in methanol gave *N,N'*-dialkyl derivatives **121**.<sup>175</sup>



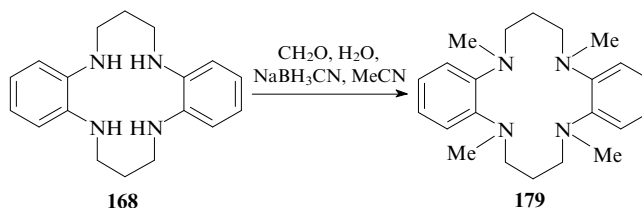
R = Me (56%), Et (62%).

Derivatives **178** have been prepared in a similar way.<sup>181–183</sup> Alkylation of dibenzodiazacrown compounds **133** with ethyl or methyl bromoacetate proceeds in the presence of potassium carbonate or 1,8-bis(dimethylamino)naphthalene (BDN). Compound **178** ( $n = m = 1$ ) has been used as an extractant for  $\text{Pb}^{2+}$  ions and in  $\text{Pb}^{2+}$  transport through plasticised membranes based on cellulose triacetate.<sup>181</sup>



| R <sup>1</sup> | R <sup>2</sup> | R <sup>3</sup> | m | n | Yield (%) |
|----------------|----------------|----------------|---|---|-----------|
| H              | H              | Et             | 1 | 1 | 71        |
| H              | F              | Et             | 0 | 2 | 54        |
| OBn            | H              | Me             | 0 | 2 | 91        |

The reductive alkylation of dibenzocyclam **168** with an aqueous solution of formaldehyde and sodium cyanoborohydride in acetonitrile yielded the tetramethyl derivative of dibenzocyclam **179**.<sup>217</sup>



## X. Conclusion

The data presented in the review were classified according to the chemical type of the synthesised structures. To sum up, it is pertinent to present a brief systematisation of the data in terms of the synthetic methods used, as shown in Table 9. It can be seen that, despite the diversity of approaches, [1 + 1]-condensation of two acyclic fragments still remains the key route to azacrown compounds. Nucleophilic aromatic substitution is widely used to prepare *N*-phenylaza- and *N,N'*-diphenyldiazacrown compounds, which is attributable to the ready availability of the starting compounds. The other methods for the synthesis of azacrown compounds are encountered much more rarely in relevant publications. Meanwhile, more and more publications deal with the synthesis of such compounds by C–N cross-coupling. Of the most recent publications on this topic, of special interest in our opinion are the studies on the synthesis of benzo-diazacrown compounds started not long ago.<sup>151</sup>

It should also be noted that the synthesis of functional derivatives of *N*-phenylaza- and *N,N'*-diphenyldiazacrown compounds is documented rather extensively. The number of known derivatives of annelated azacrown ethers is much smaller. The chemistry of benzoazacrown compounds has been poorly developed until recently because the synthesis of these compounds by condensation of two fragments is complicated and the podands needed for intramolecular condensation are difficult to obtain. We proposed a new methodology for the synthesis of functional derivatives of benzoazacrown ethers by the stepwise

**Table 9.** Brief characteristics of the main methods of synthesis of azacrown compounds (as presented in this review).

| Reaction type                                   | Desired products                          | Features of the method                               | Range of yields (%) | Number of references |
|-------------------------------------------------|-------------------------------------------|------------------------------------------------------|---------------------|----------------------|
| [1 + 1]-Condensation                            | <i>N</i> -phenylazacrown compounds        | relatively cheap                                     | 6–70                | 36                   |
|                                                 | <i>N,N'</i> -diphenyldiazacrown compounds | the same                                             | 11–85               | 13                   |
|                                                 | benzoazacrown compounds                   | "                                                    | 5–95                | 15                   |
|                                                 | dibenzoazacrown compounds                 | "                                                    | 1–95                | 47                   |
| Nucleophilic aromatic substitution              | <i>N</i> -phenylazacrown compounds        | the use of commercially available azacrown compounds | 12–95               | 13                   |
|                                                 | <i>N,N'</i> -diphenyldiazacrown compounds | the same                                             | 23–92               | 6                    |
|                                                 | benzoazacrown compounds                   | poor availability of the starting compounds          | 63                  | 1                    |
| Cross-coupling                                  | <i>N</i> -phenylazacrown compounds        | high cost of reagents and catalysts                  | 4–91                | 4                    |
|                                                 | <i>N,N'</i> -diphenyldiazacrown compounds | the same                                             | 70                  | 1                    |
|                                                 | benzoazacrown compounds                   | "                                                    | 10–47               | 1                    |
|                                                 | benzoazacrown compounds                   | poor availability of the starting podands            | 7–75                | 2                    |
| Intramolecular cyclisation of podands           | dibenzoazacrown compounds                 | the same                                             | 12–65               | 2                    |
|                                                 | benzoazacrown compounds                   | the use of commercially available benzocrown ethers  | 36–80               | 10                   |
| Macrocycle transformation in benzo-crown ethers | benzoazacrown compounds                   | the use of commercially available benzocrown ethers  | 36–80               | 10                   |
| [2 + 2]-Condensation                            | dibenzoazacrown compounds                 | applicable only in particular cases                  | 5–97                | 3                    |
|                                                 | <i>N,N'</i> -diphenyldiazacrown compounds | —                                                    | 21–80               | 3                    |
| Other methods                                   |                                           |                                                      |                     |                      |

transformation of readily available oxygen-containing analogues, which appears a promising alternative to the existing approaches.

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# Magnetic nanoparticles: preparation, structure and properties

S P Gubin, Yu A Koksharov, G B Khomutov, G Yu Yurkov

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**Abstract.** The key methods for the preparation of magnetic nanoparticles are described systematically. The experimental data on their properties are analysed and generalised. The main theoretical views on the magnetism of nanoparticles are considered. The bibliography includes 416 references.

## I. Introduction

In the last two decades, new terms with the prefix ‘nano’ have rushed into the scientific vocabulary — nanoparticle, nanostructure, nanotechnology, nanomaterial, nanocluster, nanochemistry, nanocolloids, nanoreactor and so on. A series of new journals are devoted particularly to this subject, monographs with the corresponding names have appeared, ‘nano’-specialised institutes, chairs and laboratories have been founded; and numerous conferences are held. In most cases, new names were applied to long known objects or phenomena; however, new objects inaccessible for researchers some 20 years ago have also appeared. These include fullerenes, quantum dots, nanotubes, nanofilms and nanowires, *i.e.*, the objects with at least one nanometer ( $10^{-7}$ – $10^{-9}$  m) dimension.

The enhanced interest of the researchers in nanoobjects is due to the discovery of unusual physical and chemical properties of these objects, which is related to manifestation of so-called ‘quantum size effects.’ These arise in the case where the size of

the system is commensurable with the de-Broglie wavelengths of the electrons, phonons or excitons propagating in them.

A key reason for the change in the physical and chemical properties of small particles as their size decreases is the increased fraction of the ‘surface’ atoms, which occur under conditions (coordination number, symmetry of the local environment, *etc.*) differing from those of the bulk atoms. From the energy standpoint, a decrease in the particle size results in an increase in the fraction of the surface energy in its chemical potential.

Currently, unique physical properties of nanoparticles are under intensive research.<sup>†</sup> A special place belongs to the magnetic properties in which the difference between a massive (bulk) material and a nanomaterial is especially pronounced. In particular, it was shown that magnetisation (per atom) and the magnetic anisotropy of nanoparticles can be much greater than those of a bulk specimen, while differences in the Curie ( $T_C$ ) or Neel ( $T_N$ ) temperatures, *i.e.*, the temperatures of spontaneous parallel or antiparallel orientation of spins, between nanoparticle and the corresponding microscopic phases reach hundreds of degrees. In addition, magnetic nanomaterials were found to possess a number of unusual properties — giant magnetoresistance, abnormally high magnetocaloric effect, and so on.

The magnetic properties of nanoparticles are determined by many factors, the key of these including the chemical composition, the type and the degree of defectiveness of the crystal lattice, the particle size and shape, the morphology (for structurally inhomogeneous particles<sup>†</sup>), the interaction of the particle with the surrounding matrix and the neighbouring particles. By changing the nanoparticle size, shape, composition and structure, one can control to an extent the magnetic characteristics of the material based on them. However, these factors cannot always be controlled during the synthesis of nanoparticles nearly equal in size and chemical composition; therefore, the properties of nanomaterials of the same type can be markedly different.

**S P Gubin, G Yu Yurkov** N S Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, Leninsky prosp. 31, 119991 Moscow, Russian Federation. Fax (7-095) 954 12 79, tel. (7-095) 954 71 36, e-mail: gubin@igic.ras.ru (S P Gubin), gy\_yurkov@mail.ru (G Yu Yurkov)

**Yu A Koksharov, G B Khomutov** Department of Physics, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax (7-095) 932 88 20, tel. (7-095) 939 29 73, e-mail: yua\_koksharov@rambler.ru (Yu A Koksharov), tel. (7-095) 939 30 25, e-mail: gbk@mail.ru (G B Khomutov)

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<sup>†</sup>Almost all particles are inhomogeneous because the properties of the surface and the interior of the particle are inevitably dissimilar. It can be stated with confidence that any nanoparticle has a ‘shell’ but not all of them have a clear-cut ‘core’.

The last years have seen changes in the development of magnetic nanomaterials, which can be called revolutionary, to say the least. This is related both to the development of efficient methods for the preparation and stabilisation of nano-sized magnetic particles and to the progress in the physical methods for the investigation of such particles. For example, it became possible to prepare nanometre metal or oxide particles as not only ferromagnetic fluids (the preparation process was developed back in the 1960s)<sup>2,3</sup> but also as particles included into 'rigid' matrices (polymers, zeolites, *etc.*).

The magnetic characteristics of a material consisting of a non-magnetic solid dielectric matrix with magnetic nanoparticles (3–10 nm) distributed in the matrix were described in 1980.<sup>4</sup> The presence of nanoparticles<sup>‡</sup> in these materials and their composition were established by small-angle X-ray scattering and Mössbauer spectroscopy.<sup>5</sup> More recently, these samples were investigated once again by modern methods, which largely confirmed the earlier results.<sup>6</sup>

Magnetic nanoparticles are abundant in nature and are found in many biological objects.<sup>7</sup> Magnetic nanomaterials are used in information recording and storage systems, in new permanent magnets, in magnetic cooling systems, as magnetic sensors, *etc.* All this accounts for the interest of various specialists in these systems.

Extensive literature is devoted to the applied aspects of the state-of-the-art technology of magnetic recording and its prospects.<sup>8</sup> Currently, powders with micron-size  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>, Co- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>, Fe or Fe-Co grains are used most often in magnetic tapes or discs as media for magnetic recording. In this case, recording of one bit requires about 10<sup>9</sup> atoms,<sup>9</sup> whereas with the use of nanomaterials (particles 10 nm in diameter), not more than 10<sup>5</sup> atoms. Thus, transition to magnetic nanomaterials increases the information recording density by a factor of 10<sup>3</sup>–10<sup>4</sup>.

Among the magnetic materials that have found broad practical application in technology, ferromagnets deserve attention. An important characteristic of a ferromagnet is the coercive force ( $H_c$ ), *i.e.*, the magnetic field strength  $H$  corresponding to the point with  $B = 0$  on the symmetric hysteresis loop  $B(H)$  of the ferromagnet. Here  $B$  is the magnetic field induction in a ferromagnetic sample with zero demagnetising factor (for example, in a long cylinder whose axis is directed along the field). One more characteristic, apart from  $H_c$ , is the intrinsic coercive force ( $H_{ci}$ ), defined as the magnetic field strength at the point  $M = 0$  on the symmetric  $M(H)$  hysteresis loop of the ferromagnet, where  $M$  is the magnetisation of a ferromagnetic sample with zero demagnetising factor. The coercive force and the intrinsic coercive force normally do not differ much in magnitude, but these are different physical quantities. When designing new magnetic materials, it is often a goal to attain the highest  $H_c$ . Modern magnetic materials have  $H_c = 2$ –3 kOe (see Section IX).

In terms of the coercive force, ferromagnets are subdivided into soft magnetic ( $H_c < 12.6$  Oe) and hard magnetic ( $H_c > 126$  Oe) ones. The magnets with intermediate coercive force values are referred to as semi-hard. Table 1 presents data on the dependence of the magnetic properties of ferromagnets on the dimensions of the constituent particles. Apart from the dimensions, the magnetic properties of particles depend on the external conditions: temperature, pressure and, in some cases, the local environment, *i.e.*, the medium in which the particle occurs, in particular, the crystalline or amorphous bulk matrix (for a particle), the local crystal environment (for a single atom) or the substrate (for a film).

In addition to ferromagnets in which the magnetic moments of the atoms are ordered, magnetic spin glasses — systems in which the competition of random magnetic interactions between magnetic moments results in a magnetic disordered state — also find application in technology.

The purpose of this review is to survey the state-of-the-art views on the physics, the chemistry and the methods of preparation and stabilisation of magnetic nanoparticles used in nanotechnology for the design of new instruments and devices.

## II. Nanoparticles and materials based on them (classification, definitions)

First of all, it is necessary to consider the general concepts related to the nano-sized objects.

A nano-object is a physical object differing appreciably in properties from the corresponding bulk material and having at least one nanometre dimension (not more than 100 nm).

Nanotechnology is the technology dealing with both single nano-objects and materials and devices based on them and with processes that take place in the nanometre range.

Nanomaterials are those materials whose key physical characteristics are dictated by the nano-objects they contain. Nanomaterials are classified into compact materials and nanodispersions. The first type includes so-called 'nanostructured' materials,<sup>10</sup> *i.e.*, materials isotropic in the macroscopic composition and consisting of contacting nanometre-sized units as repeating structural elements.<sup>11</sup> Unlike nanostructured materials, nanodispersions include a homogeneous dispersion medium (vacuum, gas, liquid or solid) and nano-sized inclusions dispersed in this medium and isolated from each other. The distance between the nano-objects in these dispersions can vary over broad limits from tens of nanometres to fractions of a nanometre. In the latter case, we are dealing with nanopowders whose grains are separated by thin (often monoatomic) layers of light atoms, which prevent them from agglomeration.

A nanoparticle is a quasi-zero-dimensional (0D) nano-object in which all characteristic linear dimensions are of the same order of magnitude (not more than 100 nm). Nanoparticles can basically differ in their properties from larger particles, for example, from long- and well-known ultradispersed powders<sup>12</sup> with a grain size above 0.5  $\mu$ m. As a rule, nanoparticles are shaped like spheroids. Nanoparticles with a clearly ordered arrangement of atoms (or ions) are called nanocrystallites. Nanoparticles with a clear-cut discontinuity of the system of electronic energy levels are often referred to as 'quantum dots' or 'artificial atoms' (most often, they have compositions of typical semiconductor materials).<sup>13,14</sup>

The term 'cluster', which has been widely used in chemical literature in former years, is currently used to designate small nanoparticles with sizes less than 1 nm. Thus, the term 'nanoclusters'<sup>15</sup> is excessive, because all known clusters have nanometre dimensions.

Nanorods and nanowires are quasi-one-dimensional (1D) nano-objects. In these systems, one dimension exceeds by an order of magnitude the other two dimensions, which are in the nano-range. This class includes, in particular, interesting nanostructures such as 'quantum wires'.<sup>16</sup>

The group of two-dimensional objects (2D) includes planar structures — nanodiscs, thin-film magnetic structures, magnetic nanoparticle layers, *etc.*, in which two dimensions are an order of magnitude greater than the third dimension, which is in the nanometre range.

In this review we use the molecular approach outlined in a previous publication,<sup>17</sup> namely nanoparticles are considered as giant pseudomolecules having a core and a shell and often also external functional groups. The unique magnetic properties are usually inherent in the particles with a core size of 2–30 nm. For magnetic nanoparticles, this value coincides in the order of magnitude with the theoretical estimate for the smallest dimensions of a magnetic domain in most magnetic materials (see Table 1).

‡ In those years, the term 'nanoparticle' did not yet exist and these objects were called 'ligand-free metal clusters' or just 'clusters.'

**Table 1.** Type of the change of the magnetic properties of a ferromagnet with a decrease in the substance dimensions from macroscopic to atomic.

| Object                                                                              | Characteristic size   | Specific magnetic properties                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------------------------------------------------------------------------|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Macroscopic (bulk) sample                                                           | $\geq 1 \mu\text{m}$  | spontaneous magnetisation below $T_C$ . The appearance of a nonzero magnetic moment is suppressed by the formation of a domain structure                                                                                                                                                                                                                                                                                                                                                |
| Microscopic sample                                                                  | 50–1000 nm            | magnetic characteristics strongly depend on the sample pre-history, preparation and processing method                                                                                                                                                                                                                                                                                                                                                                                   |
| Single-domain magnetic particles (small magnetic particles) in a diamagnetic matrix | 1–30 nm               | the presence of a blocking temperature <sup>a</sup> $T_b < T_C$ below which the magnetic moment of the particle retains orientation in space, while the particle ensemble demonstrates a magnetic hysteresis. At a temperature higher than $T_b$ , the particle transfers into the superparamagnetic state. In the $T_b < T < T_C$ region, the particle has a spontaneous magnetisation and a nonzero total magnetic moment, which easily changes the orientation in the external field |
| Single atom (ion)                                                                   | $\sim 0.2 \text{ nm}$ | usual paramagnetic properties                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

<sup>a</sup> For isolated nanoparticles with sizes 1–30 nm, the temperature scale has one more characteristic point apart from the Curie and Neel temperatures, namely, the ‘blocking’ point  $T_b < T_C(T_N)$ .

### III. Methods for the preparation of magnetic nanoparticles and nanomaterials

If the methods used to prepare nanoparticles are classified in terms of the type of the precursor and the features of its processing, the following key approaches to the formation of nanoparticles can be distinguished:

- preparation from macroscopic materials by dispersion;
- chemical synthesis, *i.e.*, targeted change in the substance composition with termination (in some way) of the nascent phase growth at the nano-size stage;
- transformations of nanoparticles with the change in the composition.

The last-mentioned route has found only a limited use as yet and is represented by a few examples.

A series of general methods for the nanoparticle synthesis have now been developed.<sup>18</sup> Most of them can also be used for the preparation of magnetic particles. An essential feature of their synthesis is the preparation of particles of specified size and shape (at least, the scatter of sizes should be small, 5%–10%, and controllable). The shape control and the possibility of synthesis of anisotropic magnetic structures are especially important. In order to eliminate (or substantially decrease) the interparticle interactions, magnetic nanoparticles often need to be isolated from one another by immobilisation on a substrate surface or in the bulk of a stabilising inert matrix. It is important that the distance between the particles in the matrix should be controllable. Finally, the synthetic procedure should be relatively simple, inexpensive and reproducible.

The development of magnetic materials is often faced with the necessity of preparing nanoparticles of a complex composition, namely, ferrites, complex NdFeB or SmCo<sub>5</sub> alloys, *etc.* In these cases, the range of synthetic approaches substantially narrows down. For example, the thermal evaporation of compounds with a complex elemental composition is often accompanied by a violation of the stoichiometry in the vapour phase, resulting in the formation of other substances, while the atomic beam synthesis does not yield a homogeneous distribution of elements on the substrate. The mechanochemical methods of powder dispersion also violate (in some cases, substantially) the phase composition: in particular, ferrites do not retain the oxygen stoichiometry. Finally, the preparation of a target phase from heteroelement precursors may be associated with the difficulty of synthesis of the precursors. For example, no volatile compounds with a Sm atom bonded to five Co atoms are known; the maximum chemically attainable element ratio in Sm[Co(CO)<sub>4</sub>]<sub>3</sub> is 1 : 3. It is even more difficult to propose a volatile stoichiometric precursor for the synthesis of NdFeB nanoparticles.

The physical characteristics of nanoparticles are known to be substantially dependent on their dimensions. Unfortunately, most of the currently known methods of synthesis afford nanoparticles with rather broad size distributions (dispersion  $\sigma > 10\%$ ). The thorough control of reaction parameters (time, temperature, stirring velocity and concentrations of reactants and stabilising additives) does not always allow one to narrow down this distribution to the required range. Therefore, together with the development of methods for synthesis of nanoparticles with a narrow size distribution, the techniques of separation of nanoparticles into rather monodisperse fractions are perfected. This is done using controlled precipitation of particles from surfactant-stabilised solutions followed by centrifugation (the coarsest fraction is the first to be precipitated). After decantation, the precipitate can again be dissolved and subjected to precipitation/centrifugation. The process is repeated until nanoparticle fractions with specified sizes and dispersion degrees are obtained.

The methods of nanoparticle preparation cannot be detached from stabilisation methods. For 1–10 nm particles with a high surface energy, it is difficult to select a really inert medium,<sup>17</sup> because the surface of each nanoparticle bears the products of its chemical modification, which affect appreciably the nanomaterial properties. This is especially important for magnetic nanoparticles in which the modified surface layer may possess magnetic characteristics markedly differing from those of the particle core. Nevertheless, the general methods for nanoparticle synthesis not related directly to the stabilisation and the methods where the nanoparticle formation is accompanied by stabilisation (in matrices, by encapsulation, *etc.*) will be considered separately.

The methods of generation of magnetic nanoparticles in the gas or solid phase using high-energy treatment of the material are usually called physical, while the nanoparticle syntheses, which are often carried out in solutions at moderate temperatures are chemical methods. The chemical methods for the preparation of magnetic nanoparticles have developed most intensively in recent years; however, physical methods should not yet be considered as outworn.

#### 1. Physical methods for the preparation of magnetic nanoparticles

##### a. Condensation methods

The method of nanoparticle synthesis from supersaturated metal vapours is based on the classical nucleation theory in which the nascent phase clusters are described by the spherical liquid drop model. Nanoparticles (clusters) are prepared using various ways of metal evaporation: laser vaporisation,<sup>19, 20</sup> thermal vaporisation,<sup>21, 22</sup> arc discharge, plasma vaporisation,<sup>23</sup> and solar energy-induced evaporation.<sup>24</sup> In each method, special installations are employed differing in engineering solutions of particular units.<sup>25</sup>

All the methods for metal evaporation listed above allow one to study both the physicochemical characteristics of nanoparticles in the gas phase (before the metal vapour deposition on the substrate) and the properties of films and powders obtained upon deposition. Since recently, the cryogenic method has been used to prepare nanoparticles. In this case, the condensation of metal atoms and metal compounds occurs at low temperatures in a cryogenic matrix, most often, in a liquid inert gas. This method allows the preparation of chemically highly pure nanoparticles uniform in composition and structure and having no pores or other morphological inhomogeneities.

In the classical thermal vaporisation method, a metal or alloy sample is heated in a tungsten boat in an argon or helium stream. The atoms of the vaporised metal lose kinetic energy upon collisions with inert gas atoms, gather in clusters and condense on a cooled substrate as a nanodispersed powder. By varying the evaporation rate, the substrate temperature and gas pressure and composition, one can control the particle size in the 3–100 nm range. Most often, prior to opening the installation and taking out the sample, nanoparticles are passivated by passing an inert gas/oxygen mixture for several minutes. In particular, this method was used to prepare heterometallic nanoparticles (~30 nm) with the composition Fe–M (M = Ni, Mn, Pt, Cr).<sup>21</sup> For the Fe–Cr system, it was shown that for a Cr content of 47.7 at.%, the metastable  $\sigma$ -phase with a tetragonal lattice detected in the 440–830 °C temperature range in the state diagram of the Fe–Cr alloy predominates in nanoparticles.<sup>21,22</sup>

Individual magnetic nanoparticles were first obtained by the molecular beam method.<sup>26,27</sup> In this case, metal evaporation takes place in vacuum in a diaphragm chamber. The evaporated particles pass through the diaphragm and form the molecular beam. The beam intensity determines the rate of condensation of the particles on the substrate. This method produces largely free (*i.e.*, ligand-free) clusters (nanoparticles); therefore, it can be used to determine the intrinsic magnetic properties of these particles without the distorting influence of the environment and to understand the fundamental grounds of the physics of magnetic clusters. Although unsurpassed in this respect, the molecular beam method has not found practical use for the preparation of magnetic nanomaterials.

The synthesis of nanoparticles by a hydrogen plasma metal reaction (HPMR) has been reported;<sup>28,29</sup> therefore, we do not consider this method here.

The preparation of nanoparticles by metal vapour spraying is a rather well-developed method in both practical and theoretical aspects. With thermal or laser vaporisation, this method allows the synthesis of gram amounts of nanoparticle powders. This method can be used for dispersing metals, alloys or oxides; however, the cost of nanomaterials obtained in this way remains rather high.

The low-energy cluster beam deposition (LECBD) method includes deposition of non-charged particles with a very low kinetic energy on a substrate.<sup>30</sup> In this case, the particles are not destroyed on getting on the substrate and can be inserted into various type of matrices, which are formed simultaneously by vaporisation of their components from another source. The size and composition of the deposited nanoparticles are controlled in the gas phase prior to deposition on the substrate using mass-analysing systems of various types.

#### b. Methods of nanodispersion of a compact material

The mechanochemical dispersion of a compact material in mills of various designs appears an attractive way to produce disperse systems. However, there exists a mechanical dispersion limit for solids,<sup>31,32</sup> which prevents in some cases the preparation of nanosized particles with a narrow dispersion. In addition, high energy impact on the material being ground result in intensive interaction of the nanoparticles formed with the dispersion medium. Some examples of successful use of mechanochemical dispersion for the

preparation of magnetic nanoparticles are given in the following Sections.

Electrolytic erosion can also be used to disperse metals and alloys. In this case, spraying takes place inside a dielectric liquid and the liquid transformation products coat the surface of the nanoparticles formed. Depending on the process conditions, the metal nature, and the dispersion medium, the diameter of the nanoparticles formed is usually in the 2.5–20 nm range, but some particles can be as large as 100 nm.<sup>33</sup> Presumably, small particles are formed on quenching the metal vapour, while large ones are produced from molten drops. Using electrolytic erosion, nanoparticles with a complex composition for permanent magnets have been obtained.<sup>34</sup> However, in this case, too, the nanoparticles formed interact to a noticeable extent with the medium. For example, when organic solvents are used as the dielectric medium, product carbonisation takes place, while in the case of molten sulfur, sulfides are formed.<sup>35</sup>

Electrochemical generation is used as a method for the synthesis of substantial amounts of rather small (1–2 nm) nanoparticles with a narrow dispersion.<sup>36</sup> A standard electrochemical cell containing an alcohol solution of tetraalkylammonium halide was used to obtain cobalt particles. On passing the current, the cobalt anode dissolved to give Co nanoparticles near the cathode (glass carbon). The influence of electrolysis conditions on the magnetic characteristics of the resulting nanoparticles was studied using several examples.

The average size of a particle formed upon electrochemical dispersion is inversely proportional to the current density. The colloid solution of nanoparticles formed upon electrolysis can be stored under argon for several months. Evaporation of the solvent yields crystallites, which can be readily converted again into a colloid suspension.

The electrochemical process was used to obtain  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> nanoparticles (3–8 nm), stable in organic solvents due to adsorption of cationic surfactants.<sup>37</sup>

## 2. Chemical synthesis of magnetic nanoparticles

Chemical methods for the synthesis of nanoparticles have been surveyed in a recent review;<sup>38</sup> therefore, we will mention only the latest publications illustrating the trends in the development of this approach.

Diverse metal-containing compounds (MCC) including metal carbonyls, organometallic compounds, metal carboxylates, *etc.*, are used as the precursors in the synthesis of magnetic nanoparticles. Most often, precursors decompose on heating or UV irradiation; other types of treatment of MCC, resulting in nanoparticles, have also been developed.

#### a. Thermolysis of metal-containing compounds

Thermal decomposition of metal-containing compounds has been studied in detail in relation to the development of the scientific grounds of the metal organic chemical vapour deposition (MOCVD) technique, which is used successfully to obtain nanoparticles. In a one-step CVD synthesis of nanodispersed Fe oxides, [Fe(OBu<sup>t</sup>)<sub>3</sub>]<sub>2</sub> has been proposed as the MCC.<sup>39</sup> When the reaction is carried out in a liquid medium in the presence of surfactants or polymers, it is possible to stabilise the resulting amorphous nanoparticles with diameters of up to 10 nm. An interesting example of two-stage thermolysis of Fe(CO)<sub>5</sub> has been reported.<sup>40</sup> First, an iron oleate complex is formed from Fe(CO)<sub>5</sub> and oleic acid at 100 °C; at 300 °C, the complex decomposes to give primary 'loose' nanoparticles (4–11 nm). After maintaining at 500 °C, these are converted, as shown by powder X-ray diffraction, into crystalline  $\alpha$ -Fe nanoparticles. Laser photolysis of volatile MCC (most often, metal carbonyls) is also suitable for this purpose.<sup>41</sup>

#### b. Decomposition of metal-containing compounds on ultrasonic treatment

In this method, metal carbonyls and their derivatives are used as metal-containing compounds, although cases of successful use of



other organometallic compounds are also known. For example, Co nanoparticles were synthesised by ultrasound-induced decomposition of a solution of  $\text{Co}_2(\text{CO})_8$  in toluene.<sup>42</sup> In order to retain the monodispersity and prevent aggregation of the particles formed, sodium bis(2-ethylhexyl)sulfosuccinate was added to the solution. 'Amorphous' Co-containing nanoparticles were also obtained by ultrasonic treatment of a solution of  $\text{Co}(\text{CO})_3(\text{NO})$  in decane in the presence of oleic acid.

For the synthesis of Fe-containing magnetic nanoparticles,  $\text{Fe}(\text{CO})_5$  is used most often.<sup>43</sup> Ultrasonic decomposition of iron pentacarbonyl in polyvinylpyrrolidone resulted in amorphous  $\gamma\text{-Fe}_2\text{O}_3$  nanoparticles. Their dimensions were determined by the nature and concentration of the surfactants present in the solution.<sup>44</sup> It was shown experimentally that ultrasonic treatment of labile MCC is a convenient way of producing nanoparticles under mild conditions, which is important for the preparation of metastable aggregates. However, there are no methods for controlling their dimensions.

### c. The reduction of metal-containing compounds

Magnetic metallic nanoparticles can be prepared from metal salts using strong reducing agents, namely, alkali metal dispersions in ethers or hydrocarbons, alkali metal complexes with organic electron acceptors (e.g., naphthalene),  $\text{NaBH}_4$  and other complex hydrides. By using  $\text{NaBH}_4$  in aqueous solutions at room temperature, both homo- (Fe, Co, Ni) and heterometallic (Fe–Co, Fe–Cu, Co–Cu) nanoparticles were obtained as amorphous powders containing substantial amounts of boron (20 mass % or more). The reduction of  $\text{CoCl}_2$  with  $\text{LiBH}_4$  in the presence of trialkylphosphines yields nanoparticles of pure cobalt  $\epsilon$ -phase with 2–11 nm size (depending on the alkyl chain length in trialkylphosphine).<sup>45</sup>

The general method for the preparation of metallic nanoparticles by reducing metal salts in aprotic solvents is documented.<sup>46</sup> High-boiling alcohols are often used as reducing agents. The reduction of cobalt acetate with dodecane-1,2-diol at 250 °C in oleic acid in the presence of trioctylphosphine gives 3–8 nm metal particles.<sup>47</sup> nickel-containing nanoparticles have been prepared in a similar way.<sup>48</sup>

Yet another method of synthesis is represented by radiation chemical reduction of metal ions in aqueous solutions. In particular,  $\gamma$ -irradiation of deaerated solutions of  $\text{Co}^{2+}$  and  $\text{Ni}^{2+}$  perchlorates in the presence of sodium formate and a stabiliser (surfactant) affords spherical nanoparticles (2–4 nm) of these metals with a narrow pore size distribution.<sup>49</sup>

### d. Synthesis in reverse micelles

Recent years were marked by intensive development and wide use of the synthesis nanoparticles in nano-sized 'reactors' as the size of 'nanoreactors' can be controlled within certain limits. A micelle is an example of these nanoreactors. Reverse micelles are tiny drops of water stabilised in a hydrophobic liquid phase due to the formation of a surfactant monolayer on their surface. Owing to the exactly measured amount of MCC in each micelle (as the nanoparticle formation occurs without substance supply from the outside), it is possible not only to control the composition and the average size of the particles but also to obtain monodisperse samples with a narrow particle size distribution. Thus Co nanoparticles were synthesised by mixing two colloid solutions of reverse micelles with the same diameter (3 nm), one containing  $\text{CoCl}_2$  and the other containing sodium tetrahydroborate of the same concentration.<sup>50</sup> Magnetic nanoparticles with an average diameter of 5.8 nm and a polydispersity of 11% were obtained in hexane as a colloid dispersion stable against aggregation and oxidation during a week. Syntheses of cobalt nanoparticles in reverse micelles are described in detail in the literature.<sup>51–53</sup>

### e. Sol–gel method

The sol–gel method is widely used in a number of technologies.<sup>54</sup> In nanotechnology, it is used most often to obtain metal oxides

but is also applicable to the synthesis of nanosized metals and fused bimetallic and heteroelement particles. For example, reduction of  $\text{Ni}^{2+}$  and  $\text{Fe}^{2+}$  ions inserted in silica gel in 3 : 1 ratio with hydrogen at 733–923 K resulted in  $\text{Ni}_3\text{Fe}$  nanoparticles (4–19 nm) within the  $\text{SiO}_2$  matrix.<sup>55</sup>

### e. Synthesis of magnetic nanoparticles at a gas–liquid interface

Nanoparticles can also be synthesised in the absence of solid substrates or matrices by redox reactions at an interface between two phases, one containing a metal compound (precursor) and the other, the reducing agent. This method was first implemented by Faraday back in 1857 to prepare a stable colloid solution of gold nanoparticles.<sup>56</sup> A new approach to the synthesis and self-assembly of nano-sized structures including magnetic ones in a fully anisotropic two-dimensional reaction system has been reported.<sup>57–64</sup> Nanoparticles were synthesised in a Langmuir monolayer of amphiphilic molecules,<sup>§</sup> incorporating the precursor molecules at a gas–liquid interface. Decomposition of metal compounds in such a monolayer initiates the appearance and nucleation of active intermediates and the two-dimensional growth of nanoparticles on the liquid surface. The surfactant molecules of the monolayer can react with the nanoparticles formed and affect the growth processes, thus opening the way for effective control of the size and morphology of the structures formed. The growth and self-organisation of nanoparticles can also be affected by changing the chemical composition of the liquid or gas phase, *i.e.*, by adding compounds that react with nanoparticles on the liquid surface, by varying the temperature, by exposing the monolayer to electric or magnetic fields or various types of radiation (including light).

Two-dimensional diffusion and growth of nanoparticles depend on the thermodynamic state of the Langmuir monolayer. This can exist as so-called two-dimensional gas, two-dimensional liquid or a condensed two-dimensional phase (when the molecules are located close to one another). When the monolayer passes into the condensed state, the diffusion controlled processes stop and the system state settles down. This allows one to stop the nanoparticle growth and organisation at the specified moment and then to transfer the monolayer with the resulting nanoparticles and nanostructures on solid substrates and to study the resulting planar nanostructures by various methods.

The decomposition of the precursor molecule at the interface can be induced by electromagnetic radiation (in particular, light). This photochemical decomposition of iron pentacarbonyl in the Langmuir monolayer under contact with air gives nanoparticles and nanostructures of iron oxides, mainly  $\gamma\text{-Fe}_2\text{O}_3$ .<sup>59</sup> An external magnetic field has a substantial influence on the shape of the resulting anisotropic magnetic nanoparticles, their shape and orientation being dependent on the orientation of the applied field with respect to the interface.<sup>59, 60, 62</sup>

The influence of the applied fields on the two-dimensional growth of amorphous iron-containing magnetic nanoparticles by decomposition of iron pentacarbonyl on exposure to UV radiation in a mixed Langmuir monolayer at a gas–water interface with stearic acid as the surfactant has been studied.<sup>57, 58, 60, 62</sup> During the nanoparticle formation, the monolayer existed in the 'gas-like' state (the surface pressure was equal to zero).

The magnetic properties of multilayer Langmuir–Blodgett films containing nanoparticles were studied by EPR, which revealed ferromagnetic resonance signals and superparamagnetism.<sup>60</sup> Studies by scanning tunnelling microscopy (STM), atomic force microscopy (AFM) and transmission (tunnelling) electron microscopy (TEM) have shown that the size and shape of nanoparticles may change substantially during the growth from disc-like to oriented oblong under the action of an external magnetic field directed parallel to the monolayer plane.<sup>59</sup> When the mag-

§ Stearic or arachidic acid or other surfactants are normally used as amphiphilic molecules.

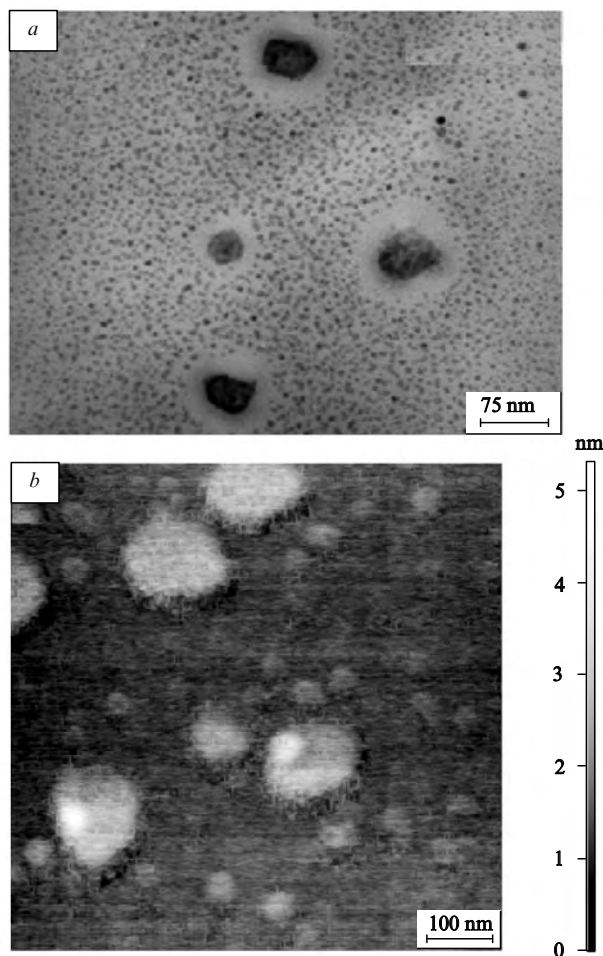


**Figure 1.** TEM (a) and ACM (b) micrographs of iron-containing nanoparticles synthesised in a Langmuir monolayer.<sup>59</sup>

netic field is perpendicular to the monolayer plane, the nanoparticles acquire an anisotropic shape symmetric relative to the axis that passes through the nanoparticle centre at right angle to the interface (Figs 1–3).

Figure 1 shows iron oxide nanoparticles synthesised in a Langmuir monolayer with the initial ratio  $\text{Fe}(\text{CO})_3 : \text{C}_{17}\text{H}_{35}\text{CO}_2\text{H} = 10 : 1$  under UV irradiation (4 min) at 21 °C and pH 5.6 in the absence of an external magnetic field. The resulting nanoparticles were planar and radially symmetric. Figure 2 shows the nanoparticles synthesised under analogous conditions but with an external magnetic field applied parallel to the monolayer plane. This gave anisotropic oblong nanoparticles whose longer axis coincided with the field direction.<sup>59</sup>

If the energy of the magnetic dipole–dipole interaction of nanoparticles exceeds the energy of thermal (Brownian) motion  $k_B T$  ( $k_B$  is the Boltzmann constant), the magnetic particles can be combined into chain structures. The formation of chain aggregates of magnetic particles is typical, in particular, of magnetic liquids. Figure 3 shows an organised chain ensembles of iron-containing magnetic nanoparticles synthesised in a Langmuir monolayer with an external magnetic field applied and with a short-term UV irradiation.<sup>60</sup>

Highly organised lamellar molecular structures obtained by the Langmuir–Blodgett method have been used as ordered matrices in the synthesis of various nanoparticles, including semiconductor particles, doped with magnetic metal ions (DMS).<sup>65,66</sup> Thus CdS (3 nm) particles doped by  $\text{Mn}^{2+}$  ions were prepared by treatment with  $\text{H}_2\text{S}$  of a Langmuir–Blodgett film consisting of a mixture of cadmium and manganese salts of arachidic acid.

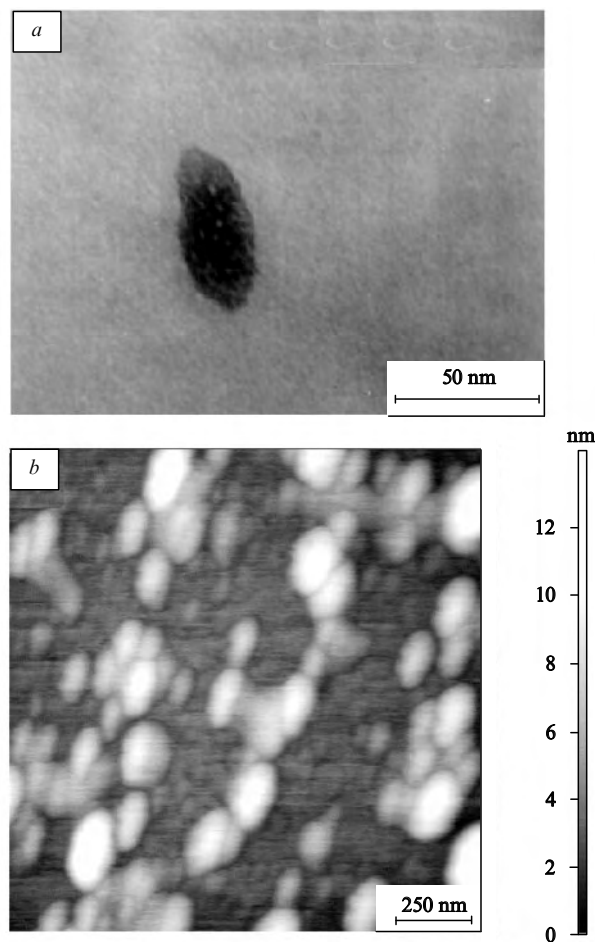


**Figure 2.** TEM (a) and ACM (b) micrographs of iron-containing nanoparticles synthesised in a Langmuir monolayer with application of a 2 kG external magnetic field directed parallel to the monolayer plane.<sup>59</sup>

Multilayer ordered structures have also been obtained by the Langmuir–Blodgett method *via* the formation of stable iron stearate monolayers on the aqueous phase surface.<sup>67,68</sup>

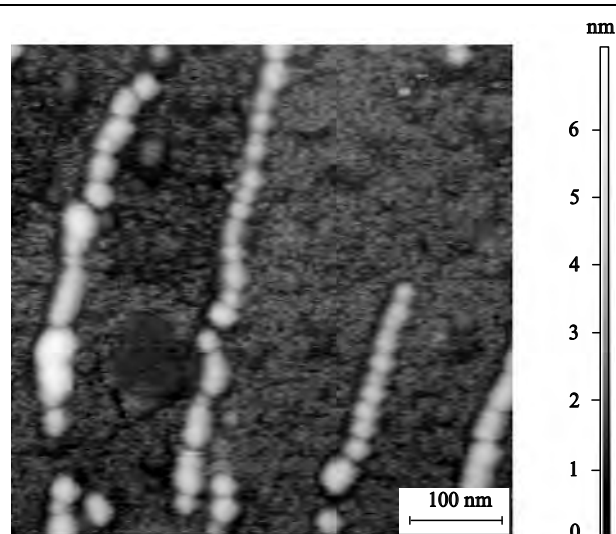


**Figure 3.** ACM micrographs of iron-containing nanoparticles synthesised in a Langmuir monolayer on a short-term (6 s) UV irradiation followed by dark incubation (4 min) with application of an external 2 kG magnetic field directed parallel to the monolayer plane.<sup>60</sup>



### 3. Specific methods for the preparation of particular types of magnetic nanoparticles

#### a. Heterometallic nanoparticles

As a rule, these particles are prepared by simultaneous thermal decomposition of two MCC of different compositions (hydrogen is used most often as the reducing agent). This method was used to prepare heterometallic nanoparticles,  $\text{Fe}_{48}\text{Pt}_{52}$  and  $\text{Fe}_{70}\text{Pt}_{30}$ , from  $\text{Pt}(\text{acac})_2$  and  $\text{Fe}(\text{CO})_5$ .<sup>69</sup> In the synthesis of Co–Pt particles, either  $\text{Pt}(\text{acac})_2$ , or  $\text{Pt}_2(\text{dba})_3$  (dba is dibenzylideneacetone) was used as the source of Pt, while sources of Co included  $\text{Co}_2(\text{CO})_8$ ,  $\text{Co}(\text{CO})_3(\text{NO})$ <sup>70</sup> and  $\text{Co}(\eta^3\text{-C}_8\text{H}_{13})(\eta^4\text{-C}_8\text{H}_{12})$ .<sup>71</sup>

Using the synthesis of  $\text{CoPt}_3$  nanoparticles as an example, the mechanism of homogeneous nucleation has been studied. This allowed researchers<sup>72</sup> to deliberately and reproducibly obtain nanoparticles of the specified composition with a narrow size distribution in the 3–18 nm range. The synthesis of so-called ‘shell’ CoPt nanoparticles has been described.<sup>73</sup> The researchers first obtained Pt nanoparticles of diameter 2.5 nm and then coated them with a controlled amount of Co layers. This resulted in Co–Pt nanoparticles with a diameter of 7.6 nm.

In some cases, heterometallic particles are called ‘alloys,’ in our opinion, this is not always appropriate. For example, using the same initial compounds,  $\text{Co}_2(\text{CO})_8$  and  $\text{Pt}(\text{hfac})_2$ , two types of Co–Pt nanoparticles with the same composition and different structures have been obtained,<sup>74</sup> namely, particles with a uniform distribution of Co and Pt atoms and particles with a cobalt core and a platinum shell, Pt@C. In the latter type of particles, mixing of the atoms of two metals is possible only at the interface.

It is also pertinent to consider the procedure for the synthesis of cobalt ferrite  $\text{CoFe}_2\text{O}_4$  nanoparticles,<sup>75</sup> in which the first stage includes the preparation of the Fe–Co heterometallic particles and the second stage, their oxidation to  $\text{CoFe}_2\text{O}_4$ . Another route to analogous particle implies the use the heterometallic  $(\eta^5\text{-C}_5\text{H}_5)\text{CoFe}_2(\text{CO})_9$  cluster as the starting compound. The cobalt ferrite nanoparticles were also prepared by the micro-emulsion method<sup>76</sup> from a mixture of Co and Fe dodecylsulfates treated with an aqueous solution of methylamine.<sup>77, 78</sup>

#### b. Ferrites

Microcrystalline ferrites form the basis of materials currently used for magnetic information recording and storage. To increase the recorded information density, it seems reasonable to obtain nanocrystalline ferrites and to prepare magnetic carriers based on them. Grinding of microcrystalline ferrite powders to reach the nanosize of grains is inefficient, as this gives particles with a broad size distribution, the content of the fraction with the optimal particle size (30–50 nm) being relatively low.

The key method for the preparation of powders of magnetic hexagonal ferrites with a grain size of more than 1  $\mu\text{m}$  includes heating of a mixture of the starting compounds at temperature above 1000 °C (so-called ceramic method). An attempt has been made<sup>79</sup> to use this method for the synthesis of barium ferrite nanoparticles. The initial components (barium carbonate and iron oxide) were ground for 48 h in a ball mill and the resulting powder was mixed for 1 h at a temperature somewhat below 1000 °C. This gave rather large particles (200 nm and greater) with a broad size distribution. Similar results have been obtained in the mechanochemical synthesis of barium ferrite from  $\text{BaCl}_2$ ,  $\text{FeCl}_3$  and alkali with subsequent oxidative annealing.<sup>80</sup>

Nanocrystalline ferrites are often prepared by the co-precipitation method. The  $\text{MnFe}_2\text{O}_4$  spinel nanoparticles with a diameter of 40 nm are formed upon the addition of an aqueous solution of stoichiometric amounts of  $\text{Mn}^{2+}$  and  $\text{Fe}^{3+}$ -chlorides to a vigorously stirred solution of alkali.<sup>81</sup> The  $\text{MgFe}_2\text{O}_4$  (6–18 nm),<sup>82</sup>  $\text{Co}_{0.2}\text{Zn}_{0.8}\text{Fe}_2\text{O}_4$  (2–45 nm)<sup>83</sup> and  $\text{BaFe}_{12-2x}.\text{Sn}_x\text{Zn}_x\text{O}_{19}$  ( $\sim 45$  nm)<sup>84</sup> nanoparticles were obtained in a similar way. The  $\text{SrFe}_{12}\text{O}_{19}$  nanoparticles (30–80 nm) were synthesised by co-precipitation of Sr and Fe citrates followed by annealing of the resulting precipitate.<sup>85</sup> Co-precipitation upon decomposition of a mixture of  $\text{Fe}(\text{CO})_5$  and  $\text{Ba}(\text{O}_2\text{C}_7\text{H}_{15})_2$  under ultrasonic

treatment has been successfully used<sup>86</sup> for the synthesis of barium ferrite nanoparticles ( $\sim 50$  nm).

Methods for the preparation of ferrite nanoparticles of different compositions in solutions at moderate temperatures have been developed. First, worth mentioning is the sol–gel method resulting in highly dispersed powders with required purity and homogeneity. Low annealing temperatures allow one to control crystallisation and to obtain single-domain magnetic ferrite nanoparticles with narrow size distributions and to easily dope the resulting particles with metal ions. This procedure was used to obtain Co- and Ti-doped barium ferrite nanoparticles (smaller than 100 nm)<sup>87</sup> and, Zn-, Ti- and Ir-doped strontium ferrite particles with a similar size.<sup>88</sup>

Smaller nanoparticles (15–25 nm) of cobalt ferrite were obtained in a hydrogel containing lecithin as the major component. Judging by the good magnetic characteristics, these particles possessed a substantial degree of crystallinity without any annealing.<sup>89</sup> The sol–gel method was successfully used to synthesise a Co ferrite nanowire 40 nm in diameter with a length of up to a micrometre.<sup>90</sup> This wire can also be obtained within carbon nanotubes.<sup>91</sup> For the synthesis of ferrite nanoparticles, oil-in-water type micelles<sup>92</sup> and reverse (water-in-oil) micelles<sup>93</sup> are also widely used.

The homogeneity of metal ion distribution in final products can be enhanced and the required stoichiometry can be attained by using pre-synthesis of heterometallic complexes of various composition. The thermal decomposition and annealing of the pre-synthesised  $[\text{GdFe}(\text{OPr})_6(\text{HOPr})]_2$  complex give  $\text{GdFeO}_3$  nanoparticles ( $\sim 60$  nm).<sup>94</sup> Virtually monodisperse nanoparticles (9 nm) of cobalt ferrite are formed<sup>75</sup> from  $(\eta^5\text{-C}_5\text{H}_5)\text{CoFe}_2(\text{CO})_9$ . First, the Co–Fe nanoparticles are prepared and then they are oxidised during annealing.

#### c. Nanoparticles of rare earth elements

Six of the nine rare earth elements (REE) are ferromagnetic.<sup>¶</sup> The magnetic nanomaterials based on these REE occupy a special place, as they can be used in magnetic cooling systems.<sup>95</sup> However, REE nanoparticles (of both metals and oxides) are still represented by only a few examples, most of all, due to the high chemical activity of highly dispersed REE. A synthesis of coarse ( $95 \times 280$  nm) spindle-shaped ferromagnetic  $\text{EuO}$  nanocrystals suitable for the design of optomagnetic materials has been reported.<sup>96</sup> The  $\text{EuS}$  nanocrystals were prepared by passing  $\text{H}_2\text{S}$  through a solution of europium in liquid ammonia.<sup>97</sup> The size of the  $\text{EuS}$  magnetic nanoparticles formed can be controlled (to within 20–36 nm) by varying the amount of pyridine added to the reaction medium.<sup>97</sup>

Gadolinium nanoparticles (12 nm) were prepared by reduction of gadolinium chloride by Na metal in THF. They proved to be extremely reactive and pyrophoric, which, however, did not prevent characterisation of these particles and measuring their magnetic parameters.<sup>98</sup> The Gd, Dy and Tb nanoparticles with an average size of 1.5–2.1 nm and an about 20% degree of dispersion were obtained in a titanium matrix by ion beam sputtering.<sup>99, 100</sup> At 4.5 K, the coercive forces for  $\sim 10$  nm Tb and Gd nanoparticles were 22 and 1 kOe, respectively. As the particle size decreases ( $< 10$  nm), the  $H_c$  value rapidly diminished to zero, which is related, in the researchers’ opinion,<sup>100</sup> to the decrease in the Curie temperature for small nanoparticles.

#### d. Magnetic nanoparticles of anisotropic shapes

The nanoparticles anisotropic in shape (non-spherical) are of special interest for magnetic recording purposes. A material containing oblong (needle-shaped) or flat (disc-shaped) particles is more easily susceptible to magnetic texturing, *i.e.*, ordering of the directions of the magnetic axes of the particles. This has long

¶ The atomic magnetic moments of rare earth elements are greater than that of Fe.

been used, for example, in audio recording tapes.<sup>101</sup> In addition, non-spherical particles possess an additional source of magnetic anisotropy, *i.e.*, the shape anisotropy. It was shown experimentally and substantiated theoretically<sup>102</sup> that planar ultrathin particles should be single-domain, irrespective of their in-plane dimensions. For these planar particles, the shape anisotropy is comparable in magnitude with the magnetic crystal anisotropy. The magnetic interaction between thin nanoparticles in plane is much lower than that between spherical nanoparticles in the bulk.

No theory of the synthesis of anisotropic particles has been developed due to the lack of methods of deliberate change of the nanoparticle shape in solutions. Although papers devoted to the synthesis of Co,<sup>103</sup> Fe<sup>104</sup> and Ni<sup>105</sup> anisotropic magnetic nanoparticles have been published, this still does not imply that the shape of magnetic nanoparticles is subject to reproducible control. Recently,<sup>106</sup> conditions for the preparation of highly anisotropic cobalt nanoparticles by the reduction of  $\text{Co}(\eta^3\text{-C}_8\text{H}_{13})(\eta^4\text{-C}_8\text{H}_{12})$  with hydrogen have been found. By varying conditions of synthesis and the oleylamine to oleic acid ratio, the researchers selectively obtained spherical nanoparticles (4–10 nm), nanoneedles (40 nm long and 9 nm in diameter) and even nanowires.

Experimental data and theoretical calculations show that the interparticle anisotropic magnetic dipole–dipole interactions and kinetic factors can play a significant role in the magnetic nanoparticle growth induced by external fields. If at the moment of synthesis of iron oxide magnetic nanoparticles, the reaction medium is exposed to a magnetic field, the process yields anisotropic (oblong) particles. Apparently, this synthesis opens up the way for effective control of the morphology of magnetic nanomaterials.

Using the preparation of magnetic nanoparticles by ultrasound-induced decomposition of  $\text{Fe}(\text{CO})_5$  in a decalin solution as an example,<sup>107</sup> the effect of an external magnetic field on the growth processes has been studied. In an external magnetic field (7 kG), amorphous  $\text{Fe}_2\text{O}_3$  nanoparticles were formed, of which 20%–30% had an anisotropic shape (50 nm long and 5 nm in diameter). In the absence of a magnetic field only quasi-isotropic nanoparticles with an average size of 25 nm were obtained. The electric arc decomposition of  $\text{Fe}(\text{CO})_5$  resulted in thread-like (10 to 100 nm in diameter) compounds also consisting of  $\alpha\text{-Fe}$  and  $\text{Fe}_3\text{C}$  nanoparticles.<sup>108</sup>

The standard way of synthesis of nanothreads and nanowires composed of anisotropic Fe and Co nanoparticles includes the electrolysis of solutions of the metals at an aluminium cathode, which is pre-coated by an  $\text{Al}_2\text{O}_3$  layer containing channels with a diameter of 18–35 nm and a depth of up to 500 nm.<sup>109</sup> During the electrolysis, these channels are filled by the reduced metal. After completion of the process, the matrix is dissolved in a mixture of acids to separate the nanoparticles. According to TEM, the nanoparticles have a length of up to 500 nm and an average diameter of 16 nm. Magnetic measurements have shown that the samples obtained have a coercive force of 2.7 kG for Fe (the highest value for pure  $\alpha\text{-Fe}$  particles) and 1.4 kG for Co. By using an upgraded procedure, it is possible to prepare Fe nanowires ( $d = 5$  nm) with a coercive force of 4.19 kG at 5 K.<sup>110</sup> Subsequently, column Co–Pt structures with a high magnetic anisotropy, promising for magnetic recording, have been obtained by this method.<sup>111</sup> An attempt has been made to control the magnetic anisotropy of Co–Pt nanoparticles.<sup>112</sup>

A peculiar procedure of thermal decomposition of carbonyls has been employed to prepare Fe and Co nanowires.<sup>113</sup> The particles were grown on the poles of a permanent magnet in the reaction area. This procedure allowed the preparation of 8–10 nm thick whiskers several millimetres long. The synthesis of monoatomic chains consisting of Co atoms has been reported.<sup>114</sup>

A simple method for the synthesis of heterometallic nanowires ( $d \approx 30$  nm, more than 10  $\mu\text{m}$  long) by heating a solution of platinum acetylacetonate and cobalt carbonyl in ethylenediamine

at 200 °C for several days has been described.<sup>115</sup> The Fe–Pt, Ni–Pt and Cr–Pt nanowires were obtained in a similar way.

#### 4. Methods for the synthesis of stoichiometrically inhomogeneous magnetic nanoparticles

The surface anisotropy markedly contributes to the total magnetic anisotropy of a nanoparticle; therefore, by controlling the surface composition, it is possible to control the magnetic properties of nanoparticles.

##### a. Oxidation of nanoparticles

No targeted research into the reactivity of oxidised nanoparticles or its comparison with the reactivity of the corresponding compact materials has been carried out; only a few publications considered the magnetic properties of the oxidised nanoparticles. For example, the magnetic properties of cobalt nanoparticles,<sup>†</sup> which were obtained by vacuum evaporation on the LiF substrate and then oxidised by exposure to air for a week, have been studied.<sup>116</sup> According to electron diffraction for two samples differing in the particle size (2.3 and 3.0 nm), the intensity of the HCP-Co reflections decreased after oxidation to become  $\sim 1/3$  of the CoO-HCP line intensity. Hence, the researchers concluded that a small stable core of unoxidised cobalt atoms remains in all particles after oxidation. Comparative X-ray diffraction studies of the samples consisting of Co nanoparticles distributed in polyvinylpyridine stored under Ar and in air (the storage time was not indicated)<sup>117</sup> revealed no significant differences. Therefore, the authors considered a low degree of oxidation for cobalt.

In a more comprehensive study,<sup>118</sup>  $^{57}\text{Co}$ -enriched cobalt nanoparticles were subjected to oxidation directly in a Mössbauer spectrometer. For this purpose, argon containing  $\sim 80$  ppm of  $\text{O}_2$  was passed through the sample at 300 K for 18 h. Analysis of the emission Mössbauer spectra showed that oxidation results in a fairly well-organised CoO layer on the surface of Co particles. Passing a pure oxygen stream through this gently oxidised sample for 1 h at 300 K did not induce any spectral changes. In the opinion of the researchers cited,<sup>118</sup> this is indicative of complete passivation of Co particles at the first oxidation stage.

It should be noted that the oxidation of magnetic metal nanoparticles during their synthesis cannot be avoided completely. Thorough mass-spectroscopic analysis of Fe nanoparticles obtained by laser vaporisation of the metal in a pure He medium showed that at least 5% of particles contain at least one oxygen atom.<sup>20</sup> If the deposition of oxygen present in the gas phase in trace amounts on the nanoparticle surface cannot be avoided even under these 'exceptional' conditions, it is evident that under 'usual' conditions, the nanoparticles of magnetic metals would always contain some amounts of oxides or suboxides of the elements on the surface. It can be plainly seen in the HRTEM micrograph (HRTEM is high-resolution tunnelling electron microscopy) of  $\alpha\text{-Fe}$  nanoparticles (20 nm) synthesised by laser pyrolysis of  $\text{Fe}(\text{CO})_5$  under inert atmosphere that the particles are coated with a (3.5 nm) layer of iron oxide (the content of the chemically bound oxygen is 14.4 mass %).<sup>119</sup>

The data on the reactivity of Fe nanoparticles with respect to oxidation reported in the literature are contradictory. Thus rather large ( $\sim 40$  nm) nanoparticles of pure Fe obtained by thermal vaporisation contained less than 8 mass % of the oxide after exposure to air for three months.<sup>120</sup>

In some studies, the preparation of metal nanoparticles (especially Fe) was followed by their passivation, for example, by keeping for several hours in an atmosphere of oxygen-diluted argon.<sup>121</sup> This procedure prevented further spontaneous particle aggregation. The structure and the magnetic characteristics of such passivated nanoparticles (15–40 nm) have been described in detail.<sup>122</sup> The continuous oxide layers that coat the metallic

<sup>†</sup> Non-oxidised particles had a hexagonal close packing (HCP), while the oxidised ones, a face-centred cubic (FCC) lattice.

nanoparticle can be clearly seen in TEM images reported in this study. The interaction of the ferromagnetic core and the oxide shell, which resembles in the magnetic characteristics the interaction of magnetic moments in spin glass, was studied.

The oxidation of amorphous  $\text{Fe}_{1-x}\text{C}_x$  nanoparticles obtained by thermal decomposition of  $\text{Fe}(\text{CO})_5$  in decalin in the presence of oleic acid for several weeks in air<sup>123</sup> has shown that the particles (6.9 nm) having a spherical shape and a very narrow size distribution consist of  $\alpha$ - and  $\gamma$ - $\text{Fe}_2\text{O}_3$ . However, passivation of nanocrystalline ( $\sim 25$  nm) Fe particles obtained by metal evaporation in a helium stream results in only a thin (1–2 nm) film of an antiferromagnetic oxide (apparently,  $\text{FeO}$ ) forming on the surface.<sup>124</sup>

#### b. Chemisorption of small molecules on a nanoparticle surface

The interaction of  $\alpha$ -Fe nanoparticles (2.4 nm) with small  $\text{CO}$ ,  $\text{H}_2$  and  $\text{O}_2$  molecules has been studied.<sup>125</sup> It was noted that chemisorption of these molecules on a nanoparticle surface induces only minor changes in the parameters of the Mössbauer spectra. The reaction of  $\alpha$ -Fe nanoparticles (2.3 nm) with nitrogen was studied *in situ* by Mössbauer spectroscopy.<sup>126</sup> It was shown that only the Fe atoms of the surface layer participate in the chemical binding of nitrogen (the process starts at 300 K). Note that the effect of the bound oxygen on the state of the metal surface atoms differs appreciably from that found for  $\text{O}_2$  (see Ref. 127) and  $\text{CO}$  chemisorption.

#### c. Targeted modification of the surface of magnetic nanoparticles

The immobilisation of biological molecules (amino acids, DNA, simple peptides, polysaccharides, lipids) on the surface of magnetic nanoparticles is of certain interest for the design of magnetic markers used in biological and medical experiments. Physical sorption is often sufficient for such immobilisation; however, in some cases, chemical binding of the nanoparticle to the biomolecule is required. A seven-stage synthesis of  $\gamma$ - $\text{Fe}_2\text{O}_3$  nanoparticles ( $\sim 20$  nm) containing on the surface fragments of long organic molecules ending with reactive aldehyde groups has been described.<sup>128</sup> By the reaction of these aldehyde groups with enzyme amino groups, stable enzyme complexes with the magnetic  $\gamma$ - $\text{Fe}_2\text{O}_3$  nanoparticle were obtained. The heterogeneous catalytic activity of the enzyme immobilised in this way was found to be retained much longer than the activity of the same enzyme sorbed on a support surface.

### IV. The most widely encountered magnetic nanoparticles

The fundamental characteristics of any nanoparticles, including magnetic ones, are the stoichiometry and the phase state. This Section considers the main types of magnetic nanoparticles and examples of their synthesis.

**Fe.** The preparation of nanoparticles consisting of pure iron is a complicated task, because they always contain oxides, carbides and other impurities.

**BCC-Fe ( $\alpha$ -Fe).** The  $\alpha$ -Fe nanoparticles with a body-centred cubic (BCC) lattice and an average size of  $\sim 10$  nm were prepared by grinding a high-purity (99.999%) Fe powder for 32 h.<sup>129</sup>

A sample containing pure iron as nanoparticles ( $d_{\text{aver}} = 10.5$  nm) can also be obtained by evaporation of the metal in an Ar atmosphere followed by deposition on a substrate.<sup>121</sup> When evaporation took place in a helium atmosphere, the particle size varied in the range of 10–20 nm.<sup>130</sup> Relatively small (100–500 atoms) Fe nanoparticles are formed in the gas phase on laser vaporisation of pure iron.<sup>20</sup>

**FCC-Fe ( $\gamma$ -Fe).** In the phase diagram of a bulk Fe sample, this phase exists at the ambient pressure in the temperature range of 1183–1663 K, *i.e.*, above the Curie point (1096 K). In some special alloys, this phase, which exhibits antiferromagnetic properties (the Neel temperature is in the 40–67 K range), was observed at room temperature.<sup>131–133</sup> However, a Mössbauer

spectroscopy study<sup>134</sup> has shown that the FCC-Fe nanoparticles (40 nm) remain paramagnetic down to 4.2 K.

Some publications dealing with the synthesis of Fe nanoparticles present fairly weighty reasons indicating that these nanoparticles had an FCC structure. Apparently, the nanoparticles containing  $\gamma$ -Fe were first obtained by Majima *et al.*<sup>135</sup> These particles contained substantial amounts of carbon (up to 14 mass %) and had an austenite FCC structure analogous to  $\gamma$ -Fe. The researchers believed that the laser they used made it possible to reach a temperature of 1173–1423 K (the region of existence of  $\gamma$ -Fe in the phase diagram) in the reaction medium at the pulse instant, while the presence of reactive atomic carbon formed upon decomposition of  $\text{CO}$  and the short time of the laser pulse (100 nm) created the necessary conditions for fixing of the metastable structure. However, later, evidence for the existence of the  $\gamma$ -phase in the Fe nanoparticles that do not contain substantial amounts of carbon have been obtained. Nanoparticles ( $\sim 8$  nm) consisting, according to powder X-ray diffraction and Mössbauer spectroscopy, of  $\gamma$ -Fe (30 at. %),  $\alpha$ -Fe (25 at. %) and iron oxides (45 at. %), were synthesised<sup>136</sup> by treatment of  $\text{Fe}(\text{CO})_5$  with a  $\text{CO}_2$  laser radiation. The content of the  $\gamma$ -phase in the nanoparticles did not change for several years; the particles remain non-magnetic down to helium temperatures.

**'Amorphous' Fe (metallic glass).** The ultrasonic treatment of  $\text{Fe}(\text{CO})_5$  in the gas phase or of a solution of  $\text{Fe}(\text{CO})_5$  in decane at 0 °C under an inert atmosphere gave an X-ray amorphous powder as rather coarse ( $\sim 30$  nm) nanoparticles. The nanoparticles consisted of  $>96$  mass % of Fe,  $<3$  mass % of C and 1 mass % of O.<sup>137</sup> Differential thermal analysis (DTA) of the powder showed an exothermal transition around 585 K, which corresponded, in the authors' opinion, to crystallisation of the amorphous iron. Smaller Fe particles (8.5 nm) were obtained by thermal decomposition of  $\text{Fe}(\text{CO})_5$  in decalin (460 K) in the presence of surfactants.<sup>138</sup> The X-ray diffraction pattern of the powder formed did not display any sharp maxima, indicating the absence of a crystalline phase. It was assumed that amorphisation was due to the high content of carbon ( $>11$  mass %) in the nanoparticles studied.

**$\text{Fe}_2\text{O}_3$ .** Among several crystalline modifications of  $\text{Fe}_2\text{O}_3$ , there are two magnetic phases, namely, rhombohedral  $\alpha$ - $\text{Fe}_2\text{O}_3$  (hematite) and cubic  $\gamma$ - $\text{Fe}_2\text{O}_3$  (maghemite) phases. In the  $\alpha$ - $\text{Fe}_2\text{O}_3$  structure, all  $\text{Fe}^{3+}$  ions have an octahedral coordination, whereas in  $\gamma$ - $\text{Fe}_2\text{O}_3$  having the structure of a cation-deficient  $\text{AB}_2\text{O}_4$  spinel, the metal atoms A and B occur in tetrahedral and octahedral environments, respectively.

The oxide  $\alpha$ - $\text{Fe}_2\text{O}_3$  is antiferromagnetic at temperatures below 950 K, while above the Morin point (260 K) it exhibits so-called 'weak' ferromagnetism.

The  $\alpha$ - $\text{Fe}_2\text{O}_3$  and  $\text{FeOOH}$  (goethite) nanoparticles are obtained by controlled hydrolysis of  $\text{Fe}^{3+}$  salts.<sup>139</sup> In order to avoid the formation of other phases, a solution of ammonia is added to a boiling aqueous solution of  $\text{Fe}(\text{NO}_3)_3$  with intensive stirring. Boiling for 2.5 h and treatment of the precipitate with ammonium oxalate (to remove the impurities of other oxides) affords a red powder containing  $\alpha$ - $\text{Fe}_2\text{O}_3$  nanoparticles (20 nm).<sup>140</sup> These nanoparticles are also formed on treatment of solutions of iron salts ( $\text{Fe}^{2+}:\text{Fe}^{3+} = 1:2$ ) with an aqueous solution of ammonium hydroxide in air.<sup>141</sup> The synthesis of regularly arranged  $\alpha$ - $\text{Fe}_2\text{O}_3$  nanowires with a diameter of 20–40 nm and a length of 2–5  $\mu\text{m}$  has been described.<sup>142</sup>

A bulk  $\gamma$ - $\text{Fe}_2\text{O}_3$  sample is a ferrimagnet below 620 °C. The  $\gamma$ - $\text{Fe}_2\text{O}_3$  nanoparticles (4–16 nm) with a relatively narrow size distribution have been obtained<sup>40</sup> by mild oxidation (on treatment with  $\text{Me}_3\text{NO}$ ) of pre-formed metallic nanoparticles. The same result can be attained by direct introduction of  $\text{Fe}(\text{CO})_5$  into a heated solution of  $\text{Me}_3\text{NO}$ . The oxidation with air oxygen is also used to prepare  $\gamma$ - $\text{Fe}_2\text{O}_3$  nanoparticles. For this purpose, the  $\text{Fe}_3\text{O}_4$  nanoparticles (9 nm) are boiled in water at pH 12–13.<sup>143</sup> The kinetics of this process was studied.

The most popular route to  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> nanoparticles is thermal decomposition of Fe<sup>3+</sup> salts in various media. Rather exotic groups are used in some cases as anions. For example, good results have been obtained by using iron complexes with cupferron.<sup>144</sup> Special-purity  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> is formed upon vaporisation of iron(III) oxide in a solar furnace with subsequent condensation.<sup>145, 146</sup> A mechanochemical synthesis of  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> has been described.<sup>147</sup> An iron powder was milled in a planetary mill with water. During milling, the Fe atoms displace hydrogen from water and are converted into  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>. The researchers consider that this is a convenient one-stage synthesis of maghemite nanoparticles (15 nm).

**Fe<sub>3</sub>O<sub>4</sub> (magnetite).** The cubic spinel Fe<sub>3</sub>O<sub>4</sub> is ferrimagnetic at temperatures below 858 K. The route to these particles used most often involves treatment of a solution of a mixture of iron salts (Fe<sup>2+</sup> and Fe<sup>3+</sup>) with a base under an inert atmosphere. For example, the addition of an aqueous solution of ammonia to a solution of FeCl<sub>2</sub> and FeCl<sub>3</sub> (1 : 2) yields nanoparticles, which are transferred into a hexane solution by treatment with oleic acid.<sup>148</sup> The repeated selective precipitation gives Fe<sub>3</sub>O<sub>4</sub> nanoparticles with a rather narrow size distribution. The synthesis can be performed starting only from FeCl<sub>2</sub>, but in this case, a specified amount of an oxidant (NaNO<sub>2</sub>) should be added to the aqueous solution apart from alkali. This method allows one to vary both the particle size (6.5–38 nm) and (to a certain extent) the particle shape.<sup>149</sup>

In some cases, thermal decomposition of compounds containing Fe<sup>3+</sup> ions under oxygen-deficient conditions is accompanied by partial reduction of Fe<sup>3+</sup> to Fe<sup>2+</sup>. Thus thermolysis of Fe(acac)<sub>3</sub> in diphenyl ether in the presence of small amounts of hexadecane-1,2-diol (probable reducer of a part of Fe<sup>3+</sup> ions to Fe<sup>2+</sup>) gives very fine Fe<sub>3</sub>O<sub>4</sub> nanoparticles (about 1 nm), which can be enlarged by adding excess Fe(acac)<sub>3</sub> into the reaction mixture.<sup>150</sup> For partial reduction of Fe<sup>3+</sup> ions, hydrazine has been recommended.<sup>151</sup> The reaction of Fe(acac)<sub>3</sub> with hydrazine is carried out in the presence of a surfactant. This procedure resulted in superparamagnetic magnetite nanoparticles with controlled sizes, 8 and 11 nm.

Previously, Fe<sub>3</sub>O<sub>4</sub> nanoparticles with an average size of 3.5 nm have been prepared by thermal decomposition of Fe<sub>2</sub>(C<sub>2</sub>O<sub>4</sub>)<sub>3</sub> · 5 H<sub>2</sub>O at  $T > 400$  °C.<sup>152</sup> The controlled reduction of ultradispersed  $\alpha$ -Fe<sub>2</sub>O<sub>3</sub> in a hydrogen stream at 723 K (15 min) is a more reliable method of synthesis of Fe<sub>3</sub>O<sub>4</sub> nanoparticles. Particles with ~13 nm size were prepared in this way.<sup>153</sup>

**FeO (wustite).** Cubic Fe<sup>2+</sup> oxide is antiferromagnetic ( $T_C = 185$  K) in the bulk state. Joint milling of Fe and Fe<sub>2</sub>O<sub>3</sub> powders taken in a definite ratio gave nanoparticles (5–10 nm) consisting of FeO and Fe.<sup>154</sup> On heating of these particles at temperatures of 250–400 °C, the metastable FeO phase disproportionates to Fe<sub>3</sub>O<sub>4</sub> and Fe, while above 550 °C it is again converted into nanocrystalline FeO.<sup>155, 156</sup>

**$\alpha$ -FeOOH (goethite).** Among the known oxide hydroxides Fe<sub>2</sub>O<sub>3</sub> · H<sub>2</sub>O, the orthorhombic  $\alpha$ -FeOOH (goethite) is antiferromagnetic in the bulk state and has  $T_C = 393$  K,<sup>157</sup>  $\beta$ -FeOOH (akagenite) is paramagnetic at 300 K,<sup>158</sup>  $\gamma$ -FeOOH (lipidocrokit) is paramagnetic at 300 K and  $\delta$ -FeOOH (ferroxhyte) is ferrimagnetic.<sup>159</sup> Although the bulk  $\alpha$ -FeOOH is antiferromagnetic, in the form of nanoparticles it has a nonzero magnetic moment due to the incomplete compensation of the magnetic moments of the sublattices. Goethite nanoparticles have been studied by Mössbauer spectroscopy.<sup>160, 161</sup> As a rule,  $\alpha$ -FeOOH is present in iron nanoparticles as an admixture phase.

**Fe<sub>x</sub>C<sub>y</sub>.** Iron carbide is often present in Fe-containing nanoparticles. It is formed either upon decomposition of organic ligands present in the starting MCC or upon the reaction of Fe with the organic medium in which the synthesis is carried out. Data on the preparation of nanoparticles wholly consisting of iron carbide of one or another composition are few. It has been shown by Mössbauer spectroscopy<sup>162</sup> that thermal decomposition of

Fe(CO)<sub>5</sub> (353 K) on a carbon support forms Fe<sub>78</sub>C<sub>22</sub> nanoparticles (3.9 nm).

**Ferrofluids** or so-called magnetic liquids are suspensions of colloid magnetic particles stabilised by surfactants in liquid media.<sup>2, 3</sup> The magnetic phase in ferrofluids can be represented by magnetite,<sup>163</sup> ferrites<sup>164</sup> and Fe<sub>x</sub>C<sub>y</sub> particles resulting from the thermal decomposition of Fe(CO)<sub>5</sub>.<sup>165</sup> Decalin or silicone oil are the usual liquid phases. The dimensions of magnetic particles are 5–10 nm. The commercial magnetic liquids most often contain magnetite.<sup>2, 166, 167</sup> Description of magnetic liquids with a Curie point below the boiling point has been reported.<sup>164, 168, 169</sup> The use of these composites is considered in a review.<sup>170</sup>

Apart from the 'classical' ferrofluids, ferrofluid emulsions in which oil drops containing a magnetic phase are dispersed in water by means of surfactants are also known.<sup>171</sup> The preparation of lyotropic ferromagnetics stable for several months with a high content (up to 1 vol.%) of the magnetic component,  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> nanoparticles (~6 nm), based on a ferrofluid has been reported.<sup>172</sup>

**Fe–Co alloys.** The saturation magnetisation of Fe–Co alloys reaches a maximum at a Co content of 35 at.%; other magnetic characteristics of these metals also increase when they are mixed. Therefore, Fe<sub>x</sub>Co<sub>y</sub> nanoparticles attract considerable attention. Thus Fe, Co and Fe–Co (20 at.%, 40 at.%, 60 at.%, 80 at.%) nanoparticles (40–51 nm)<sup>173</sup> with a structure similar to the corresponding bulk phases have been prepared in a stream of hydrogen plasma. The Fe–Co particles reach a maximum saturation magnetisation (61 cm<sup>3</sup> g<sup>−1</sup>) at 40 at.% of Co and a maximum coercive force (860 Oe) is attained at 80 at.% of Co.

**Fe–Ni.** The bulk samples of the iron–nickel alloys are either nonmagnetic or are magnetically soft ferromagnets (for example, permalloys containing >30% of Ni and various doping additives). When the content of nickel is ~30%, their magnetic properties approach the properties of invar (36% of Ni, 64% of Fe, about 0.05% of C). The Fe–Ni nanoparticles have a much lower saturation magnetisation than the corresponding bulk samples over the whole concentration range.<sup>174</sup> An alloy containing 37% of Ni has a low  $T_C$  and a FCC structure. It consists of nanoparticles (12–80 nm) superparamagnetic over a broad temperature range.<sup>175</sup> Theoretical calculations predict a complex magnetic structure for these Fe–Ni particles (clusters).<sup>176</sup>

**Fe–Pt.** Nanoparticles of this composition have received much attention in recent years due to the prospects for a substantial increase in the information recording density for materials based on them.<sup>69</sup> The Fe–Pt nanoparticles (6 nm) with a narrow size distribution were prepared by joint thermolysis of Fe(CO)<sub>5</sub> and Pt(acac)<sub>2</sub> in the presence of oleic acid and oleylamine. Hexadecane-1,2-diol served as the reducing agent for Pt<sup>2+</sup>. Further heating resulted in the formation of a protective film from the products of thermal decomposition of the surfactant on the nanoparticle surface, which does not change significantly the particle size. These particles can be arranged to form regular films and so-called 'colloid crystals'.<sup>177</sup> The reaction of FePt nanoparticles with Fe<sub>3</sub>O<sub>4</sub> followed by heating of the samples at 650 °C in an Ar + 5% H<sub>2</sub> stream resulted in the FePt–Fe<sub>3</sub>Pt nanocomposite with unusual magnetic characteristics.<sup>178</sup>

**Co.** Methods for the synthesis and magnetic properties of cobalt nanoparticles have been described in detail in a review;<sup>18</sup> therefore, we do not consider them here.

**CoO.** Cubic cobalt oxide is antiferromagnetic and has  $T_N = 291$  K. Cobalt monoxide has played an important role in the discovery of the 'exchange shift' of the hysteresis curve,<sup>179, 180</sup> first found for samples consisting of oxidised Co nanoparticles.<sup>181</sup> Data on the dependence of  $T_N$  on the particle size were obtained in a study of CoO nanoparticles dispersed in a LiF matrix.<sup>116</sup> The particles obtained by vacuum deposition contained a small metal core, according to powder X-ray diffraction. As the particle size decreased from 3 to 2 nm,  $T_N$  decreased from 170 to 55 K, which can be explained satisfactorily in terms of the mean-field theory.<sup>122</sup> Apparently, the presence of an oxide layer on cobalt

nanoparticles can markedly increase the coercive force. For example, the coercive forces (at 5 K) of monodisperse 6 and 13 nm oxidised Co particles obtained by plasma gas condensation in an installation for the investigation of molecular beams were  $\sim 5$  and 2.4 kOe, respectively.<sup>182</sup> Unfortunately, the blocking temperature for 6 nm nanoparticles was lower than room temperature ( $\sim 200$  K); therefore, under normal conditions, their coercive force was equal to zero.

**Co<sub>3</sub>O<sub>4</sub>.** The Co<sub>3</sub>O<sub>4</sub> nanoparticles (cubic spinel) with sizes of 15 to 19 nm dispersed in an amorphous silicon matrix exhibited ferrimagnetic<sup>‡</sup> properties at temperatures below 33 K (for bulk samples,  $T_N = 30$  K).<sup>183</sup> A method for controlled synthesis of Co<sub>3</sub>O<sub>4</sub> cubic nanocrystallites (10–100 nm) has been developed.<sup>184</sup>

**Ni.** The number of publications devoted to the preparation of Ni nanoparticles is small, unlike Co and, the more so, Fe nanoparticles. In addition to the conventional metal evaporation methods,<sup>150</sup> thermal decomposition of organonickel compounds [Ni(CO)<sub>4</sub>, Ni(C<sub>5</sub>H<sub>5</sub>)<sub>2</sub> (see Ref. 185) and Ni(COD)<sub>2</sub> (COD is cyclo-octadiene)<sup>186</sup>] and the reduction of NiBr<sub>2</sub> in the presence of PPh<sub>3</sub> by treatment with potassium metal deserve attention.<sup>187</sup> In the latter case, Ni nanoparticles ( $\sim 3$  nm) coated by a thin oxide film are formed.

**Materials for magnetic information recording.** The following compositions are usually considered in the literature as media for magnetic information recording:  $\alpha$ -Fe,  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>, Fe<sub>2</sub>O<sub>3</sub>–Fe<sub>3</sub>O<sub>4</sub>, Co– $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>, CrO<sub>2</sub>, BaFe<sub>12</sub>O<sub>19</sub>. The compositions used in reality are much more complex, because they are doped by various additives that influence particular characteristics of the material. In recent years, nanocrystalline (5–10 nm) CoPr, FePt, CoPt, CoSm, SmFeSiC and SmFeAlC films are regarded as most promising.<sup>188</sup>

## V. Methods of nanoparticle stabilisation

### 1. Encapsulation of nanoparticles and the preparation of magnetic nanoparticles in a shell

Nanoparticles of some metals are known to be pyrophoric, *i.e.*, they spontaneously ignite in air at room temperature; therefore, the creation of a protective shell on such nanoparticles (encapsulation) is a widely used protection and stabilisation method. Carbon is often used as the protective coating. The carbon layers formed on the metal surface are usually graphite-like and, hence, conductive. In those cases where an electrically insulating coating is required, boron nitride layers are used.<sup>189</sup>

Encapsulation of magnetic nanoparticles makes them stable against oxidation, corrosion and spontaneous aggregation, which allows them to retain the single-domain structure. The magnetic particles coated by a protective shell can find application as the information recording media, for example, as magnetic toners in xerography, magnetic ink, contrasting agents for magnetic resonance images, ferrofluids and so on. If the nano-sized magnetic particles are retained after compaction, the materials based on them can serve as excellent initial components for the preparation of permanent magnets.

The coating of metal particles by carbon (carbonisation) was first observed in the research of heterogeneous catalysis almost 50 years ago. Subsequently, this process (deleterious to oil refining and other industries) was comprehensively studied and, in recent years, it has been used deliberately to stabilise nanoparticles. The first structurally characterised carbon-encapsulated nanoparticles were obtained as side products in the electric arc synthesis of fullerenes. Subsequently, special studies have been carried out to identify the possibilities of using this method for the targeted

synthesis of encapsulated nanoparticles, especially magnetic ones. These investigations have been surveyed.<sup>190</sup>

The original version of the arc method allowed one to prepare reliably only encapsulated nanoparticles of REE carbides. Subsequently, the yield of encapsulated nanoparticles has been increased due to a decrease in the amount of fullerenes formed. In this variant, the method became applicable for the synthesis of reasonable amounts of encapsulated magnetic nanoparticles (Fe–Co, Mn–Al). The encapsulated Fe and Co nanoparticles with a saturation magnetisation reaching  $200 \text{ cm}^3 \text{ g}^{-1}$  were synthesised in this way. The perfection of the experimental technique allowed the researchers to eliminate completely the formation of pure carbon-containing products. This procedure was used to obtain Fe, Co and Ni nanoparticles (56, 40 and 37 nm, respectively) coated by 3 or 4 layers of graphitised carbon.<sup>191</sup> The authors emphasise that in none of the cases were metal carbide phases detected. However, the attempts to prepare encapsulated nanoparticles of hard magnetic materials, NdFeB or SmCo<sub>5</sub>, proved unsuccessful — each element formed separate encapsulated particles.

Other methods for the synthesis of encapsulated magnetic nanoparticles are based on the use of high-temperature plasma, laser pyrolysis and thermal vaporisation. Thus the cobalt and carbon vapours formed upon an arc discharge in a helium atmosphere were condensed in the gas phase prior to deposition onto a cooled substrate.<sup>192</sup> This gave spherical particles with a radius of 10 to 100 nm consisting of a metallic core and a carbon shell, which contains up to 30 graphite-like carbon layers. Such a shell is considered to prevent oxidation of the metallic core.<sup>193</sup> Other compounds can also be used to form the protective shell. Thus treatment of a mixture of boron and cobalt powders with H<sub>2</sub> and NH<sub>3</sub> at 800 °C for 3 h furnished Co nanoparticles (20–60 nm) coated by a  $\sim 5$ -nm thick BN coating.<sup>189</sup> A CVD process for one-stage synthesis of  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> nanoparticles (20–30 nm) coated by a SiO<sub>2</sub> layer with the same thickness has been developed.<sup>194</sup>

Due to the high temperature of carbon evaporation, the synthesis in radiofrequency plasma burners is considered to be most promising for obtaining large-scale amounts of encapsulated magnetic nanoparticles. Nanoparticles of metals, alloys, carbides and oxides can be prepared by this method. A drawback of this method is inhomogeneity of nanoparticles and differences in their composition.

Chemical methods are also used successfully for encapsulating magnetic nanoparticles. Thus stirring of a solution of tetraethoxysilane in alcohol with an aqueous suspension of  $\alpha$ -Fe<sub>2</sub>O<sub>3</sub> nanoparticles (24 h, 50 °C) gives Fe<sub>2</sub>O<sub>3</sub> nanoparticles (4–5 nm) coated by amorphous SiO<sub>2</sub>. The particles were found to retain the composition, the size and the shape after heating at 250 °C in an O<sub>2</sub> atmosphere.

Hydrolysis of Si, Ti and Zr alkoxides in the presence of metal nanoparticles is a general method for forming shells of the oxides of these elements on the particle surface. In some cases, the synthesis of oxides takes place simultaneously with the synthesis of the nanoparticles. This method was used to prepare<sup>195</sup> Co magnetic nanoparticles coated by SiO<sub>2</sub> layers. The starting compounds used were Fe(acac)<sub>3</sub> and Si(OEt)<sub>4</sub>, the oxidative thermal decomposition of which in a flow reactor at 1000 °C gave the corresponding particles.

The coating of magnetic nanoparticles by a thin layer of a non-magnetic metal is considered to be a promising method for their stabilisation. For example, the synthesis of Fe<sub>3</sub>O<sub>4</sub> nanoparticles (5 nm) coated by metallic gold has been reported.<sup>196</sup> When determining the composition and the structure of these objects, the researchers faced serious difficulties. Much attention has been devoted in recent years to the methods for the formation of thin polymeric coatings (especially those based on biocompatible and readily biodegradable polymers) on the surface of magnetic nanoparticles.<sup>197</sup>

<sup>‡</sup> Ferrimagnetism below  $T_N$  is typical of nanoparticles of all antiferromagnetic phases, because, unlike bulk samples, the magnetic moments of sublattices are not fully compensated. In particular, the arrangement of magnetic moments in the near-surface layer of nanoparticles differs appreciably from that in the bulk, which is specified by the type of crystal lattice and the type of exchange interactions.

## 2. Self-assembled monolayers on the nanoparticle surface

Self-assembled monolayers (SAM) on the nanoparticle surfaces are represented by monomolecular layers of amphiphilic molecules, which protect the particles from aggregation and simultaneously stabilise their suspensions (solutions) in certain solvents. In a typical example of the self-assembly of a monolayer of amphiphilic molecules of fatty acids on the  $\text{Fe}_3\text{O}_4$  nanoparticle surface,<sup>198</sup> the freshly prepared nanoparticles (obtained by the standard procedure by treatment of a mixture of  $\text{Fe}^{2+}$  and  $\text{Fe}^{3+}$  chlorides with aqueous  $\text{NH}_3$ ) were washed, separated into fractions by centrifuging and treated with an excess of lauric or decanoic acid, whose molecules were adsorbed on the surface of each particle. The protective role of amphiphilic molecules was manifested most clearly in the targeted synthesis of Co–Pt<sub>3</sub> nanoparticles of a strictly specified size (1.5–7.2 nm).<sup>199</sup> In the researchers' opinion, the success of the synthesis is related first of all to the use of a new stabilising agent, 1-adamantanecarboxylic acid.

The effect of cationoid (cetyltrimethylammonium bromide, CTAB) and anionoid (sodium dodecylbenzenesulfonate, DBS) surfactants on the stabilisation of  $\gamma\text{-Fe}_2\text{O}_3$  nanoparticles (4–5 nm) has been studied.<sup>200</sup> A nanoparticle having a large number of defects and dangling bonds on the surface is considered to interact with the surfactant rather strongly. This interaction has a pronounced influence on the electronic structure of the particle surface.<sup>201</sup>

Self-assembled monolayers are needed to create aqueous dispersions of magnetic nanoparticles.<sup>202</sup> Diverse magnetic colloid isotropic (magnetic emulsions<sup>203</sup> and vesicles<sup>204–206</sup>), anisotropic (steric and electrostatic ferrosmections<sup>207, 208</sup>) and lyotropic ferronematics have been obtained on the basis of nanoparticles coated by a surfactant monolayer (see Section IV).<sup>172</sup>

## VI. Types of materials containing magnetic nanoparticles

We discussed above 'free' nanoparticles as powders or suspensions (in the gas or liquid media). In practice, magnetic nanoparticles are normally used as films (2D systems) or compact materials (3D systems). The mere compacting of magnetic nanoparticles even those having a protective coating on the surface often results in the loss or substantial change in their unique physical characteristics. An optimal material should be a non-magnetic dielectric matrix with single-domain magnetic nanoparticles with a narrow size distribution regularly arranged in the matrix.

### 1. Nanoparticles on a substrate surface

The methods for the preparation of magnetic nanoparticles on substrates have been described in detail in a review.<sup>209</sup> The same review presents comparison of the properties of these systems with the properties of free clusters.

The crystalline surface of the substrate exerts an 'organising' influence on the magnetic nanoparticles, thus promoting the growth of well-crystallised particles (replication effect), even when their dimensions do not exceed 3 nm. This was confirmed by the data of high-resolution tunnelling electron microscopy, which allows one to examine the atomic structure. The Co nanoparticles with dimensions not exceeding 3 nm were obtained by the LECBD method (see Section III) on a niobium foil; the structure of these particles was modelled by a truncated multi-wall octahedron containing 1289 metal atoms.<sup>30</sup> Scanning tunneling microscopy<sup>210</sup> has been used to study the formation of bimetallic Co–Pd nanoparticles by metal vapour deposition on an  $\text{Al}_2\text{O}_3$  surface. Due to the substantial difference between the crystal structures of the two metals, their joint crystallisation and growth on the same substrate proceed according to different patterns, either the growth of a Pd layer on the Co base or the growth of a Co nanoparticle on the Pd base.

The influence of the nanoparticle size and the distance between them in the matrix on their magnetic characteristics has been studied by the LECBD technique.<sup>211</sup> Iron and cobalt nanoparticles containing about 300 atoms ( $d \approx 1.5$  nm) have been prepared by laser vaporisation. Before getting on the substrate, the particle beam passes through a time-of-flight mass spectrometer. Magnetic, structural and electric studies of these films demonstrated that the effect of the matrix on the properties of nanoparticles is slight. The obtained dependences of the magnetic properties of the material on the particle concentration in the beam allowed the researchers to trace the system evolution from the superparamagnetic to ferromagnetic state following the enhancement of the interaction between the particles.

It was shown by powder X-ray diffraction and TEM that the  $\text{ZrO}_2$  surface influences the morphology of the nanocrystallites of, for example,  $\alpha\text{-Fe}$  and  $\text{Fe}_3\text{O}_4$  formed thereon.<sup>212</sup> To prepare these, Fe was applied by the ion implantation process on a polished (100) face of cubic  $\text{ZrO}_2$  stabilised by yttrium. The subsequent heat treatment of the samples on the surface gave (depending on the conditions) either  $\alpha\text{-Fe}$  nanoparticles (10–20 nm) (1100 °C, Ar + 4%  $\text{H}_2$ ) or  $\text{Fe}_3\text{O}_4$  nanoparticles (3–9 nm) (milder conditions). To our knowledge, the formation of  $\gamma\text{-Fe}$  nanocrystallites (FCC phase) on the  $\text{ZrO}_2$  surface was detected for the first time in the same study.

In another study,<sup>213</sup> an ordered ensemble of nanoparticles was formed using a hydroxide substrate (the composition of which was not indicated) pre-modified by a polyvinylpyrrolidone or polyethyleneimine monolayer. The modified substrate was immersed for a short period (30 s) into a solution of Fe–Pt nanoparticles stabilised by oleic acid and oleylamine. The molecules of the stabilising agents weakly linked to the nanoparticle surface were displaced by the polymer functional groups, which resulted in attachment of the particle to the substrate. Repeating this process many times gave regular three-dimensional structures of magnetic nanoparticles.

### 2. Nanoparticles in matrices

It has already been noted that stabilisation of nanoparticles is a necessary condition for the production of materials with reproducible properties. A highly promising method of stabilisation is the introduction of nanoparticles in different types of matrices.

#### a. Inorganic matrices

**Zeolites and molecular sieves.** The rigid matrices (zeolites) with fixed cavities and channels have long been used to prepare and stabilise nanoparticles. A frequently used matrix is faujasite, a NaX type zeolite with cavities having a diameter of 1.3 nm and connected by channels with a diameter of 0.8 nm. Before preparing nanoparticles in zeolite channels, water is removed from the channels at 673 K. The subsequent adsorption of  $\text{Fe}(\text{CO})_5$  on the faujasite surface at 77 K and its decomposition at 453 K in vacuum result in  $\alpha\text{-Fe}$  nanoparticles (4 mass %) formed in the zeolite channels.<sup>214</sup> The X-ray diffraction data and the results of magnetic measurements do not rule out completely the possibility of formation of  $\alpha\text{-Fe}$  nanoparticles also on the external surfaces of the zeolite grains. When the NaY zeolite is used as the matrix, the standard procedure for the preparation of nanomaterials includes dehydration (2 h, 500 °C) in an inert gas flow, filling of the cavities that have become vacant with  $\text{Co}_2(\text{CO})_8$ , controlled thermal decomposition of the carbonyl inside the zeolite cavities at 200 °C and the removal of CO ligands with a hydrogen flow.<sup>215</sup> The  $^{59}\text{Co}$  NMR data (spin echo method) led the researchers to the conclusion that the NaY cavities in the resulting material contained unoxidised cobalt particles with a 0.6–1.0 nm size.

The method for nanoparticle introduction into the LTA zeolite  $\text{Na}_{12}\text{Si}_{12}\text{Al}_{12}\text{O}_{48} \cdot 27\text{H}_2\text{O}$  is basically different.<sup>216</sup> The method includes the introduction of 7.72 mass % of  $\text{Fe}^{3+}$  into ion channels by conventional ion exchange, zeolite dehydration in vacuum at 673 K and the reduction of iron ions with sodium metal vapour. The material thus obtained contained  $\alpha\text{-Fe}$  nanoparticles

(1.1 nm) in the matrix cavities. In the synthesis<sup>217</sup> of Fe nanoparticles (4–6 nm) in X- and Y-zeolites,  $\text{NaN}_3$ , which gives highly reactive Na metal upon thermal decomposition, was used as the reducing agent.

Apart from zeolites, other porous matrices, for example, molecular sieves are also used to stabilise nanoparticles. A method for the introduction of  $\gamma\text{-Fe}_2\text{O}_3$  nanoparticles (5.6 nm) into porous aluminosilicates synthesised simultaneously with nanoparticles has been developed.<sup>218</sup> The presence of nanometre-sized regular channels in the molecular sieves can be used to prepare magnetic nanostructures with anisotropic shapes inside the channels. In particular, the introduction of an aqueous solution of iron nitrate into a silicate molecular sieve (SBA-15) sample impregnated with a toluene solution of [(2-aminoethyl)amino]propyltrimethoxysilane (to modify the internal surface of the matrix) and the subsequent annealing of the sample at 600 °C in air gives  $\alpha\text{-Fe}_2\text{O}_3$  nanowire 6 nm in diameter in the matrix channels.<sup>219</sup> To take out the nanowire, the matrix was dissolved in alkali. The impregnation of a silicate molecular sieve powder of a different composition (MCM-41) with an aqueous solution of  $\text{CoCl}_2$  followed by matrix annealing for 3 h in an oxygen flow at 750 °C gave<sup>220</sup> an antiferromagnetic material containing 6 mol.% of  $\text{Co}_3\text{O}_4$  as nanoparticles (1.6 nm).

**Glass.** The conventional glass and its porous modifications are convenient matrices for nanoparticle stabilisation. A powder consisting of sodium glass ground to a grain size of several microns can exchange some  $\text{Na}^+$  ions for  $\text{Fe}^{3+}$  ions in an aqueous solution. The subsequent reduction of  $\text{Fe}^{3+}$  with hydrogen at 823–923 K affords nanoparticles (5.5–8.5 nm) consisting of  $\alpha\text{-Fe}$  and small amounts of  $\text{FeO}$ .<sup>221</sup> In another method, the  $\text{Fe}(\text{CO})_5$  vapour adsorbed by a porous glass (Porous Vycor Glass) with an average pore diameter of 10 nm was subjected to photolysis. The decomposition products filling the pores were 65% iron metal (in the researchers' opinion the rest were oxides).<sup>222</sup>

**Xerogel and silica gel.** The xerogel formed after drying (< 100 °C) of a silicic acid gel possesses good mechanical properties and a transparency comparable to that of glass. This makes this material an appropriate matrix for nanoparticle stabilisation. For example,  $\gamma\text{-Fe}_2\text{O}_3$  nanoparticles (~10 nm) were prepared in a xerogel.<sup>223</sup> The shortest distances between the particles in the matrix were shown to be 50 nm, which may imply that they are magnetically isolated. The bulk samples containing magnetically oriented superparamagnetic maghemite  $\gamma\text{-Fe}_2\text{O}_3$  nanoparticles introduced in the silica gel matrix exhibited an optical anisotropy in an external magnetic field induced by magneto-optical effects.<sup>224</sup>

**Highly dispersed  $\text{SiO}_2$  and  $\text{Al}_2\text{O}_3$ .** The methods of synthesis of highly dispersed metallic catalysts supported on the  $\text{SiO}_2$  and  $\text{Al}_2\text{O}_3$  oxides are also applicable for the preparation of magnetic nanoparticles.<sup>225</sup> Thus ultrasonic treatment of solutions of  $\text{Fe}(\text{CO})_5$  and  $\text{Co}(\text{CO})_3\text{NO}$  in decane containing ultradisperse silica gel has given silica gel particles whose pores contained (TEM data) magnetic nanoparticles, Fe, Co or Fe–Co alloy [when both  $\text{Fe}(\text{CO})_5$  and  $\text{Co}(\text{CO})_3\text{NO}$  were used simultaneously].<sup>226</sup> A high catalytic activity of these particles for the reforming of hydrocarbons or catalytic hydrogenation of CO was demonstrated. The difficulties faced by identification of Co nanoparticles on the  $\text{Al}_2\text{O}_3$  surface obtained by the reduction of Co aluminates have been discussed.<sup>227</sup>

**Magnetic nanoparticles in non-magnetic metals.** Magnetic metals can be dispersed in non-magnetic metals forming no alloys; this gives magnetic nanoparticles in a non-magnetic metal matrix. The mutual diffusion of the metal atoms in these samples is very limited. The non-magnetic matrices used most often are copper,<sup>228</sup> chromium and silver.<sup>211</sup> To prepare Co–Ag samples, a version of the LECBD method was used: a silver matrix was formed on a substrate simultaneously with deposition of Co nanoparticles (3–4 nm). A similar outcome can be attained by joint evaporation of Ag and Fe (or Co).<sup>229</sup> Cobalt nanoparticles (~3 nm) in a platinum matrix were synthesised in a similar way.<sup>230</sup>

To prepare samples containing Fe nanoparticles in mercury, 2 mass % of Na was first dissolved in mercury and the amalgam thus obtained was placed in an aqueous solution of an iron salt. After some period, iron reduced to the metallic state passed into mercury to give  $\alpha\text{-Fe}$  nanoparticles (about 4000 atoms per particle).<sup>231</sup>

An interesting series of studies is devoted to the reaction of nanodispersed non-mixing metals. The joint condensation of Fe and Li vapours onto a liquid nitrogen-cooled substrate (pentane) gives  $\alpha\text{-Fe}$  nanoparticles (3 nm) coated by a lithium metal layer.<sup>232</sup> The oxidation of these particles in air gave a powder of  $\alpha\text{-Fe}$  nanoparticles coated by a  $\text{Li}_2\text{CO}_3$  layer stable for several months. Iron nanoparticles coated by a Mg or  $\text{MgF}_2$  layer were synthesised in a similar way.<sup>233</sup>

**Dispersed carbon.** The impregnation of dispersed carbon with an aqueous solution of cobalt nitrate containing  $^{57}\text{Co}$  (10  $\mu\text{Cu}$ ), subsequent drying (1 mass % Co) and reduction in an  $\text{H}_2$  flow (573 K, 20 h) directly in the cell of a Mössbauer spectrometer resulted in the formation of Co particles with a size from 2 to 5 nm.<sup>118, 234</sup>

## b. Organic polymer matrices

The stabilisation of nanoparticles in polymer matrices is the first method for the production of magnetic nanomaterials.<sup>235, 236</sup> The monograph<sup>41</sup> devoted to the synthesis of metal nanoparticles in polymers includes a small chapter describing the preparation of magnetic materials. In recent years, a number of new interesting publications on this topic have appeared.

**Ion exchange resins.** A widely used method for the production of nanoparticles is based on the ability of ion exchange resins to absorb substantial amounts of metal ions. Further reduction or, more rarely, oxidation gave nanoparticles of the required composition inside the matrix.<sup>237</sup> Thus treatment of a resin preliminarily saturated with  $\text{Co}^{2+}$  ions with excess  $\text{NaBH}_4$  yielded Co–B-containing nanoparticles with a broad size distribution (3–30 nm).<sup>238</sup> The resin saturation with  $\text{Fe}^{2+}$  and  $\text{Fe}^{3+}$  ions and the subsequent treatment with alkali at 65 °C afforded  $\text{Fe}_3\text{O}_4$  nanoparticles with sizes of 4–15 nm.<sup>239</sup> In the case of resin impregnation with only iron(II) ions, these were partially oxidised by heating the resin at 70 °C in an aqueous solution containing a mixture of potassium nitrate and hydroxide. The magnetite nanoparticles formed inside the resin had an average diameter of 17 nm.<sup>240</sup> Using the standard Dowex resin, well characterised  $\gamma\text{-Fe}_2\text{O}_3$  nanoparticles (8.5 nm) with a narrow size distribution were obtained.<sup>241</sup>

**Soluble polymers.** If a MCC is decomposed in a polymer-containing solution, the new phase nuclei formed, after having reached a size of several nanometres, would be built into the polymer matrix due to the high surface energy. When the polymer contains heteroatoms or functional groups capable of coordination, the process is more efficient. For example, a sol of  $\gamma\text{-Fe}_2\text{O}_3$  nanoparticles is easily incorporated into polyvinyl alcohol to give a dispersion with an average particle size of 6.4 nm.<sup>242</sup> A method for the preparation of Co nanoparticles in polyvinylpyrrolidone has been reported.<sup>117, 243</sup> In this case, decomposition of  $\text{Co}(\eta^3\text{-C}_8\text{H}_{13})(\eta^4\text{-C}_8\text{H}_{12})$  is carried out in the presence of a polymer in a THF solution at 60 °C in a hydrogen flow (10 h). The black powder thus formed is purified by reprecipitation from THF or  $\text{CH}_2\text{Cl}_2$ . A similar procedure starting from the corresponding organometallic compounds<sup>244</sup> gave small (2 nm) heterometallic nanoparticles, Co–Rh and Co–Ru, in polyvinylpyrrolidone. The use of a simpler method (treatment of the polyvinylpyridine– $\text{Co}^{2+}$  complex with alkali)<sup>245</sup> gives large nanoparticles (50 nm) containing both CoO and  $\text{CoCl}_2$ .

For the synthesis of Fe containing particles,  $\text{Fe}(\text{CO})_5$  is used most often. A large series of polymers containing Fe nanoparticles (7–16 nm)<sup>246</sup> have been obtained by heating solutions of polymers and  $\text{Fe}(\text{CO})_5$  in decalin under argon (130–160 °C, 16 h). The polymers used included polybutadiene, polystyrene and styrene copolymers with butadiene, 4-vinylpyridine, *N*-vinylpyr-

rolidone, phenylvinylketoxime. The magnetic properties of the samples, which contained, according to the researchers' statement,<sup>247</sup> Co nanoparticles in polystyrene, were described.

**Carbochain polymers without heteroatoms and functional groups.** The possibility of using polymers containing no functional groups or heteroatoms as matrices for stabilisation of magnetic nanoparticles seems quite attractive, as these polymers (e.g., polyethylene and polypropylene) are good dielectrics; they are stable, inexpensive and easily processable into articles of any shape. The advantages of magnetic materials obtained using these polymers are low specific gravity, high homogeneity of nanoparticle distribution and, what is the most important, isolated arrangement of the nanoparticles at distances much greater than their dimensions. However, the lack of solubility (or poor solubility) of most polymers of this type in organic solvents appreciably restricts the possibilities of introduction and homogeneous distribution of magnetic nanoparticles with a narrow size distribution in these polymers.

The mechanochemical dispersion process, i.e., long-term grinding (up to 200 h) of an iron powder with polyethylene grains under Ar, proved to be inefficient for the preparation of a Fe–polyethylene nanocomposite.<sup>248</sup> The minimum size of the obtained particles was 10 nm (based on X-ray reflection broadening), the size distribution was broad and the distribution of particles in the matrix was nonuniform. The well developed method for forming nanoparticles (2–8 nm) in a solution (melt) of polymers in mineral oil is more promising. This method is versatile as regards both the composition of the resulting magnetic nanoparticles (Fe, Co, Ni, Fe–Co, Fe–Mo, Fe–Pt, Fe–Nd, Fe–Sm, Fe<sub>2</sub>O<sub>3</sub>, Fe<sub>3</sub>O<sub>4</sub>, ferrites) and type of polymer (low- and high-density polyethylene, polypropylene, polyamides). The content of nanoparticles in the sample can reach 60 mass %. The synthesis of magnetic nanomaterials as washers (25 × 5 mm) and thick (3 mm) films possessing good magnetic characteristics has been reported.<sup>5, 6, 249</sup>

The introduction of nanoparticles into a practically versatile carbochain polymer, namely, polytetrafluoroethylene, has been a difficult task until recently. However, recently<sup>250, 251</sup> a method for immobilisation of magnetic (Fe, Co, Ni) nanoparticles (6–12 nm) on the surface of ultradisperse polytetrafluoroethylene nanograins (150–200 nm) has been developed. Using this method, a readily magnetised sample was obtained.

**Polymers containing heteroatoms.** The polymers containing coordinating atoms can act as macromolecular ligands with respect to both metal ions and nanoparticles. In particular, they are able to replace other ligands. The introduction of Co, Fe, Fe–Pt and Co–Pt nanoparticles stabilised by oleic acid and oleylamine into a solution of polyvinylpyrrolidone or polyethyleneimine in CH<sub>2</sub>Cl<sub>2</sub> resulted in a soluble polymer containing the above-listed nanoparticles. This method was used to create polymer films with a regular arrangement of nanoparticles.

Polyvinylpyrrolidone was used<sup>252</sup> to stabilise Ni nanoparticles (3–4 nm) synthesised by the reduction of Ni(COD)<sub>2</sub> with hydrogen at room temperature, while polyacrylamide was used to produce Ni nanoparticles on  $\gamma$ -irradiation.<sup>253</sup>

**Polyimines.** An original method for the introduction of nanoparticles into polyimines<sup>254</sup> that present interest from the applied standpoint consists of saturation of the polymer by magnetic metal ions (Fe<sup>2+</sup>, Co<sup>2+</sup>) followed by air exposure of the material. The spontaneous hydrolysis of the Fe<sup>2+</sup> and Co<sup>2+</sup> salts in the polymer after the removal of water from it (during drying of the sample) yields Fe<sub>2</sub>O<sub>3</sub> and CoO nanoparticles, respectively.

Implantation of high-energy Fe<sup>+</sup> ions (40 keV) into ~1  $\mu$ m-thick polymer films has been used<sup>255</sup> to prepare Fe nanoparticles (mainly,  $\alpha$ -Fe).

**Block copolymers.** Block copolymers contain regular cavities with a lamellar, cylindrical or spherical shape, which can serve as nanoreactors for the synthesis of nanoparticles.<sup>256</sup> The synthesis of films of the [NORCOOH]<sub>30</sub>[MTD]<sub>300</sub> block copolymers (NORCOOH is 2-norbornerne-5,6-dicarboxylic acid, MTD is

methyltracyclododecene) containing  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> nanoparticles (5 nm) has been described.<sup>257</sup>

## VII. Magnetic nanoparticles in biological objects

Long before the first magnetic nanoparticles have been synthesised, they were detected in natural biological complexes. It was found that magnetic nanoparticles play an important role in the metabolism and functioning of living organism. The magnetic nanoparticles found most often in living organisms are magnetite and ferrihydrite (the mineral core of ferritin).

Magnetite-containing magnetosomes are rather abundant and have been repeatedly observed by TEM.<sup>258</sup> Highly ordered quasi-one-dimensional chain ensembles of magnetic nanoparticles of iron oxides (Fe<sub>3</sub>O<sub>4</sub> with a  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> impurity) are present in the magnetic bacteria *Magnetotactic spirillum* and play an important functional role by ensuring the orientation of bacteria in the Earth's magnetic field.<sup>7</sup> The formation of inorganic nanostructures in biological systems occurs spontaneously on contact with a highly organised molecular matrix; it is highly reproducible as regards the particle shape and composition and takes place at nearly ambient temperatures (much below 100 °C) and in the aqueous phase. These processes include a set of complex and not fully understandable reactions that substantially depend on the supramolecular organisation of particles and the structure of the organic matrix, which influences the nanoparticle nucleation and growth. For example, the bacterial protein *Listeria innocua*, having an inner cavity with a diameter of 5 nm, has been used to prepare the  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> nanoparticles with a narrow size distribution ( $9.3 \pm 0.2$  nm).<sup>259</sup> Elucidation of the mechanism of biomineralisation and their use for the development of new methods for the synthesis of nanoparticles and the effective control of their composition, structure, size and morphology can form a rather promising approach in nanobiotechnology and in the development of new nanomaterials.

The magnetic nanoparticles are found not only in bacteria but also in the cells of higher living organisms. It is considered that the anisotropic magnetite nanoparticles present in cells can interact with the Earth's magnetic pole and transfer information to other bioreceptors of the organism. Presumably, the stable space sense of many higher living organisms (for example, in the seasonal migration of birds and fishes) is related to their ability to locate themselves with respect to the Earth's magnetic field at each particular instant.

Ferritin is the most abundant form of non-haem iron in living organisms and plants.<sup>260</sup> Its major role is to preserve the biological reserve of iron.<sup>261</sup> This water-soluble protein consists of an inorganic core with a diameter of ~7 nm and a protein shell with ~6 nm thickness. The core contains ~4500 Fe<sup>3+</sup> ions<sup>262</sup> as a hydrated oxide close in composition to FeOOH<sup>263</sup> and has H<sub>2</sub>PO<sub>3</sub> groups on the external surface.<sup>264, 265</sup> In terms of the type of magnetic structure, ferritin is an antiferromagnet; however, due to the incomplete compensation of magnetic moments of the two sublattices, the ferritin core has a nonzero magnetic moment, like other magnetic nanoparticles of similar sizes. Ferritin itself exhibits superparamagnetic properties. Horse spleen ferritin is commercially available and has been comprehensively studied.<sup>266</sup>

Since natural ferritin mainly contains antiferromagnetic ferrihydrite with a relatively low magnetic moment as the core, modified magnetoferritin in which the ferrihydrite core has been replaced by a magnetite or maghemite core with a higher magnetisation is used more often for applied purposes (Fig. 4).<sup>267, 268</sup> The protein shell ensures the biocompatibility of ferritin and magnetoferritin particles.

The synthetic polymer colloids containing magnetic nanoparticles were first obtained in the mid-1970s. They have found application in biochemical experiments on the targeted interaction with cells and biologically active compounds, gene transfer and DNA extraction.<sup>269</sup> Of considerable interest is the synthesis of inorganic magnetic nanoparticles using organised molecular



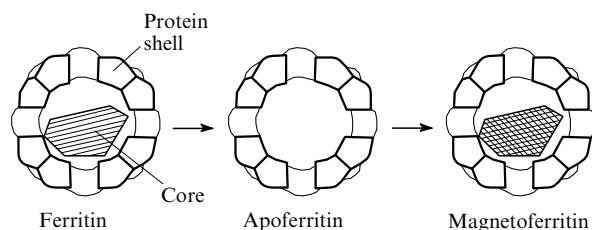


Figure 4. Scheme of the change in the magnetic core of ferritin.

structures analogous to biological systems. In particular, inclusion of magnetic nanoparticles into multilayer polyelectrolyte shells of latex particles containing glucose oxidase allowed the efficiency of these particles as nanobioreactors to be markedly increased due to the effective stirring of their colloid solution in the alternating magnetic field.<sup>270</sup>

Organised polymer systems and even single macromolecules are now widely used in nanotechnology for the formation of ordered ensembles of nanoparticles and nanostructures. The preparation of new organised planar complexes of amphiphilic polycations with DNA formed in a monolayer on the aqueous surface has been described.<sup>271</sup> In addition to individual quasi-linear DNA molecules, DNA complexes with a toroidal structure and complexes with planar, extended, and net-like structures were found on the monolayer surface. The monolayer and multilayer films formed on the basis of these complexes were used as nanoreactors for the synthesis of inorganic nanostructures. First, binding of  $\text{Fe}^{3+}$  cations from the aqueous phase took place followed by the formation of the inorganic phase in the presence of a reducing agent ( $\text{NaBH}_4$  or ascorbic acid) at pH 9–10 in air. This gave superthin stable polymeric nanocomposite films incorporating DNA molecules and assembled quasilinear ensembles of 2–4 nm iron oxide nanoparticles (magnetite and maghemite) as structural units.<sup>272–274</sup>

The introduction of iron oxide nanoparticles into DNA complexes can be used to elucidate the role of iron ions in the change in the composition and magnetic properties of nucleoprotein DNA complexes at certain stages of the cell cycle. It has been reported<sup>275</sup> that the magnetite nanoparticles formed upon mixing of  $\text{Fe}^{2+}$  and  $\text{Fe}^{3+}$  ions in the presence of DNA practically did not react with DNA. The corresponding DNA complexes with magnetite nanoparticles have been prepared by reduction (increase in the pH) of pre-synthesised DNA complexes with  $\text{Fe}^{2+}$  and  $\text{Fe}^{3+}$  ions.

Magnetic nanoparticles can be used in the systems of targeted transfer of biologically active compounds and drugs (in particular, for the cancer therapy using the hyperthermic effect caused by magnetic heating<sup>269, 276, 277</sup>), in the detection, isolation, immobilisation and modification of biologically active compounds, cells and cell organelles, and as contrasting materials in magnetic resonance tomography.<sup>258</sup> Of particular interest is the synthesis of so-called biocompatible magnetic nanoparticles, which is attained by modification and structuring of their surface.<sup>278</sup> A serious problem that can restrict the application of magnetic nanoparticles is their potential toxicity.<sup>279</sup>

## VIII. Physical methods for determination of the composition and dimensions of nanoparticles

Nanomaterials represent a relatively new object for studies by physical methods. There is no unique method for determination of the nanoparticle composition and dimensions; as a rule, a set of methods including powder X-ray diffraction, TEM, EXAFS, *etc.*, are used. Detailed analysis of the potential of these methods is beyond the scope of our review. We only outline, using a number of examples, the problems faced by researchers in determination of the nanomaterial structures and the ways for solving these problems.

X-Ray diffraction analysis of nanomaterials seldom produces diffraction patterns with a set of narrow reflections adequate for identification of the composition of the particles they contain. Some X-ray diffraction patterns exhibit only two or three broadened peaks of the whole set of reflections typical of the given phase. First of all, this is the case for freshly prepared samples containing nanoparticles with dimensions of several nanometres. To obtain more reliable information on the composition of these samples, they are 'hardened' on heating, which makes the X-ray diffraction pattern more informative.

In the case of larger particles (provided that high-quality X-ray diffraction patterns can be obtained), it is often possible not only to determine the phase composition but also to estimate, based on the reflection width, the size of coherent X-ray scattering areas, corresponding to the average crystallite (nanoparticle) size. This is usually done by the Scherrer formula

$$d = \frac{0.9\lambda(54.7)}{b \cos \theta},$$

where  $\lambda$  is the X-ray wavelength,  $b$  is the width at half-height of the reflection after correction for the instrumental broadening, deg, and  $2\theta$  is the diffraction angle.

In some cases, it is possible to identify fine structural effects, for example, phase transitions in Co metal particles. In most cases, the synthesis of cobalt nanoparticles at moderate temperatures gives the high-temperature FCC  $\beta$ -Co phase<sup>116</sup> whose heating and cooling (down to 28 K) do not result in phase transformations. In a special study<sup>280</sup> devoted to the preparation of nanoparticles of the Co metal with a hexagonal close packing, the possible reasons for the stability of Co nanoparticles as the  $\beta$ -phase and the driving forces and the mechanism of the  $\beta \rightarrow \alpha$  transition are discussed. It was found that long-term (for more than a week) keeping of samples containing  $\beta$ -Co nanoparticles in air did not cause any significant changes in their X-ray diffraction patterns. It was shown that even in thin Co films alternating with thicker Cu layers, the FCC structure of the  $\beta$ -phase is retained.

The modern possibilities of the use of synchrotron radiation for determination of the structures of magnetic materials have been discussed.<sup>281</sup>

The nanoparticle dimensions are determined most often using TEM, which directly shows the presence of nanoparticles in the material under examination and their arrangement relative to one another (Fig. 5). The phase composition of nanoparticles can be derived from electron diffraction patterns recorded for the same sample during the investigation. Note that in some cases, TEM investigations of dynamic processes are also possible. For example, the development of dislocations and disclinations in the

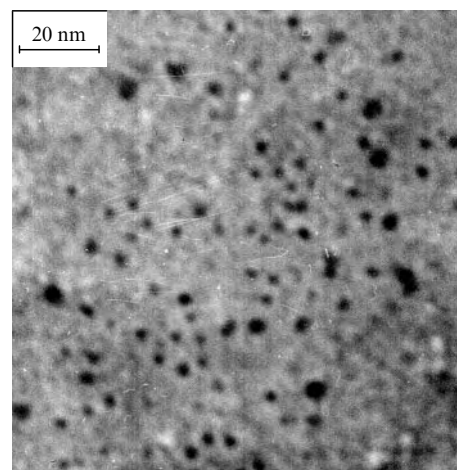


Figure 5. Micrograph of a sample containing Co nanoparticles in a polyethylene matrix.

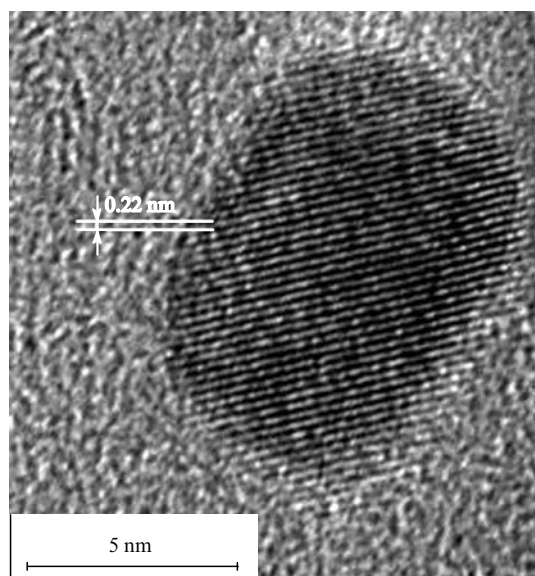


**Figure 6.** Typical HRTEM micrograph of a cobalt nanoparticle in a LDPE matrix.

nanocrystalline BCC-Fe during the mechanochemical treatment has been observed.<sup>282</sup>

More comprehensive information is provided by high-resolution transmission electron microscopy, which allows one to study the structure of both the core and the shell of a nanoparticle with atomic resolution, and in some cases, even to determine their stoichiometric composition. Figure 6 shows a typical HRTEM image of a cobalt nanoparticle in a polyethylene matrix, which allows one to determine the particle shape and dimensions, the type of crystal lattice, the distance between the layers and the presence of a shell.

The structures of non-crystalline samples are often studied by EXAFS spectroscopy. An important advantage of this method is its selectivity, because it provides the radial distribution (RDA) curve for the atoms of the local environment of the chosen chemical element in the sample. The interatomic distances ( $R$ ) and coordination numbers ( $N$ ) obtained by EXAFS are then compared with the known values for the particular phase. Thus using this method, two types of cobalt atoms were detected in the Co nanoparticles formed on laser vaporisation, namely, the internal atoms with a shortest Co–Co distance of 2.50 Å (comparable with that observed in the Co metal) and the surface atoms with a Co–Co distance of 2.80 Å.<sup>211</sup> The total number of Co–Co bonds for a Co atom, *i.e.*, its coordination number  $N$ , was equal to 11 according to EXAFS (for the bulk FCC-Co,  $N = 12$ ). The decrease in the coordination number was attributed to the presence of a large portion of surface atoms with low coordination numbers. This was used to estimate the average Co particle size (3–4 nm). These data are in good agreement with the results obtained by TEM and small-angle X-ray scattering (SAXS) for these samples.

Mössbauer spectroscopy provides data on the phase composition of nanoparticles, especially, magnetic phases. The method is widely used to determine the structure of Fe-containing nanoparticles.<sup>283–285</sup> For example, Mössbauer spectroscopy has been used to establish the composition of magnetic particles formed upon thermal decomposition of  $\text{Fe}(\text{CO})_5$  in a polyethylene matrix.<sup>6</sup> It was shown that the particles consist of  $\alpha$ -Fe,  $\gamma$ - $\text{Fe}_2\text{O}_3$  and iron carbides in ratios depending on the nanoparticle concentration in the matrix.

Other physical methods are used more rarely to study the nanoparticle structures. Integrated research makes it possible to determine rather reliably the structures of simple nanoparticles; however, determination of the structures of nanoparticles com-

posed of a core and a shell of different compositions are often faced with difficulties.

The structural studies of nanoparticles should result ultimately in the construction of structural models. Unfortunately, this is not always done. Meanwhile, the results obtained by EXAFS are difficult to interpret without model construction. For example, the construction of models for the spherical Co nanoparticles ( $d = 1.6$ – $2.6$  nm) with HCP, FCC, BCC and mixed types of packing and comparison of the RDA curves calculated for them with experimental curves indicate that the inner and surface areas of the particle have different structures.<sup>117</sup> The arrangement of atoms in the core corresponded to a BCC lattice with short Co–Co distances, while on the particle surface the arrangement of the cobalt atoms was less ordered, the relationship of distances rather resembling the HCP structure. However, the Co–Co distances inside the particle and on the surface determined experimentally differed from each other by a greater value than the corresponding postulated distances, which was not quite consistent with the model proposed.

The nanoparticle shell always contains light atoms (O, C, B, *etc.*). The problem of identification of these atoms, determination of their number and the mode of interaction with the core metal remain most challenging. The ‘cluster’ model of a nanoparticle accounts for a number of structural features of its surface layer in which the metal crystal lattice is ‘diluted’ with light atoms (O, C) according to a pattern well-known in the cluster chemistry.<sup>286</sup> According to this model, the surface layer of a particle has three types of binding between light atoms and metal polyhedra (*i.e.*, with fragments of the metal packing), namely, terminal, bridging and intrapolyhedral.

A typical example of the construction of models of these nanoparticles has been reported.<sup>50</sup> The reduction of  $\text{CoCl}_2$  with  $\text{NaBH}_4$  is accompanied by insertion of the boron atoms into the Co particle, especially, the surface layers. The comparison of the calculated dependences of the electron density for a number of model nanoparticles (neat Co;  $\text{B}_2\text{O}_3$ -coated cobalt or cobalt boride) with the experimental dependences obtained by SAXS showed that none of these models corresponds to the experimental data. It was suggested that the Co nanoparticles formed are either devoid of the ligand shell or are surrounded by a monoatomic layer, which cannot be detected by SAXS.

A number of models of the structure of nanoparticles with complex compositions are discussed in the literature. A study of iron-containing nanoparticles in the ethylene–tetrafluoroethylene (FT-40) copolymer matrix by Mössbauer and X-ray emission spectroscopy has shown<sup>287</sup> that the particle is composed of  $\alpha$ -Fe and iron carbide and fluoride (the fluoride results from defluorination of the matrix). For interpreting the results, the researchers proposed so-called ‘onion’ model for the structure of the nanoparticle with an  $\alpha$ -Fe core coated by iron fluoride and carbide shells. Figure 7 shows a version of this model describing the

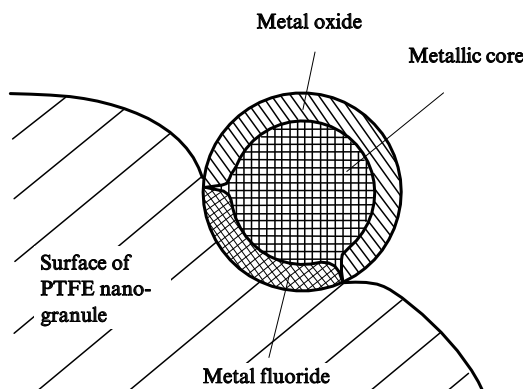


**Figure 7.** Model of the structure of a metallic nanoparticle stabilised by a PTFE grain.

structure of a nanoparticle located on the surface of a super-dispersed polytetrafluoroethylene (PTFE) nanograin.

## IX. Characteristic features of the nanoparticle magnetism (theory)

It will not be an exaggeration to say that the intensive studies of nanoparticles as a special class of objects started from the discovery of unusual magnetic properties. In 1930, Frenkel and Dorfman showed on the basis of energy considerations that particles of a sufficiently small size should be single-domain. In the mid-20th century, the theory of single-domain particles started to be actively developed<sup>288–299</sup> and the related phenomena were studied experimentally.<sup>300–309</sup> These studies identified a substantial increase in the coercive force of a ferromagnet on passing from a multidomain to the single-domain structure, which is important for the creation of permanent magnets. The results of calculation of the characteristic particle size (for different magnetic materials) where the particle becomes single-domain are presented in Table 2.

**Table 2.** Critical diameter (for room temperature) of a single-domain spherical particle with the axial magnetic anisotropy.

| Material                           | Critical diameter /nm  |                  |                  |
|------------------------------------|------------------------|------------------|------------------|
|                                    | from<br>Ref. 310       | from<br>Ref. 311 | from<br>Ref. 312 |
| Co                                 | 70                     | 70               | 68               |
| Ni                                 | —                      | 55               | 32               |
| Fe                                 | 30 (see <sup>a</sup> ) | 14               | 12               |
| BaFe <sub>12</sub> O <sub>19</sub> | —                      | —                | 580              |
| Fe <sub>3</sub> O <sub>4</sub>     | —                      | 128              | —                |
| γ-Fe <sub>2</sub> O <sub>3</sub>   | —                      | 166              | —                |
| Nd–Fe–B                            | 200                    | —                | 214              |
| SmCo <sub>5</sub>                  | 1500                   | —                | 1528             |

<sup>a</sup> A similar value (26 nm) is reported in another publication.<sup>313</sup>

The critical diameter values corresponding to particle transition from the multidomain to the single-domain state presented in the Table were calculated for spherical particles with an axial magnetic anisotropy. For other types of anisotropy (cubic, hexagonal, *etc.*) and other particle shapes, the numerical estimation of the critical diameter for the single-domain character changes. In particular, the particle can be transferred into the single-domain state without decreasing the volume if it has a shape other than a sphere, for example, an oblong ellipsoid. Experimental determination of the critical diameter above which a single-domain particle becomes multidomain is a complicated task, although now it has become possible to observe this transition directly through a magnetic force microscope<sup>314,315</sup> or a quantum magnetic interferometer (μ-SQUID).<sup>316–318</sup> For a 20 nm-thick disc-like cobalt particle, a study by a magnetic force microscope gave a critical diameter for the single-domain state of 200 nm. Elliptical particles with the same thickness became single-domain at sizes less than 150 × 450 nm. These values are markedly greater than the calculated ones (see Table 2).

To put it more exactly, the term ‘single-domain’ does not require a necessary uniform magnetisation throughout the whole particle bulk but only implies the absence of domain walls. In addition, a single-domain particle is not necessarily a ‘small’ particle (as opposed to a ‘bulk’ particle) as regards specific magnetic characteristics. Data of a publication<sup>319</sup> and their analysis<sup>320</sup> demonstrate that a rather large particle can be single-domain but still possessing the physical properties of a bulk material. Thus, the specific properties of nanoparticles start to be manifested at sizes much smaller than the ‘single-domain limit’.

It is considered that significant changes in the main physical characteristics of a bulk material appear when the dimensions of its particles decrease to an extent where the ratio of the number of surface atoms  $N_s$  to the total number  $N$  of atoms in the particle approaches 0.5.<sup>17</sup> An interesting formulation of this criterion as applied to magnetic nanoparticles has been proposed. Assuming that in a surface layer of thickness  $\Delta r$  (defectiveness parameter), the number of exchange bonds is twice as low as that in the particle bulk and that the Curie temperature is directly proportional to the bulk density of exchange bonds, Nikolaev and Shipilin<sup>320</sup> have analysed the dependence of  $T_C$  on the magnetite particle size obtained earlier.<sup>319</sup> The defectiveness parameter  $\Delta r$  was found to depend on the particle radius  $r$ . In particular, for magnetite  $\Delta r \rightarrow 0$  for  $r \geq 20$  nm (the radius for the single-domain state of magnetite is  $\sim 70$  nm, see Table 2). As the particle radius decreases, the parameter  $\Delta r$  substantially increases and for  $r = 2.5$  nm, it amounts to 0.5 nm. Thus, the smaller the magnetic particle size, the greater the effective depth to which the violation of the regular structure extends.

One more remarkable property of the nanoparticles, which allowed their experimental discovery in the mid-20th century, is the superparamagnetism. The higher the particle magnetic moment, the lower the magnetic field  $H_s$  that is required to observe the magnetisation saturation phenomenon. In a rough approximation, the  $H_s$  value (saturation field) can be estimated from the formula

$$\mu_{\text{ef}} H_s \approx k_B T,$$

where  $\mu_{\text{ef}}$  is the effective magnetic moment of the particle. For paramagnetic Gd(SO<sub>4</sub>)<sub>3</sub> · H<sub>2</sub>O, the effective magnetic moment of the Gd<sup>3+</sup> ion is 7  $\mu_B$ . Thus, the  $H_s$  value for this paramagnet at room temperature would be  $H_s \approx 300 k_B / 7 \approx 10^6$  Oe. For a particle with an effective magnetic moment of 10<sup>4</sup>  $\mu_B$ , the saturation field would decrease to 10<sup>3</sup> Oe. The phenomenon of saturation of the magnetisation curve in low (for a usual laboratory) fields of  $\sim 1$  kOe has been called ‘superparamagnetism,’ while a material exhibiting such properties is called a ‘superparamagnetic’.<sup>§</sup>

The model of an ideal superparamagnetic was mainly worked out by the early 1960s,<sup>321</sup> but now it continues to develop.<sup>312,322</sup> The simplest variant of this model considers a system of  $N$  non-interacting identical particles with the magnetic moment  $\mu_{\text{ef}}$ . Since the magnetic moment of the particle is assumed to be large, its interaction with the magnetic field  $H$  is calculated without taking the quantum effects into account. In the case of isotropic particles, the equilibrium magnetisation of the  $\langle M \rangle$  system is described by the Langevin equation

$$\langle M \rangle = N \mu_{\text{ef}} \left[ \text{cth} \left( \frac{\mu_{\text{ef}} H}{k_B T} \right) - \frac{k_B T}{\mu_{\text{ef}} H} \right]. \quad (1)$$

Equation (1) has been derived with the assumption that single particles are magnetically isotropic, *i.e.*, all directions for their magnetic moments are energetically equivalent, but this condition is hardly ever fulfilled. If the particles are magnetically anisotropic, the calculation of the equilibrium magnetisation becomes more complicated. According to the nature of factors giving rise to the non-equivalence of the directions of magnetic moments, one can distinguish the magnetically crystalline anisotropy; the shape anisotropy; anisotropy associated with the internal stress and external impact; exchange anisotropy, and so on.<sup>323</sup>

For nanoparticles, the surface magnetic anisotropy plays a special role. Unlike other kinds of magnetic anisotropy, the surface anisotropy is proportional to the surface area of the particle  $S$  rather than to its volume  $V$ . The surface anisotropy

§ Typical features of a superparamagnetic include also the absence of a magnetic hysteresis and the presence of thermal fluctuations of the magnetic moment of a nanoparticle (similar to the thermal fluctuations in a conventional paramagnetic).

appears due to the violation of the symmetry of the local environment and the change in the crystal field, which acts on magnetic ions located on the surface. Uniaxial anisotropy is the simplest type of magnetic anisotropy as regards the symmetry properties.<sup>¶</sup> In the general case, the equation for the energy of the uniaxial magnetic anisotropy is written as the sum of two contributions:

$$E(\theta) = (K_V V + K_S S) \sin^2 \theta, \quad (2)$$

where  $K_V$  is the volume anisotropy constant,  $V$  is the particle volume,  $K_S$  is the surface anisotropy constant,  $\theta$  is the angle between the vector of the particle magnetic moment  $\mathbf{m}$  and the anisotropy axis.

When the surface makes no contribution to the anisotropy, the angular dependence of the particle energy has the form

$$E(\theta) = K_V V \sin^2 \theta.$$

If no external magnetic field or surface anisotropy are present, the minimum energy of the particle is attained at the orientation of the magnetic moment  $\mathbf{m}$  along the anisotropy axis. In this case, two neighbouring minima are separated by a barrier with height  $K_V V$ . In an external magnetic field  $H$  applied at the angle  $\psi$  to the anisotropy axis, the particle energy is equal to

$$E(\theta) = K_V V \sin^2 \theta - M_s V H \cos(\theta - \psi). \quad (3)$$

(The particle is assumed to be uniformly magnetised to saturation, its magnetic moment being  $m = M_s V$ .) The dependence of the particle energy on the angle  $\theta$  for different angles  $\psi$  is shown in Fig. 8 for  $K_V = 4.5 \times 10^5 \text{ J m}^{-3}$ ,  $V = 10^3 \text{ nm}^3$ ,  $M_s = 1.4 \times 10^6 \text{ A m}^{-1}$ ,  $H = 10^5 \text{ A m}^{-1}$ . It can be seen that in the vicinity of  $\theta = 0, \pi$  and  $2\pi$ , there are three energy minima separated by non-equivalent barriers [in the case of  $\psi = 0$  and  $\pi$  (curves 1 and 5), the barriers are equivalent].

In the general case, in the presence of an external magnetic field, rotation of the magnetic moment of the particle to reach the orientation corresponding to an energy minimum requires overcoming an energy barrier,  $\Delta E \approx K_V V$ . The relation for the characteristic time of thermal fluctuations of the magnetic moment of a single-domain particle with a uniaxial anisotropy provided that  $\Delta E/k_B T \geq 1$  was obtained by Neel<sup>295</sup>

$$\tau = \tau_0 \exp\left(\frac{\Delta E}{k_B T}\right). \quad (4)$$

Later, relation (4) was extended by Brown<sup>296–299</sup> to the cubic anisotropy case.<sup>†</sup>

The pre-exponential factor  $\tau_0$  depends on many parameters including temperature, gyromagnetic ratios, saturation magnetisation, anisotropy constants, the height of energy barrier, and so on.<sup>324, 325</sup> However, for the sake of simplicity  $\tau_0$  is often considered to be a constant in the range of  $10^{-9} - 10^{-13} \text{ s}$ .<sup>311</sup>

Relation (4) determines the characteristic time needed for the thermal equilibrium in a system of non-interacting single-domain magnetic particles to establish. At higher temperatures,  $\Delta E/k_B T \ll 1$ ; the time required for system transition into a state with the minimum energy is short compared to the characteristic time of measurements  $\tau_{\text{meas}}$ , and the system is not expected to show a magnetic hysteresis. In the case where  $\Delta E/k_B T \gg 1$ , the system transition into an equilibrium state may take a very long time depending appreciably on the particle. For  $\tau_0 = 10^{-9} \text{ s}$ ,  $K_V = 10^5 \text{ J m}^{-3}$  and  $T = 300 \text{ K}$  for a magnetically anisotropic

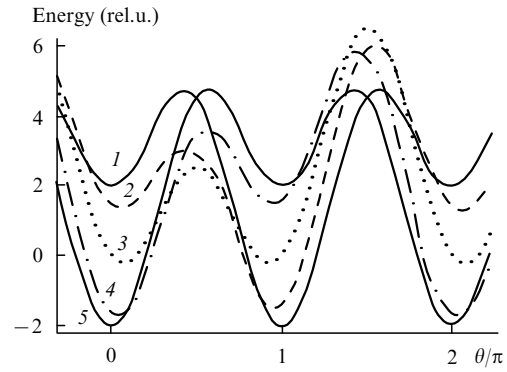


**Figure 8.** Angular dependence of the energy of a uniaxial magnetic particle  $E(\theta)$  at different orientations of the external magnetic field  $H$ .  $\psi = 180$  (1),  $135$  (2),  $90$  (3),  $35$  (4),  $0$  (5).

spherical particle  $11.4 \text{ nm}$  in diameter, we get  $\tau = 10^{-1} \text{ s}$  and for a particle with a diameter of  $14.6 \text{ nm}$ ,  $\tau = 10^8 \text{ s}$ .<sup>311</sup>

If  $\tau_{\text{meas}} \gg \tau$ , the system occurs in the superparamagnetic state and rapidly reaches an equilibrium magnetisation on changing the temperature or the external field. Otherwise ( $\tau_{\text{meas}} \ll \tau$ ), after a change in the external magnetic field, the system does not arrive to a new equilibrium state over the time  $\tau_{\text{meas}}$  and its magnetisation does not change. The case  $\tau = \tau_{\text{meas}}$  in relation (4) corresponds to the blocking temperature  $T_b$ . If  $\tau_{\text{meas}} = 100 \text{ s}$  (characteristic time for the static magnetic measurements) and  $\tau_0 = 10^{-9} \text{ s}$ , the condition  $\tau_{\text{meas}} = \tau$  in relation (4) gives  $K_V V \approx 25.3 k_B T$ . Hence,

$$T_b = \frac{K_V V}{25 k_B}. \quad (5)$$

It is noteworthy that relation (5) specifies the blocking temperature for a zero magnetic field. As the external magnetic field is enhanced, the blocking temperature decreases by a power law

$$T_b(H) = T_b(0) \left(1 - \frac{H}{H_c}\right)^\kappa, \quad (6)$$

where  $\kappa = 2$  (for low fields<sup>326</sup>) and  $2/3$  (for high fields<sup>327</sup>),  $H_c = 2 K/M_s$ .

The experimental data obtained for magnetite nanoparticles show that upon an increase in the field from zero to  $700 \text{ Oe}$ , the blocking temperature decreases from  $140$  to  $75 \text{ K}$ , relation (6) being fulfilled rather accurately below  $50 \text{ Oe}$  with  $\kappa = 2$ , and for fields from  $50$  to  $700 \text{ Oe}$ , with  $\kappa = 2/3$ .<sup>328</sup>

When investigating the magnetic properties of the samples containing nanoparticles, the magnetisation curve is usually measured up to saturation magnetisation (Fig. 9).<sup>329</sup> To deter-

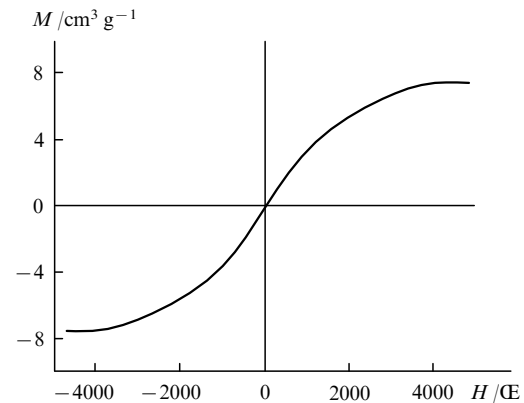


**Figure 9.** Magnetisation vs. magnetic field value (at  $295 \text{ K}$ ) for a sample containing  $\gamma\text{-Fe}_2\text{O}_3$  nanoparticles in a polyethylene matrix.<sup>329</sup>

<sup>¶</sup> The anisotropy is called uniaxial if the magnet has only one axis of easy magnetisation. The easy magnetisation axis in a magnetically anisotropic medium corresponds to a direction of the magnetisation vector relative to the crystal lattice of the magnet such that the energy of the magnetically anisotropic medium is minimum.

<sup>†</sup> In the case of cubic anisotropy, there are three mutually perpendicular easy magnetisation axes.

mine the temperature dependence of the magnetic moment  $m$ , two types of measurements are carried out, namely, zero-field cooling (ZFC) and field cooling (FC). According to the ZFC procedure, the sample is cooled (usually down to the liquid helium temperature) in the absence of a magnetic field and then a moderate measuring field is applied (1–100 Oe) and the temperature is gradually raised, the magnetic moment  $m_{\text{ZFC}}(T)$  values being recorded. The FC procedure differs from ZFC only by the fact that the sample is cooled in a nonzero magnetic field. For magnetic nanoparticles, the  $m_{\text{FC}}(T)$  and  $m_{\text{ZFC}}(T)$  curves usually coincide at relatively high temperatures but start to differ below a certain temperature  $T_{\text{ir}}$  (irreversibility temperature). The  $m_{\text{ZFC}}(T)$  curve has a maximum at some temperature  $T_{\text{max}}$ , and the  $m_{\text{FC}}(T)$  curve, most often, ascends monotonically to very low temperatures (Fig. 10). The dependence of magnetisation on the applied field at various temperatures is often additionally measured (Fig. 11).<sup>330</sup> Electron magnetic resonance and Mössbauer spectroscopy data are also used for analysis of the magnetic properties.

For an idealised system containing identical nanoparticles with uniaxial anisotropy and a random orientation of easy magnetisation axes, the difference between the temperature dependences of  $m_{\text{FC}}$  and  $m_{\text{ZFC}}$  at a qualitative level follows from Eqn (3) and Fig. 8. In the case of a zero field, on cooling below the blocking temperature, the magnetic moments of particles are oriented along their easy magnetisation axes [ $\theta = \psi = 0$  in Eqn (3)], the total magnetic moment of the system being equal to zero both at the beginning and at the end of cooling. After the

external field  $H$  has been switched on, the magnetic moments for which  $\theta - \psi < 90^\circ$  [see Eqn (3)] do not need to overcome an energy barrier and they rotate to the minimum-energy position, thus creating a non-zero magnetisation. For example, for the curve  $\psi = 35^\circ$  in Fig. 8, the rotation angle will be  $29^\circ$ . Conversely, the magnetic moments for which  $\theta - \psi > 90^\circ$  on switching on the magnetic field are separated from the energy minimum by a potential barrier which they can overcome only over a long period of time [see Eqn (4)]. Therefore, in the case of ZFC measurements for  $T < T_b$ , the system gets into a metastable state with a relatively low total magnetic moment  $M_s^2 H / 3K_V$ , which does not depend on the temperature.<sup>331</sup> When  $T = T_b$ , the system passes *via* a jump<sup>‡</sup> into a stable superparamagnetic state with the magnetic moment

$$m_{\text{ZFC}} = \frac{M_s^2 V H}{3k_B T}. \quad (7)$$

For  $M_s V H / k_B T$  and a random orientation of the axes of easy magnetisation of particles, relation (7) holds also for  $T > T_b$ .<sup>310</sup>

In the FC measurements, cooling of the sample takes place in a nonzero magnetic field; at any temperature above  $T_b$ , magnetisation is determined by Eqn (7). When  $T < T_b$ , the system magnetisation can no longer change over the time of measurements. Therefore, the magnetic moment in the FC procedure at  $T < T_b$  is equal to

$$m_{\text{FC}} \approx \frac{M_s^2 V H}{3k_B T} = \text{const.}$$

For a system consisting of single-domain nanoparticles with a size, shape, *etc.* dispersions, the  $m_{\text{ZFC}}(T)$  and  $m_{\text{FC}}(T)$  curves are not separated at  $T = T_b$ , but are separated at a higher temperature  $T_{\text{ir}} > T_b$ , which is called the irreversibility point.<sup>332</sup> Another characteristic point in the  $m_{\text{ZFC}}(T)$  curve is the temperature  $T_{\text{max}}$ , which is often identified as the average temperature of system blocking ( $T_b$ ). For a temperature below  $\langle T_b \rangle$ , an increase in  $m_{\text{FC}}(T)$  is observed, which is then replaced by a ‘saturation’ section and in some cases, by a maximum.<sup>310</sup> The  $T_{\text{ir}}$  value can be identified with the blocking temperature for the largest particles, and  $T_{\text{max}}$ , with the blocking temperature for the smallest particles. However, it should be borne in mind that all these characteristic temperatures (and their relationship with the volume distribution of particles) can depend on the rate of sample cooling and subsequent heating<sup>333</sup> and on the intensity of the interparticle interactions. If the rate of sample heating is much lower than the cooling rate, the  $m_{\text{FC}}(T)$  may have a maximum at  $T < \langle T_b \rangle$ .<sup>310</sup> In the case of strong interparticle interactions, the energy distribution of particles  $\Delta E$  [see Eqn (2)] may narrow down (in relative units  $\sigma/\mu$ , where  $\sigma$  is the dispersion,  $\mu$  is the average value) with respect to the volume distribution.<sup>310</sup> In this case, a more accurate calculation of the local magnetic field acting on a single particle is required.

‡ In experimental studies at  $T = T_b$ , sharp changes in magnetisation are never observed, because a size spread (and, generally, other types of spread) always exists for the particles. Small particles pass into the superparamagnetic state at a lower temperature than large particles and the magnetisation jump is smeared. The temperature corresponding to the maximum in the  $m_{\text{ZFC}}(T)$  curve roughly coincides with the average temperature of particle transition into the superparamagnetic state, which corresponds to the maximum distribution of all particles over the volume  $V$ . In addition, even for absolutely identical particles, the relaxation time increases smoothly rather than by a jump, although rapidly. It follows from relation (4) that

$$\frac{d\tau}{\tau} = - \left( \frac{dT}{T} \right) \left( \frac{\Delta E}{k_B T} \right) \approx -25 \left( \frac{dT}{T} \right),$$

*i.e.*, near  $T_b$  the relative change in the relaxation time is 25 times as fast as the relative change in the temperature.

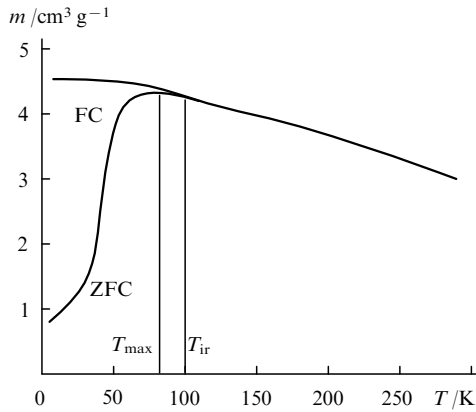


**Figure 10.** Temperature dependences of the magnetic moment (ZFC and FC measurements) for a sample containing  $\gamma\text{-Fe}_2\text{O}_3$  nanoparticles in a polyethylene matrix.

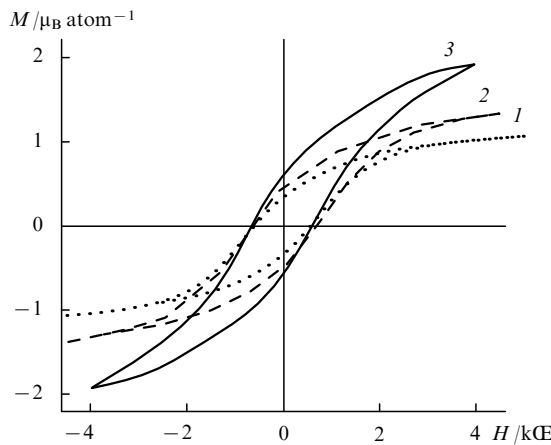


**Figure 11.** Magnetisation vs. the magnetic field at 295 (1), 77 (2) and 4.2 K (3) for a sample containing Co nanoparticles (4 mass %) in a polyethylene matrix.<sup>330</sup>

Note that the  $m_{ZFC}(T)$  and  $m_{FC}(T)$  curves differ not only for the systems of magnetic nanoparticles but also for macroscopic magnets with disorder elements (exchange coupling frustration, topological disorder, structural defects) and even in ordered ferromagnets with a substantial magnetic anisotropy.<sup>334</sup>

The difficulty of the theoretical investigation of the magnetic hysteresis in nanoparticles lies in the fact that this non-linear, non-equilibrium and non-local phenomenon caused by the existence of energy minima (resulting from the magnetic anisotropy) and the barriers separating them depends, in a complex manner, on the external magnetic field. The results of theoretical studies using relatively simple models seldom provide a plausible description for real magnetic nanomaterials as they do not take into account their microstructure, in particular, the effect of boundaries and defects on the local magnetisation.<sup>317</sup>

An important role of the microstructure in the formation of magnetic characteristics is indicated by the studies of nanocomposite materials (for example, Nd–Fe–B/ $\alpha$ -Fe<sup>335</sup> and FePt–Fe<sub>3</sub>Pt<sup>178</sup> systems), which represent a magnetically soft medium with nano-sized grains distributed therein ( $< 100$  nm).<sup>336</sup> In these materials, the magnetically hard phase ensures a high coercive force, while the magnetically soft phase provides a high saturation magnetisation. In addition, the substantial exchange interaction between the grains ensures a relative residual magnetisation higher than 0.7.<sup>335, 336</sup> Therefore, materials of this type are called exchange-coupled magnets.

In recent years attempts have been undertaken to study the effect of the internal structure (microstructure) of a nanoparticle on the magnetic characteristics of real nanomaterials.<sup>312</sup> Most successful was the use of numerical calculations within the framework of the micromagnetism theory (so-called ‘computer micromagnetism’).<sup>337–340</sup> Even when a nanoparticle has a defect-free crystal structure, the different local environments of atoms at the particle boundary and inside the particle result in a nonuniform magnetisation in the particle and distortion of the perfect collinear magnetic structure.<sup>341, 342</sup> The calculations show that at the final temperature, magnetisation decreases along the direction from the particle centre toward the boundary,<sup>343</sup> and the magnetic moment of each particular surface atom can be greater than that of the bulk atoms.<sup>344</sup> The decrease in the magnetisation on the particle surface compared to that in the bulk is due a lower energy of the surface spin wave excitations,<sup>322</sup> in other words, more pronounced action of the thermal fluctuations on the surface. The increase in the magnetic moment of surface atoms can be attributed, within the framework of the band theory, to the decrease in the coordination number, and, as a consequence, to narrowing the corresponding energy band and an increase in the density of states. Apparently, this also accounts for the rare cases of magnetic order appearing in metal nanoparticles whose bulk analogues are non-magnetic.<sup>345–348</sup>

The qualitative isothermal dependence of the coercive force  $H_c$  on the characteristic size of magnetic particles is shown in Fig. 12a. The increase in  $H_c$  upon a decrease in the particle size follows from the Stoner–Wohlfarth theory according to which the spins of atoms forming a nanoparticle rotate coherently, *i.e.*, concertedly. It is known from experiments that the coercive force in real magnetic materials (including nanomaterials) is much lower<sup>8</sup> than the limiting values predicted by the theory even at very low temperatures. One reason is that under the action of an external magnetic field, the spins of the atoms forming the nanoparticle can rotate not only coherently but also in a more complex manner to form spin modes: ‘swirls’ (Fig. 13), ‘fans’, *etc.*<sup>312</sup> The appearance of non-coherent spin modes is facilitated if nanoparticles form agglomerates (for example, chains). The coherent

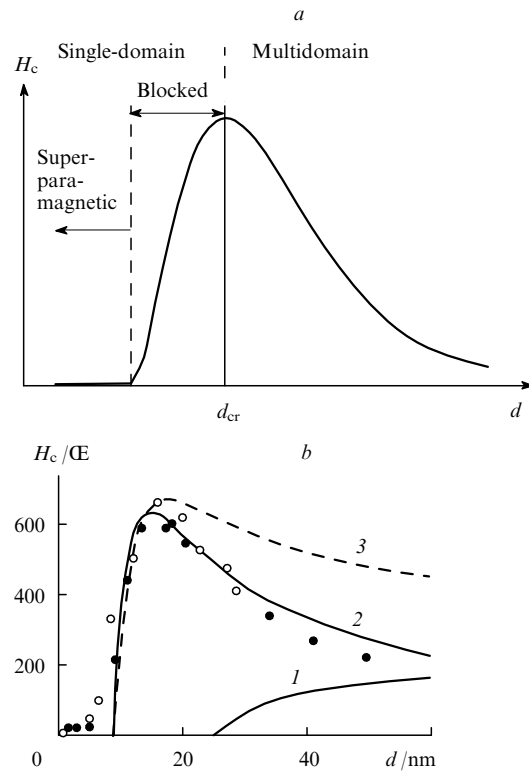


**Figure 12.** Qualitative (a) and quantitative (b) dependences of the coercive force  $H_c$  on the particle diameter.<sup>318</sup>

(a) Qualitative dependence that follows from the simple model of single-domain particle; (b) experimental (dots) and calculated (curves 1–3) dependences for iron nanoparticles. The experimental values were obtained for iron particles in oxide  $\text{Al}_2\text{O}_3$  (light dots) and  $\text{SiO}_2$  (dark dots) matrices. The calculation was carried out with the assumption that  $K_s = 4 \times 10^{-4} \text{ J m}^{-2}$  and  $K_v = 5 \times 10^4 \text{ J m}^{-3}$ ; (1) cubic bulk anisotropy, (2) axial surface anisotropy, (3) simultaneous account for the axial surface anisotropy and bulk anisotropy.

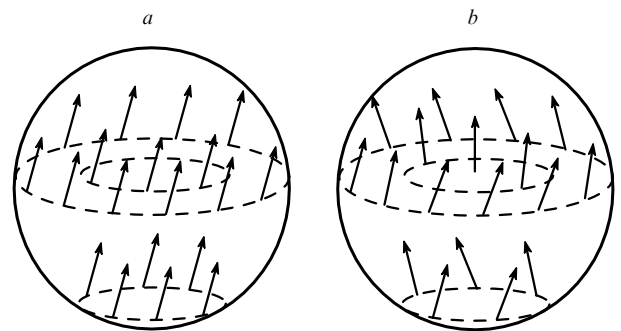


**Figure 13.** Simplest spin modes formed upon magnetisation reversal in a single-domain particle: (a) coherent rotation, (b) eddy mode.<sup>312</sup>

rotation can, apparently, take place only in absolutely defect-free uniform particles with a zero surface anisotropy.

It is evident by intuition that the coercive force should be the lower the greater the number of options (mechanisms) for spin rotation in the direction opposite to the initial one. In a multidomain particle, this rotation can be additionally associated with the displacement of domain boundaries.<sup>349</sup> As the particle size decreases, the number of domains decreases, and the role of interdomain boundaries in magnetisation reversal becomes less pronounced. Therefore, up to the critical particle size ( $d_{cr}$ , see Fig. 12a), the coercive force increases with a decrease in  $d$ . However, further decrease in the particle size and transition to

§ According to the Stoner–Wohlfarth model, the anisotropy field  $H_A = 2K_v/M_s$  is the upper limit for  $H_c$ . According to a publication,<sup>312</sup> the  $H_c$  value in real materials varies in the range of  $(0.2–0.4)H_A$ .

single-domain particles entails an increase in the role of thermal fluctuations. This explains a decrease in  $H_c$  at  $d < d_{cr}$  (see Fig. 12 a, b).

Important information on the magnetic properties of nanoparticles and material based on them can be derived from measurements of slow relaxation processes.<sup>310, 322, 328, 350</sup> In the simplest cases, for a system of identical magnetic nanoparticles, the equilibrium magnetisation upon the change in the magnetic field (for example, quick switching off) is described by the equation

$$M(t) = M_0 \exp\left(-\frac{t}{\tau}\right), \quad (8)$$

where the relaxation time  $\tau$  is determined by relation (4).

For low-temperature measurements of the residual magnetisation of systems containing magnetic nanoparticles which can exist in the blocked state, three types of experimental procedures are used<sup>¶</sup> (see Ref. 351). During the measurements of isothermal residual magnetisation (IRM), the sample is cooled in a zero magnetic field; after that, the field  $H$  is first applied and then switched off at a constant temperature  $T$ . In this case, the residual magnetisation of  $M_{IRM}$  depends on the  $H$  and  $T$  values. In the measurements of the thermal residual magnetisation  $M_{TRM}$ , the sample is placed in a constant magnetic field  $H$  at a high temperature (when all particles are superparamagnetic) and then cooled to low temperature and the field is switched off. Finally, the DC demagnetisation is measured in the same way as  $M_{IRM}$ , but the sample is first magnetised to saturation at low temperature, then the field  $H$  is switched on in the opposite direction and then switched off. In the absence of interparticle interactions<sup>328</sup>

$$M_{DCD}(H) = M_{IRM}(\infty) - 2M_{IRM}(H). \quad (9)$$

The non-observance of this rule is considered to indicate the presence of interaction between the particles,<sup>352</sup> although for a particle with mixed anisotropy (for example, uniaxial + cubic), this conclusion should be used with caution.<sup>353</sup>

For real systems, the function  $f(E)$  of particle distribution over the heights of the energy barrier always has a finite width, which is associated with the size, shape, morphology and composition differences between the particles. In this case, the relaxation properties of a system cannot be described using one parameter. For a rectangular distribution  $f(E)$ , the simple equation (8) should be replaced by the following relation<sup>311</sup>

$$M(t) = M_0 - S \ln\left(\frac{t}{\tau_0}\right), \quad (10)$$

where  $S$  is the magnetic viscosity coefficient.

If the applied external magnetic field  $H$  varies at a constant temperature, the maximum magnetic viscosity coefficient is attained at  $H = H_c$ . The logarithmic law (10) is usually confirmed experimentally only for relatively short observation periods.<sup>310</sup> The deviations from the logarithmic law can provide information on the symmetry of magnetic anisotropy, size distribution of particles, and so on.

Taking account of magnetic interactions between nanoparticles is a complicated theoretical task. In a recent discussion<sup>310, 354, 355</sup> dealing with the effect of interparticle interactions on the blocking temperature, two models were proposed, one predicting an increase in  $T_b$ ,<sup>345</sup> whereas the other, conversely, a decrease in  $T_b$ <sup>310</sup> following an enhancement of the interparticle interactions. The interactions change the height of the energy barrier separating two states of a particle with the opposite directions of the magnetic moment. If the barrier grows,  $T_b$  increases and *vice versa*. The influence of the change in the distances between the maghemite nanoparticles with a diameter

of 6–7 nm on the blocking temperature has been studied experimentally.<sup>356</sup> The distances between the particles were changed by compacting the sample. The maximum increase in the sample density was 55%; simultaneously,  $T_b$  [corresponding to the maximum in the curve  $m_{ZFC}(T)$ ] increased from 50 to 80 K. Assuming that for noncharged nanoparticles, the predominant magnetic dipole–dipole interactions are inversely proportional to the cubed distance between the particles, one can expect a linear dependence of  $T_b$  on the sample density. This is in good agreement with a publication.<sup>356</sup>

In the presence of interparticle interactions, the qualitative picture of the behaviour of a system of magnetic nanoparticles following a decrease in temperature may become more complicated than the mere transition to the blocked state.<sup>357</sup> The possible transitions are shown in Fig. 14.<sup>310</sup> If the particles are arranged irregularly in space, the interparticle interactions should transfer the system into the ‘spin glass’ type state at some temperature  $T_g$ .<sup>357</sup> Which of the temperatures, either  $T_g$  or the average blocking temperature  $\langle T_b \rangle$  would be higher for the given type of particles depends on the particle size and on the average distance between them. Since the temperature dependences of the magnetic moment (ZFC–FC) for a system of non-interacting particles and for a ‘spin glass’ are similar,<sup>358</sup> determination of the nature of the transition is a non-trivial task.

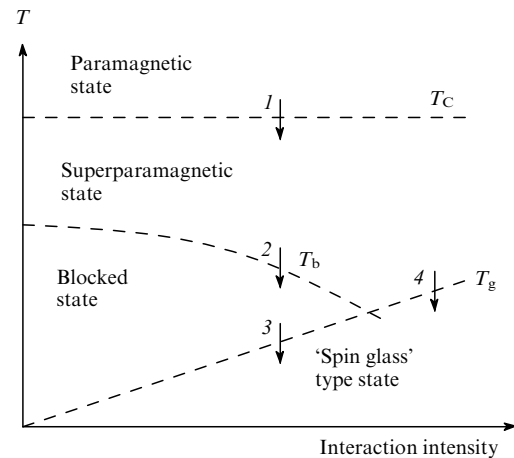


**Figure 14.** Scheme of the possible transitions in a system of magnetic nanoparticles arranged randomly in space taking into account interparticle interactions.<sup>310</sup>

(1) Transition from the paramagnetic to superparamagnetic state within single particles; (2) transition from the superparamagnetic into ‘blocked’ state; (3) transition from the ‘blocked’ state into a ‘spin glass’ type state; (4) transition from the superparamagnetic state to a ‘spin glass’ type state.

To choose theoretically between these states, one first has to know the way of estimating the interacting force in the nanoparticle system. Often, it is assumed that the interparticle interactions can be neglected if the particle concentration in the matrix is low and, hence, the average distance between them is rather high (1.5 times higher than the average particle diameter).<sup>351</sup> This assumption can be proved by verifying experimentally the fulfillment of relation (9).

Recently,<sup>359</sup> an interesting approach to taking account of the effect of interparticle interactions on the magnetisation curves of nanoparticles has been proposed. On the basis of the monotonic decrease in  $\mu_{ef}$  with a decrease in temperature observed experimentally, the researchers cited introduced phenomenological corrections into relation (1). It was assumed<sup>359</sup> that the magnetic dipole–dipole interactions, which predominate in the systems under consideration, act as a random factor and prevent magnetisation (ordering) of the system, *i.e.*, function in the same way as the temperature. It is worth noting that, although the proposed

<sup>¶</sup> These measurements are carried out at relatively low temperatures so that the particles (or their substantial portion) passed into the blocked state.

approach<sup>359</sup> is strictly applicable only to equilibrium systems, it describes satisfactorily the magnetisation curves at any temperatures, including those below the blocking temperature  $T_b$  [in this case, the average value over two branches of the hysteresis loop should be taken as  $M(H)$ ]. The applicability of this model for  $T < T_b$  is apparently due to the predominance of interparticle interactions over one-particle effects for all the samples studied.<sup>359</sup>

## X. Magnetic characteristics of nanoparticles (experimental data)

The first experimental data on the properties of magnetic nanoparticles were obtained in experiments with cluster beams.<sup>26,27</sup> Despite the difficulty of interpretation, these experiments provided the unique possibility of determining the dependence of magnetic parameters on the number of atoms in the nanoparticle. Thus isothermal dependences of the average atomic magnetic moment  $\langle\mu_{\text{ef}}\rangle$  on the number of atoms  $n$  in Fe, Co, Ni nanoparticles demonstrated for the first time that the specific magnetic moment of a nanoparticle increases with a decrease in the particle size. This trend is the most pronounced for Ni, which may be due to a higher density of the valence electrons.<sup>26</sup> The Co nanoparticles with a number of atoms  $n$  of 56 to 215 are superparamagnetic at 97 K having  $\langle\mu_{\text{ef}}\rangle = 2.24 \mu_B$ . This value is greater than the  $\mu$  values for macroscopic samples of cobalt.<sup>26,27</sup>

Thus, the experimental data imply that the effective magnetic moment of atoms in 3d-metal nanoparticles can be greater than its magnetic moment in a bulk metal. This may be attributed to the fact that the magnetic moment of an atom on the cluster surface should be regarded as localised, while in the bulk metal with band magnetism, as a delocalised (this delocalisation results in a decrease in the average magnetic moment of the atom in the bulk metal). It is noteworthy that for the smallest Ni nanoparticles, the magnetic moment barely changes with temperature over the whole temperature range studied, due to the large number of surface atoms.<sup>26</sup> For larger clusters, a non-zero contribution of surface atoms into the magnetic moment is retained even at temperatures above 631 K (the Curie temperature of the bulk phase). For Ni<sub>550–600</sub> nanoparticles, the magnetic moment at 631 K amounts to 25% of the low-temperature value  $0.6 \mu_B$ .

Thus, it follows from experiments with molecular beams that the magnetic order is retained in nanoparticles at higher temperatures than in the bulk samples,<sup>26,27</sup> which is manifested as an increase in the Curie temperature with respect to bulk phases. For cobalt ( $T_C \approx 1400$  K), the atomic magnetic moment in nanoparticles with the numbers of atoms  $n = 50–600$  changes only slightly with an increase in the temperature to  $\sim 1000$  K and always remains greater than the bulk value. The temperature dependences of the average magnetic moment for iron nanoparticles follow a more complex pattern. A possible reason is in the specific features of the iron phase diagram and structural transitions, which complicate the pattern of magnetic behaviour. No transitions to the conventional paramagnetic state were detected up to the highest temperatures ( $\sim 1000$  K).

The properties of REE clusters, namely, Gd<sup>26</sup> and Tb<sup>360</sup> clusters, are even more peculiar. Whereas 3d-metal nanoparticles behave in molecular beam experiments as either superparamagnetic particles or particles with a ‘frozen’ magnetic moment, Gd<sub>*n*</sub> clusters exhibit a dual behaviour.<sup>27</sup> Two types of clusters with the same mass but different properties have always been observed in experiments,<sup>361</sup> namely, those having properties of superparamagnetic particles and those with the properties of ‘frozen’ moment particles. It is yet unclear whether this is related to the existence of structural or magnetic isomers of the same Gd<sub>*n*</sub> cluster.

Among the gadolinium clusters studied with numbers of atoms from 11 to 92, superparamagnetic properties were found for Gd<sub>22</sub>, Gd<sub>30</sub> and Gd<sub>33</sub> (even at low temperatures).<sup>26,27,361</sup> Conversely, the Gd<sub>11–16</sub>, Gd<sub>19–21</sub>, Gd<sub>23–26</sub>, Gd<sub>53</sub>, Gd<sub>54</sub> and

some other clusters clearly exhibit ‘frozen’ magnetic moments at 100 K. As the temperature increases to room temperature, some of these clusters become superparamagnetic (for example, Gd<sub>17</sub>), whereas some other (Gd<sub>12–16</sub>, Gd<sub>19–21</sub>, Gd<sub>23</sub>, Gd<sub>26</sub>, Gd<sub>55</sub>) remain ‘frozen’. At  $800 \pm 200$  K, all the gadolinium clusters studied become superparamagnetic, the atom magnetic moments in the clusters remaining ordered, *i.e.*, the Curie temperature for gadolinium clusters is much higher than for the bulk phase (293 K). It should be noted that the effective magnetic moment per atom in all Gd<sub>*n*</sub> clusters is at least twice lower than the bulk value equal to  $7 \mu_B$ .

Terbium clusters behave similarly to gadolinium clusters.<sup>360</sup> At room temperature, the vast majority of terbium clusters are superparamagnetic. At low temperatures, many of them pass to a state characterised by a ‘frozen’ magnetic moment but some remain superparamagnetic. Using the Tb<sub>*n*</sub> clusters as examples, the influence of the addition of oxygen to a metal cluster was studied. It was found that the addition of oxygen to Tb<sub>*n*</sub> clusters, except for Tb<sub>22</sub>, does not change their magnetic properties. The magnetic moment of the superparamagnetic Tb<sub>22</sub> cluster ‘freezes’ at  $\sim 250$  K upon the addition of oxygen.

Clusters of some other elements: chromium ( $n = 9 \pm 31$ ), palladium ( $n = 100 \pm 120$ ) and vanadium ( $n = 8 \pm 99$ ) have also been studied using cluster beams.<sup>26</sup> They all proved to be paramagnetic.<sup>†</sup>

The interest in magnetic nanoparticles inserted into various matrices is due, first of all, to their potential practical use. In addition to traditional catalysis,<sup>363</sup> magnetic nanoparticles can be used for superhigh-density information recording,<sup>364–366</sup> for solving some medical problems (for example, as drug carriers)<sup>367,368</sup> and for creation of heavy-duty magnets,<sup>335,369,370</sup> ‘spin’ electronics elements<sup>281,371–374</sup> and various sensors,<sup>371,375</sup> including biomolecular ones.<sup>376</sup>

The last 10 years were marked by impressive progress in the development of materials for high-density magnetic recording. In 1992, the highest density of magnetic recording in commercial hard discs was about 10 Mbit in<sup>–2</sup>. With this recording density, the dimensions of one bit in the plane of a round-shaped magnetic medium equals  $800 \times 64 \text{ nm}^2$ . This corresponds to 40 000 bpi along the track and 25 000 tpi (see<sup>‡</sup>) in the radial direction.

In 2001, a magnetic recording density of 100 Gbit in<sup>–2</sup> was attained,<sup>366</sup> which corresponds to a bit dimensions of  $300 \times 15 \text{ nm}^2$ . In view of the fact that one storage bit now forms up to 1000 separate grains (this is due to the need to maintain the signal-to-noise ratio at a plausible level), to reach a recording density of 100 Gbit in<sup>–2</sup>, the size of one particle in the radial direction should be about 0.3 nm, *i.e.*, 2–4 atoms. Further increase in the density suggests both a decrease in the particle size and modification of the record format.

Owing to the magnetic nanomaterials, the amount of the stored information has been increased by 4 orders of magnitude during the last 20 years. The size of the hard discs of home personal computers has increased from 10 Mbyte (in the mid-1980s) to 300–500 Gbyte (currently). These achievements in the magnetic recording became possible, first of all, due to the decrease in the size of the transition region<sup>§</sup> between the neighbouring bits and a decrease in the distance between the recording head and the surface of the magnetic medium.<sup>377</sup>

† The magnetism of the nanoparticles of non-magnetic metals is beyond the scope of this review; therefore, we refer only to the most significant publications.<sup>345,346,362</sup>

‡ The plane of the round-shaped magnetic medium is divided into concentric tracks.

§ The width of the transition region for a continuous magnetic medium equals the minimum distance between the regions with opposite directions of magnetisation. For a discrete medium containing magnetic particles in a non-magnetic matrix, the width of the transition layer is equal to the average distance between the particles.



The existence of the transition region between the neighbouring 'bits' with a parallel orientation of magnetic moments (lying in the plane of the magnetic layer) is due to their 'demagnetising' fields and also the scattered field of the recording head. The width of the transition region  $a$  can be estimated from the formula

$$a \approx \frac{dM_R D}{H_c}, \quad (11)$$

where  $d$  is the distance between the recording head and the magnetic medium surface,  $M_R$  is the residual magnetisation,  $D$  is the magnetic layer thickness.<sup>377</sup> It can be seen from relation (11) that the greater the coercive force and the smaller the  $M_R D$  product, the thinner the transition layer. Thus, these two parameters are the most important characteristics of a material for magnetic recording.

Although an increase in  $H_c$  results in a higher recording density, the coercive force should not be too high, because in this case, the recording head would require creation of strong magnetic fields for magnetisation reversal.<sup>¶</sup> The characteristic  $H_c$  values for modern materials used in magnetic recording amount to  $\sim 2500$  Oe (for floppy discs)<sup>365</sup> and  $\sim 3500$  Oe (for hard discs).<sup>378, 379</sup> The recording heads with a higher coercive force should be fabricated from materials with a high saturation magnetisation, for example,  $\text{Fe}_{65}\text{Co}_{35}$ .<sup>366</sup> According to forecasts, the use of these heads would make it possible to reach a 500 Gbit in<sup>-2</sup> density of the vertical recording for a medium containing 5 nm nanoparticles with  $H_c \approx 16000$  Oe.<sup>366</sup> Among the known magnets, this coercive force is demonstrated only by Nd–Fe–B (14000 Oe) and  $\text{Sm}_2\text{Co}_{17}$ – $\text{SmCo}_5$  (9000 Oe) produced by sintering.<sup>312, 380</sup>

For  $\alpha$ -Fe, the record-breaking  $H_c$  value at room temperature ( $\sim 2700$  Oe) was observed for large cylindrical nanoparticles with a length of 250–500 nm and a diameter of 16 nm obtained in a porous aluminium matrix.<sup>109</sup> At low temperatures ( $\sim 10$  K), the values  $H_c \approx 2400$ – $2600$  Oe were found for much smaller particles (3–5 nm).<sup>121</sup> The particles formed were virtually unoxidised on the surface and their forced oxidation resulted in lowering of  $H_c$  to 2100 Oe. The coating of  $\alpha$ -Fe nanoparticles by rare earth oxides resulted in a decrease of  $H_c$  to 1750–1950 Oe.<sup>381</sup> In the researchers' opinion,<sup>382</sup> the reversal of magnetisation of these nanoparticles is a coherent rotation, *i.e.*, it corresponds to the classical Stoner–Wohlfarth model.

The coercive force of a ferromagnetic material is generally described by the formula<sup>381</sup>

$$H_c = \frac{2\alpha K_V}{M_s} - N_{\text{ef}} M_s, \quad (12)$$

where  $\alpha$  and  $N_{\text{ef}}$  are the 'microstructure defectiveness' parameter of the material.<sup>†</sup> The first term in Eqn (12) corresponds to the contribution of the crystalline magnetic anisotropy and the second one is due to the shape anisotropy. For an isolated particle,  $N_{\text{ef}}$  means the demagnetising factor; in this case,  $\alpha = 1$ . The theoretical limit for the coercive force is often estimated from the formula  $(H_c)_{\text{max}} = 2 K_V/M_s$ , which corresponds to a single-domain spherical particle with coherent magnetisation rotation. For iron, nickel and cobalt nanoparticles, the calculated  $(H_c)_{\text{max}}$  values are  $\sim 600$ ,  $\sim 200$  and  $\sim 7500$  Oe, respectively.<sup>312</sup> Note that owing to the shape anisotropy [the second term in relation (12)], coercive force values of  $\sim 14$ ,  $\sim 11$  and  $\sim 4$  kOe can be obtained for single-domain iron, cobalt and nickel particles,<sup>383</sup> which is markedly greater than  $(H_c)_{\text{max}}$ . Unfortunately, the experimental values of  $H_c$  for magnetic materials (including those containing nanocryst-

allites, nanoparticles or nanograins) rarely exceed 25%–30% of  $(H_c)_{\text{max}}$  (so-called Brown paradox).<sup>382, 384</sup>

The up-to-date permanent magnets can be assigned to nanocrystalline materials, as they consist of separate magnetic grains usually compacted by either of two methods, by sintering or from a melt. The former method yields multidomain grains with characteristic sizes of 1–20  $\mu\text{m}$  and the latter one furnishes single-domain grains with a size of 10–200 nm.<sup>381</sup> The materials for magnetic recording are also granulated. The use of a single grain as an information bit can be taken as a natural limit to the increase in the magnetic recording density.<sup>378</sup>

For reliable information storage, the magnetic moment of a particle should not change under the action of thermal fluctuations for a long period of time. To this end, the particle size should satisfy the 'superparamagnetic limit' condition according to which the particle should be in the blocked state at room temperature. At  $K_V V/300k_B = 40$ , the lifetime of a one-particle information bit is  $\sim 10$  years, while at  $K_V V/300k_B = 60$ , it is  $10^9$  years.<sup>378</sup> Thus, a decrease in the particle size requires an increase in their magnetic anisotropy.

It has already been noted that the magnetic anisotropy of nanoparticles includes a number of constituents: crystalline magnetic anisotropy, shape anisotropy, surface anisotropy and other (see Section IX).<sup>310</sup> The crystalline magnetic anisotropy, which makes the major contribution to the magnetic anisotropy, depends on the chemical composition and the crystal structure of the compound. Now the record values for the crystalline magnetic anisotropy<sup>‡</sup> (in  $\text{J m}^{-3}$ ) were found for  $\text{SmCo}_5$  ( $17.0 \times 10^6$ ),  $\text{Sm}_2\text{Fe}_4\text{B}$  ( $12.0 \times 10^6$ ),  $\text{Sm}_2\text{Fe}_{17}\text{N}_3$  ( $8.9 \times 10^6$ ),  $\text{PtFe}$  ( $6.6 \times 10^6$ ),  $\text{Pr}_2\text{Fe}_{14}\text{B}$  ( $5.6 \times 10^6$ ),  $\text{YCo}_5$  ( $5.2 \times 10^6$ ),  $\text{Nd}_2\text{Fe}_{14}\text{B}$  ( $5.0 \times 10^6$ ),  $\text{CoPt}$  ( $4.9 \times 10^6$ ),  $\text{Sm}(\text{Fe}_{11}\text{Ti})$  ( $4.9 \times 10^6$ ) and  $\text{Sm}_2\text{Co}_{17}$  ( $3.3 \times 10^6$ ).<sup>312</sup>

In the modern hard discs, the CoPt alloy with Cr, Ta, B, Mn additives needed to reduce the interaction between single grains, are used as the magnetic layer. This decreases the length of the transition region, and, as a consequence, leads to a higher recording density. The possibility of using compounds with a higher anisotropy, in particular, compounds of magnetic 3d metals with rare earth metals for magnetic recording is currently under investigation.<sup>335</sup>

Figure 12b shows the dependences of the coercive force of iron nanoparticles on their diameter  $d$  at room temperature.<sup>313</sup> Nanoparticles were obtained by radiofrequency sputtering of iron under argon (at a low pressure) followed by annealing in a vacuum. It can be seen that  $H_c$  reaches a maximum at  $d = 18$  nm, which approximately corresponds to the single-domain structure limit for  $\alpha$ -Fe. For  $d > 18$  nm, the coercive force decreases according to the law  $\sim 1/d$ . To interpret the obtained dependence, Chen *et al.*<sup>313</sup> had to assume the presence of the effective surface magnetic anisotropy  $K_{\text{ef}}$  in a particle

$$K_{\text{ef}} = \frac{6K_S}{d}. \quad (13)$$

The parameter  $K_S$  found in the study cited<sup>313</sup> was  $4 \times 10^{-4} \text{ J m}^{-2}$ . In an earlier work<sup>127</sup> in which relation (13) was first proposed, the value  $K_S \approx 10^4 \text{ J m}^{-2}$  was found to explain the presence of giant magnetic resonance in  $\alpha$ -Fe nanoparticles on a carbon (soot) surface. From the symmetry considerations, the parameter  $K_S$  for perfect spherical nanoparticles should be equal to zero;<sup>322</sup> therefore, it can apparently be used to estimate the deviation of the nanoparticle shape from spherical.<sup>127</sup>

Note that the surface anisotropy can serve as a resource for increasing the coercive force of the nanoparticle. Calculation of the influence of the surface anisotropy on  $H_c$  for the ellipsoidal maghemite nanoparticles with a longer axis of  $\sim 300$  nm has shown that for  $K_S \approx 2 \times 10^{-2} \text{ J m}^{-2}$  the coercive force ( $\sim 2$  kOe) is twice as great as that for  $K_S = 0$ .<sup>385</sup> The reasons for the difference between the magnetic properties of nanoparticles

¶ This can be avoided by heating the writable region by a laser beam, which would induce a temporary decrease in the coercive force.

† The microstructure defectiveness means any deviation from the perfect crystal structure inherent in single crystals.<sup>382</sup>

‡ All anisotropy values refer to room temperature.

formed by this class of compound with similar sizes and chemical composition have been discussed.<sup>386</sup>

The temperature dependence of the saturation magnetisation of the  $\alpha$ -Fe nanoparticles<sup>§</sup> coated by a Mg or MgF<sub>2</sub> shell has been studied.<sup>223</sup> Particles with a size of 3–18 nm were prepared by condensation in pentane at 77 K in evacuated quartz tubes. The magnetic moment was measured at a field strength of up to 55 kOe. The saturation magnetisation for iron nanoparticles with sizes of <7 nm was much lower than that for the bulk iron ( $\sim 220$  s cm<sup>3</sup> g<sup>-1</sup>).<sup>¶</sup> The temperature dependence of the magnetisation for all the particles studied corresponded approximately to the law

$$M_s(T) = M_0[1 - BT^b], \quad (14)$$

where  $B$  and  $b$  are a constant and the Bloch factor, respectively. For the bulk ferromagnets,  $b = 1.5$ , *i.e.*, the '3/2 law' holds. However, in the study cited,<sup>223</sup> this rule is valid only for particles with the characteristic size  $d > 7$  nm, whereas for smaller particles, the parameter  $b$  is much lower (thus for the Fe@MgF<sub>2</sub> nanoparticles with  $d = 3$  nm,  $b = 0.37$ ). However, for 2–3 nm iron nanoparticles in a SiO<sub>2</sub> matrix, the parameter  $b$  was 3/2,<sup>387</sup> while for MnFe<sub>2</sub>O<sub>4</sub> particles (5–15 nm),  $b = 1.5$ –1.9 were found.<sup>388</sup> A similar value ( $b = 1.9$ ) was found for the Fe<sub>x</sub>C<sub>y</sub> nanoparticles ( $d = 3.1$  nm).<sup>389</sup> The Bloch constant  $B$  for both types of nanoparticles is several orders of magnitude higher than the value for the bulk material. For the Fe@MgF<sub>2</sub> particle with  $d < 4$  nm, the  $B$  value is an order of magnitude greater than for Fe@Mg. Thus, the magnetic properties of nanoparticles (magnetisation and its temperature variation) depend more crucially on the state of the particle surface than on the particle volume.

A similar conclusion can be drawn from the results of another publication<sup>390</sup> in which three types of samples containing iron nanoparticles were studied. The average diameter of particles obtained by the reduction of oxides was about 20 nm in all samples, but the thickness of the oxide shell surrounding the metallic core was different in different samples. The saturation magnetisation  $M_s$  was  $\sim 970$ –1300 kA m<sup>-1</sup> at  $T = 1.5$  K and decreased as the oxide shell became thicker. Since the magnetisation of iron oxides is lower than that of  $\alpha$ -Fe, the decrease in  $M_s$  can be attributed to an increase in the proportion of the oxide phase in the particle volume. The different magnetisation levels can also be observed for the same phase with different levels of defectiveness.<sup>386</sup>

The smaller the particles, the more pronounced the effect of the surface layer on the magnetic properties. Figure 15 shows the temperature dependences of the coercive force of iron nanoparticles in the amorphous matrix of aluminium oxide obtained by laser vaporisation in a high vacuum.<sup>391</sup> It can be seen in HRTEM images that the particles are well isolated: the distance between separate elliptical nanoparticles is about 2.5–3.7 nm. The blocking temperatures [determined from the maximum in the  $m_{ZFC}(T)$  curve] and the coercive force (at 10 K) depend on the particle diameter.

§ The crystal structure of the particles and almost complete absence of oxide phase were proved by powder X-ray diffraction.

¶ The decrease in the saturation magnetisation of ferro-, ferri- and antiferromagnetic nanoparticles with respect to bulk samples, which is observed in experiments almost in all cases, is usually attributed to off-orientation of the atomic magnetic moments in the particle.<sup>121, 386</sup> For iron nanoparticles, the decrease in magnetisation is often correlated with an increase in their oxidation state. The magnetisation of  $\alpha$ -Fe nanoparticles was found<sup>119</sup> to be 95 S cm<sup>3</sup> g<sup>-1</sup> and the magnetisation of Fe<sub>3</sub>C nanoparticles obtained in the same way (thermal decomposition of OMC) was 132 S cm<sup>3</sup> g<sup>-1</sup>. For bulk samples, an opposite relationship between the magnetisations is observed (220 for  $\alpha$ -iron and 14 S cm<sup>3</sup> g<sup>-1</sup> for iron carbide). This inversion was attributed<sup>119</sup> to different susceptibilities of these two types of nanoparticles to oxidation (the  $\alpha$ -Fe particles are more oxidised at the surface).

| $d$ / nm | $T_b$ / K | $H_c$ / Oe |
|----------|-----------|------------|
| 4.5–4.7  | 60        | 150        |
| 7.0–7.8  | 280       | 350        |

For the largest particles, the dependence  $H_c(T)$  is described by the relation

$$H_c(T) = H_c(0) \left(1 - \frac{T}{T_b}\right)^{0.5}, \quad (15)$$

derived<sup>321</sup> with the assumption of uniform magnetisation of the nanoparticle (this cannot be the case when a substantial surface layer is present). For smaller particles, the role of the surface is more pronounced and the temperature dependence of the coercive force has a more complicated pattern (see Fig. 15). Similar changes in the course of the  $H_c(T)$  curve were observed for nanoparticles (6–8 nm) depending on the oxidation state of the surface.<sup>392</sup>

The estimate of the particle size from the  $T_b$  values using the magnetic anisotropy parameter  $K_V = 4.8 \times 10^4$  J m<sup>-3</sup> for the 'bulk'  $\alpha$ -Fe almost coincided with the TEM data. The magnetic anisotropy values of  $\alpha$ -Fe particles ranged from  $8.4 \times 10^4$  to  $1.6 \times 10^5$  J m<sup>-3</sup>, the  $K_V$  value decreased with an increase in the shell thickness. Approximately the same values of magnetic anisotropy for iron nanoparticles were reported in other publications.<sup>121, 221, 392</sup>

The dependence of the coercive force on the temperature provides one more way for the determination of the blocking temperature.<sup>248, 330, 393</sup> Figure 16 shows the temperature dependences of the saturation magnetisation  $M_s$  and the coercive force  $H_c$  for iron nanoparticles with a diameter of 5–10 nm in a silicon nitride matrix.<sup>393</sup> It can be seen that at low temperatures, the coercive force is well described by relation (15), whereas near  $T_b$  (at 100 K), determined by extrapolating  $H_c(T^{0.5})$  to zero, the experimental  $H_c$  values markedly deviate from those calculated using relation (15). This may be due to the size spread of the particles or with strong interparticle interactions.<sup>248</sup> Note that the dependence of the saturation magnetisation  $M_s$  of these particles on temperature is well described by relation (14)<sup>393</sup> over the whole temperature range because inside a nanoparticle, the magnetic order is retained even at  $T \gg T_b$ . This method for determination of the blocking temperature from the  $H_c(T)$  dependence is especially convenient in the case where  $T_b$  is much higher than room temperature. This was demonstrated<sup>330</sup> using a cobalt nanoparticle in the polyethylene matrix.

The influence of modification of nanoparticles on their magnetic properties was also studied for 'layered' particles obtained by the reverse micelle method.<sup>394</sup> In the Fe–Au particles consisting of a ferromagnetic iron core (8–10 nm) and an Au shell, a shell thickness of 2–3 nm did not influence the blocking temperature ( $\sim 50$  K) or coercive force ( $\sim 400$  Oe) to within the

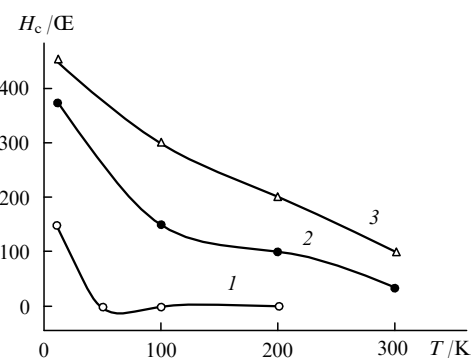


**Figure 15.** Coercive force  $H_c$  vs. temperature  $T$  for the iron nanoparticles in the Al<sub>2</sub>O<sub>3</sub> matrix.<sup>391</sup> Average particle size /nm: 4.5 (1), 7.0 (2), 9.0 (3).

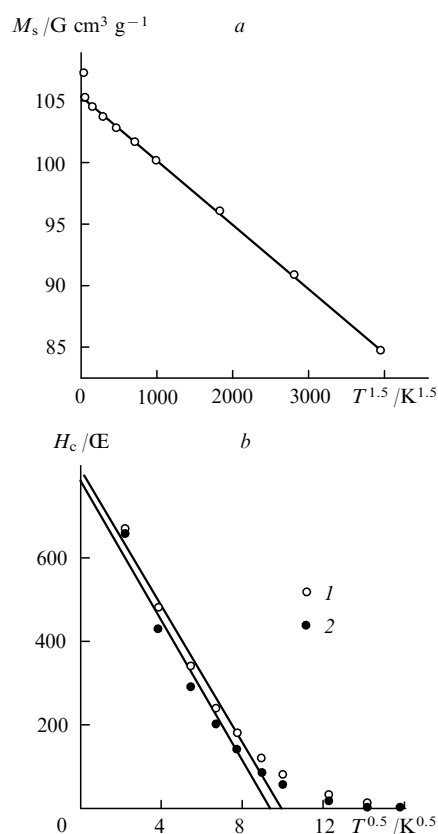


**Figure 16.** Temperature dependences of the saturation magnetisation  $M_s$  (a) and coercive force  $H_c$  (b) for iron nanoparticles (with a diameter of  $\sim 5-10$  nm) in the silicon nitride matrix.<sup>393</sup>

The dots show the experimental data and the lines correspond to calculations in terms of the simple spin wave model; dots 1 and 2 correspond to two samples obtained under roughly the same conditions (given for evaluation of reproducibility of the results).

error of measurements. Approximately equal values of  $T_b$  and  $H_c$  were observed for nano-sized ‘onion’ particles consisting of an Au core and a Fe shell, which is in turn coated by gold<sup>394</sup> (Fig. 17). On the basis of these data, it was concluded that the contact with gold does not have any noticeable influence on the magnetic properties of Fe nanoparticles.<sup>394</sup> Note that nickel particles ( $\sim 700$  nm) coated by palladium ( $\sim 10$  nm) demonstrate, conversely, a marked (approximately twofold) growth of the coercive force compared to that of Ni particle devoid of this shell.<sup>395</sup> This

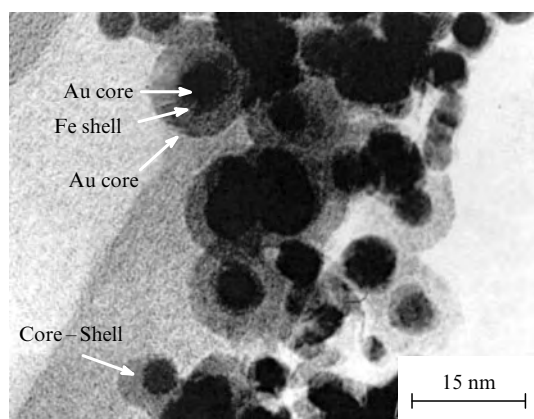


**Figure 17.** Micrograph of nanoparticles having the ‘onion’ nanostructure.<sup>394</sup>

might be due to the polarising magnetic effect of palladium atoms with respect to the ferromagnetic matrix.<sup>349</sup>

## XI. Further prospects for the study of magnetic nanoparticles

The fields considered above do not exhaust all possible aspects for the use of magnetic nanoparticles and nanomaterials. In particular, further development of electronics will be largely related to the use of magnetic nanoparticles. This is indicated by numerous works on spintronics — a new field of electronics dealing with charges and spins.<sup>371, 372, 396</sup> In recent years, considerable attention has been devoted to nanostructures based on magnetic semiconductors.<sup>397</sup> This is due to the prospects opened by the use of not only the charge of the current carriers (electrons and holes) in electronic semiconductor materials but also the magnetic moments directly related to the spin. Spin–orbit coupling may become an important tool for the control of magnetic characteristics in nanostructures.<sup>398</sup> It is expected that the use of the magnetic moment of the charge carrier would markedly extend the scope of the design of new electronic devices,<sup>399</sup> in particular, this would help to solve the problem of non-volatile superdense magnetic memory (MRAM — Magnetic Random Access Memory) which is not subject to wear on recording and reading operations.<sup>400, 401</sup>

Several groups of currently studied physical phenomena that may find application in spintronics can be distinguished:

- dependence of the electrical conductivity of a uniform material on an external magnetic field: anisotropic magnetoresistance (AMR) in thin ferromagnetic films (for example, in permalloy), giant magnetoresistance (CMR) in manganites;
- giant magnetoresistance (GMR) in structures with alternating layers of ferromagnetic and paramagnetic (or antiferromagnetic) metals and granulated structures;
- tunnelling magnetoresistance (Spin Depending Tunneling) in layered structures containing a paramagnetic (or antiferromagnetic) dielectric between layers of the ferromagnetic metal;
- injection of spin-polarised current carriers from a ferromagnetic material into a non-magnetic one;
- mutual influence of the magnetism and the density of various charge carriers in ferromagnetic semiconductors.

Many magnetoelectronic effects can be interpreted using the Mott–Campbell–Fert model according to which electrons with opposite spins are not mixed in scattering processes in a ferromagnet (two-current model). Since the density of the electron states depends appreciably on the spin, the probability of transition of a conduction electron between regions in a ferromagnet can be varied by changing their magnetisation. Thus the probability of transition between regions with a parallel orientation of the magnetisation vectors is higher (the electrical resistance is, correspondingly, lower) than that for the antiparallel orientation.

Study of the mutual influence of the magnetism and the electrical conductivity in ferromagnetic semiconductors (for example, ZnO–Mn) is a more complicated task. In these systems, the charge carriers are simultaneously mediators of the magnetic interaction between the localised magnetic moments of transition metal ions. By changing the concentration of the charge carriers (for example, by injection), one can control the strength of the magnetic interactions and, hence, the magnetic properties of the material, for example, magnetisation, which can affect the conductor resistivity.

Although the calculations show that the p-type magnetic semiconductors based on ZnO or GaN with 5% Mn and a charge carrier density of  $3.5 \times 10^{20} \text{ cm}^{-3}$  can form the basis of a material with  $T_C > 300 \text{ K}$ ,<sup>397</sup> no ferromagnetic semiconductors with a Curie temperature higher than room temperature have been obtained as yet.<sup>402</sup> Numerous accounts concerning overcoming this barrier for various compounds have not been reliably substantiated. The recognised record in this field now belongs to the

GaMnAs semiconductor with  $T_C = 110$  K.<sup>403</sup> Ferromagnetism above room temperature was discovered in the Co–ZnO, Fe, Cu–ZnO, V–ZnO and Co–TiO<sub>2</sub> samples (films or bulk samples); however, the obtained data are not perfectly reproducible.<sup>402</sup> The GaMnN, ZnO–Mn and Co–TiO<sub>2</sub> systems and other oxide semiconductors have also been mentioned as promising materials.<sup>403, 404</sup> For nanoparticles of this class, optical studies have been mainly carried out,<sup>405, 406</sup> while their magnetic properties have not been adequately studied.

Yet another problem of spintronics is the appearance of barriers at the boundaries between the layers with different magnetic or electric properties, which prevent realisation of spin–polarisation effects.

Some of the phenomena listed above have already been implemented in the GMR sensors (used, in particular, in the read heads of hard discs)<sup>371</sup> and in the first MRAM chips.<sup>407</sup> However, most of the enormous number of the proposed magnetoelectronic devices (spin filters, diodes, transistors) have not been implemented even on a laboratory scale (for example, Datta–Das spin-field-effect transistor). Some other (for example, the SPICE transistor) have been implemented as laboratory specimens, but not brought to a level of practical application as yet.<sup>408</sup>

The magnetic properties of nanoparticles can also prove quite useful for the design of quantum computers.<sup>409, 410</sup>

A revolutionary achievement is the design of MRAM chips.<sup>401</sup> This type of memory appears to be universal, because it surpasses the existing types of memory (SRAM, DRAM, FLASH, FRAM) in all important characteristics. The MRAM devices are able to compete successfully with hard discs, because at a comparable (in the future) recording density they do not contain moving parts. An especially attractive feature of the MRAM is non-volatility and wear resistance (infinite number of recording and reading events). Currently existing MRAM specimens with a 4 Mbit capacity are based on 0.18  $\mu\text{m}$  CMOS technology with a recording and reading time of 25 ns<sup>411</sup> and magnetic cells based on a magnetic tunnelling transition (MTJ).

To increase the recording density and decrease the current, it is most expedient to use ring magnetic cells.<sup>412, 413</sup> Their advantage over particles of other shapes is in the higher stability of the magnetic eddy configuration due to the absence of boundary distortions of the magnetic structure. This, in particular, can result in a decrease in the superparamagnetic limit, which would allow the use of particles of the minimum possible size. A method for the formation of ring cells on the silicon surface by means of electron lithography and subsequent molecular-beam epitaxy has been proposed.<sup>413</sup> The minimum inner diameter of particles obtained by this technique was 100 nm. A decrease in the particle size to 10 nm can increase the recording density to 400 Gbyte in<sup>–2</sup>, which is comparable with the recording density limit predicted for hard discs.<sup>412</sup>

Thus, by changing the morphology of nanoparticles (size, shape, composition, core–shell relationship, particle arrangement in the matrix), one can influence their magnetic characteristics. The crystal structure of the core and shell of the particle can be changed by heat treatment (annealing) or other methods of targeted change of nanoparticle properties. Complex particles have been obtained with regions responsible for different properties (for example, the magnetic nucleus and the biologically active shell) clearly separated in space and particles with extremal spatial characteristics (hyperplanar and ultrafine particles — nanowires). In some cases, valuable characteristics appear due to the lucky combination of the properties of particles and the matrix containing them (elastic exchange magnets, see Section IX).<sup>381, 414</sup>

However, the science of magnetic nanoparticles still has a broad spectrum of unsolved theoretical and practical problems. We would like to mention some of them.

A quantitative theory for the internal magnetic structure of nanoparticles is still lacking. The experience of using the simple theory of single-domain particles developed in the main in the mid-20 century by Neel and Brown shows that the model of

uniform (collinear) magnetisation of a nanoparticle without splitting into domains does not necessarily correspond to the real situation.<sup>312</sup> Since the solution of the static problem of distribution of magnetic moments in a nanoparticle is rather complicated, it is not surprising that a more complex dynamic task on nanoparticle magnetisation reversal is far from being solved.

One more practical problem which remains unsolved and thus holds up approaching the natural limit of the magnetic memory density is the insufficiently large (much lower than the theoretical value) coercive force of the nanoparticles suitable for the use in hard discs for technological reasons. Apparently, this is due to the complex internal magnetic structure of real nanoparticles.

The design of new highly ordered functional nanostructured composite materials with enhanced properties requires the development of effective methods for nanoparticle organisation. The future research will be aimed at development of the approaches to the synthesis of composite nanoparticles characterised by a set of practically valuable properties (magnetic, electrical, optical). Undoubtedly, magnetic nanoparticles would also find application in other fields, of which nanobiotechnology is expected to become most important. The possible use in biology and medicine, for example, as magnetic biomarkers, anticancer drugs, etc.<sup>269, 276, 277</sup>

## XII. Conclusion

Magnetic nanoparticles play an important role in the rapidly developing branches of science specialising in the study of objects (existing in nature or, more often, artificially produced) with nano-sized structural blocks. Despite the fact that the extensive use of magnetic nanoparticles (especially for biological applications<sup>415</sup>) and nanomaterials containing them is delayed by the difficulty of producing materials with a narrow size distribution of particles and stable reproducible characteristics and the high cost of their large-scale production,<sup>416</sup> such nanoparticles are used more and more often in the everyday practice. Some companies have already arranged the manufacture of the first samples of nanomaterials. In our opinion, it is time for extensive search for the ways of practical use magnetic nanoparticle.

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<sup>b</sup> — *Mendelev J. (Engl. Transl.)*

<sup>c</sup> — *Inorg. Mater. (Engl. Transl.)*

<sup>d</sup> — *Dokl. Chem. (Engl. Transl.)*

<sup>e</sup> — *Russ. J. Phys. Chem. (Engl. Transl.)*

<sup>f</sup> — *Chem. Sust. Devel. (Engl. Transl.)*

<sup>g</sup> — *J. Exp. Theor. Phys. (Engl. Transl.)*

<sup>h</sup> — *Polym. Sci. (Engl. Transl.)*

<sup>i</sup> — *Biophysics (Engl. Transl.)*

# The structures of organic molecules in crystals: simulations using the electrostatic potential

A V Yatsenko

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**Abstract.** Studies devoted to simulations of crystal lattice effects on the electronic and spatial structures of organic molecules in molecular crystals with inclusion of the external potential created by the crystal environment into the Hamiltonian of the isolated molecule are surveyed. Various methods for the representation of the charge distribution in a molecule by atomic point charges or multipoles are compared and the necessity of the empirical correction of the molecular electrostatic potential obtained using the Hartree–Fock and semiempirical calculations is substantiated. The procedures for the modification of the Hamiltonian are analysed. The limits of applicability of this approach to simulations of specific intermolecular interactions (hydrogen bonds) are discussed. Examples of the use of methods based on the application of the electrostatic potential in the calculation of the crystal lattice energy, simulations of the molecular conformations in crystals and electronic excitations are presented. The importance of the results of computation of the electronic structures of molecules in crystals for systematisation of the crystal structures and, in particular, for comparative analysis of the structures of polymorph modifications is demonstrated. The bibliography includes 117 references.

## I. Introduction

Nowadays, various quantum chemistry methods are widely applied to simulate the spatial and electronic structures of molecules. *Ab initio* calculations of molecules comprising 15–25 second-row elements using extended basis sets and taking into account the electron correlations by the Müller–Plesset method have become routine.<sup>1</sup> Calculations within Density Functional Theory (DFT) require less computational resources but are not applicable to specific problems.<sup>2</sup> Semiempirical methods are utilised in calculations of systems composed of a few hundred atoms.<sup>3,4</sup> Since researchers are interested in predicting properties of not only isolated molecules but of molecules in condensed phases (*i.e.*, in solutions, crystals, amorphous films, *etc.*) as well,

the last 15 years have witnessed the intensive development of methods that account for the medium effects in quantum-chemical calculations.

Especially tremendous progress has been achieved in the simulations of interactions between solute and solvent molecules in solutions. Such investigations exploit two approaches that make it possible to reduce the duration of calculations to an acceptable level. The first approach uses a hybrid description of the system under consideration, *i.e.*, the central molecule is represented at the quantum-mechanical level, whereas solvent molecules are treated using molecular mechanics.<sup>5</sup> Within the second approach, the solvate environment of the central molecule is represented as a dielectric continuum.<sup>6,7</sup> It is remarkable that the energy of solvation of a number of molecular ions can be predicted quite precisely and, for instance, the fact of the existence of glycine molecules as zwitter-ions in aqueous solutions can be rationalised even within a simple continuum model without taking into account specific interactions between the solute molecule and its first solvate shell.<sup>8</sup> The continuum models are also used to calculate solvatochromic effects.<sup>9–11</sup>

Taking into account that crystals are characterised by long-range ordering, one can suggest that the long-range electrostatic interactions therein play an even more important role than in solutions. Numerous theoretical and methodical procedures developed for solvation models can also be adapted to simulations of the crystalline state.

The strict quantum-chemical approach implies the calculation of the band structure of the crystal under periodic boundary conditions.<sup>12,13</sup> A number of software codes suitable for the solution of this problem are available based on the Hartree–Fock (HF),<sup>14</sup> DFT<sup>15</sup> or semiempirical<sup>16</sup> methods. In organic crystallography, however, this approach is rarely applied, probably, for two reasons: first, the band structure calculations require significantly larger computational resources than respective calculations of isolated molecules; second, direct comparison of the results of the crystal band structure and isolated molecules calculations are difficult. Still, in the majority of cases, the electronic structures of molecules in crystals do not differ, in principle, from those of isolated molecule, and thus the effects of the intermolecular interactions can be taken into account by including the external electrostatic potential (EP) into the effective Hamiltonian. Definitely, this is not valid for crystals of charge-transfer molecular complexes and for homomolecular stacking structures of organic photoconductors. But even in these cases, a one-dimensional representation<sup>17</sup> usually appears sufficient, and

**A V Yatsenko** Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation.  
Fax (7-095) 939 08 98, tel. (7-095) 939 50 89,  
e-mail: yatsenko@struct.chem.msu.ru

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the interactions between the stacks can be described in terms of the external potential.

The present review is devoted to methods for the calculation of the electrostatic interactions in organic molecular crystals and to the application of these methods to the prediction of the crystal lattice energy and simulations of the spatial and electronic structures of molecules in crystals, including the dependence of the colour of crystals on the molecular packing therein.<sup>18</sup>

## II. Two definitions of the crystal electrostatic potential

The crystal electrostatic potential can be defined as an effective potential that is experienced by an infinitely small point charge placed in the crystal lattice. For any point in space with coordinates  $r$ , it can be represented by a scalar function  $\varphi(r)$ , which depends on the charge density distribution  $\sigma(r)$

$$\varphi(r) = \int_V \frac{\sigma(r')}{|r - r'|} dr', \quad (1)$$

where the integration is performed over the entire crystal volume  $V$ .

The charge density  $\sigma(r)$  contains the nuclear and electronic terms

$$\sigma(r) = \left[ \sum_i Z_i \delta(r - R_i) \right] - \rho(r), \quad (2)$$

where  $Z_i$  and  $R_i$  are the charge and coordinates of the  $i$ -th atomic nucleus, respectively,  $\delta$  is the delta-function, and  $\rho(r)$  is the electron density.<sup>19</sup> If a crystal has a finite size, the expression for  $\varphi(r)$  should also include the potential  $\varphi_0$  dependent on the shape and structure of the crystal surface.<sup>20</sup> The distribution  $\varphi(r)$  in a crystal can be derived experimentally, for instance, using X-ray diffraction.<sup>21</sup>

A different definition of the electrostatic potential can be formulated from the standpoint of energy. The total energy of a molecular crystal can be represented within the atom–atom approximation as

$$E = E_{r-d} + E_e, \quad (3)$$

where  $E_{r-d}$  is the sum of the energies of repulsion of complete electronic shells and the dispersion attraction of atoms for all molecules in the crystal,  $E_e$  is the total energy of the intermolecular Coulomb interactions.<sup>22</sup>

The first term in formula (3) is determined using the empirical pairwise potentials 6–12 or 6–exp, the second term is calculated from the charge density distribution in the crystal given by formula (2):

$$E_e = - \sum_i \sum_j \int_V \int_V \frac{\sigma_i(r_1) \sigma_j(r_2)}{|r_1 - r_2|} dr_1 dr_2, \quad (4)$$

the integration is performed over the entire crystal volume  $V$  and the summation is performed over all pairs of molecules ( $i < j$ ) in the crystal. The expression for  $E_e$  can be reformulated as

$$E_e = -N \int_V U(r) \sigma_A(r) dr, \quad (5)$$

where  $N$  is the number of molecules in the crystal and  $U(r)$  is the electrostatic potential experienced by the molecule A, which is created by other  $N-1$  molecules in the crystal. Sometimes, the potential  $U(r)$  is referred to as the Madelung potential to differentiate it from  $\varphi(r)$  (see Ref. 23).

Analysis of topological features of the electrostatic potential distribution  $\varphi(r)$  in different crystals gives important information on the electric field inside the crystal,<sup>24,25</sup> and, in particular, on specific features of the intermolecular interactions. However, in

the present review we are concerned only with the potential  $U(r)$  and focus on the methods for its calculation and inclusion into the computational schemes of quantum chemistry.

## III. Calculation of the electrostatic potential and modification of the molecular Hamiltonian

Direct inclusion of a set of point charges (from several tens to several hundreds) around a molecule into the molecular Hamiltonian is the simplest way to model the electrostatic interactions of the molecule within its crystal environment. This does not result in any significant increase in the computational time since only the number of one-electron integrals increases. Such a procedure was used for the first time more than 30 years ago<sup>26</sup> for simulations of distortions of the structure of  $\text{H}_3\text{O}^+$  ions in crystals of  $\text{HCl} \cdot \text{H}_2\text{O}$  and  $\text{H}_2\text{SO}_4 \cdot 2\text{H}_2\text{O}$  using the HF method. The account of the effects of the environment was realised by specifying 50 point charges located at the van der Waals surface of the molecular ion. A similar approach was used in a study of crystals of cyanofornamide:<sup>27</sup> all atoms of 8 molecules from the closest environment were represented by 84 point charges, which were updated in every cycle of the self-consistent field (SCF) procedure. At present, options on the use of point charges are included in several common software codes for non-empirical calculations, such as Gaussian, Gamess and ADF.

Since the series (4) converges very slowly, the Ewald method is normally applied in crystallography for the calculation of the lattice sums.<sup>28</sup> The Ewald method was adapted to HF calculations in such a way that the calculated ‘pairwise Madelung constants’ are used for the modification of Coulomb integrals without recourse to redetermine the lattice sums in every SCF cycle.<sup>29,30</sup>

It is of note that calculation of the electrostatic contribution to the crystal lattice energy requires accurate determination of the EP, whereas changes in the structure of a molecule in the crystal are caused primarily by the potential gradients within its boundaries. The series in the expression for the potential gradient converges much faster than series (4), the rate of convergence being dependent on the space group of the crystal. Thus, in some cases, consideration of only closest neighbours (typically, within a sphere of 10–20 Å) gives quite accurate results, which are virtually not improved upon inclusion of more distant molecules into the calculation.<sup>31</sup> However, the error due to the series truncation increases for crystals composed of molecules with large dipole moments and for non-centrosymmetric space groups. In those cases, the summation has to be performed over a sphere of 100–200 Å to achieve satisfactory accuracy.<sup>32</sup>

In early studies,<sup>26,27,33</sup> the EPs of crystals were estimated from the point atomic charges calculated using the Mulliken prescription. Presently, it is widely accepted that the Mulliken charges are inappropriate for calculation of the molecular electrostatic potential (MEP)<sup>34,35</sup> and do not reproduce the dipole moments of molecules.<sup>36</sup> Therefore, alternative schemes for the representation of charge densities in molecules have been developed. Charges obtained by fitting to the MEP calculated from the charge density distribution<sup>37,38</sup> are common in molecular mechanics, however this charge retrieval procedure is an ill-posed problem and cannot be efficiently accomplished for large molecules. A procedure of empirical correction for the Mulliken charges obtained in semi-empirical [Austin Model 1 (AM1),<sup>39</sup> Parametrisation 3 (PM3),<sup>40</sup> Intermediate Neglect of Differential Overlap-Spectroscopic Parametrization (INDO/S)<sup>41</sup>] and *ab initio* calculations parametrised versus the experimental dipole moments of small organic molecules has been proposed by Truhlar *et al.*<sup>42,43</sup> These authors hoped not only to overcome the drawbacks resulting from the definition of the Mulliken charge itself but also to largely compensate for the systematic errors intrinsic to the semiempirical and HF calculations as well as for the errors of DFT calculations due to the restricted basis sets. Indeed, the above procedure reproduces the experimental values of the dipole moments with root-mean-square errors of 0.25–0.17 D (depending on the

quantum-chemical method used) for the original sample of 198 small molecules, which is 1.5–2 times smaller than those achieved in the direct calculations of the dipole moments from the charge densities. However the efficiency of the correction procedure decreases for compounds beyond the sample used for the parametrisation. For example, since nitro-compounds were not represented in the sample, the procedure not only fails to compensate for the overestimated dipole moments of compounds with an NO<sub>2</sub> group typically predicted by the AM1 and PM3 methods but gives even increased theoretical dipole moments.<sup>44</sup>

We note that the AM1 and PM3 methods provide nearly the same accuracy of calculation of the dipole moments for molecules composed of only first- and second-row elements as do the *ab initio* methods, which require significantly larger computational resources. Nitriles and nitro-compounds are the exception to this: the semiempirical methods underestimate the dipole moments of nitriles by 0.7–0.9 D and overestimate those of nitro-compounds by 0.6–0.8 D. The dipole moments calculated using the semiempirical methods better correlate with the results of the *ab initio* calculations with account for correlation effects<sup>†</sup> than those from the HF calculations.<sup>44</sup> Therefore, the semiempirical wave functions with empirical corrections for nitriles and nitro-compounds can indeed be used in the calculations of the MEPs of organic compounds without loss of accuracy.<sup>32</sup> On the other hand, the dipole moments of molecules containing sulfur, phosphorus or chlorine atoms are predicted by the semiempirical methods with significantly lower accuracy than by the *ab initio* methods with polarised basis sets.<sup>42</sup>

Among methods for the determination of atomic charges, the Hirshfeld method<sup>45</sup> is worth a special note, which assumes that the electron density at every point of the molecule should be divided over all constituent atoms proportional to their contributions to the electron density of the ‘protomolecule’, *viz.*, the respective set of atoms that do not interact chemically. Despite this unusual formulation, this method yields atomic charges that often reproduce the energy of the intermolecular interactions better than the Mulliken charges.

An extensive verification of different models based on point atomic charges has demonstrated that none of them is capable of reproducing the MEP with high accuracy.<sup>35</sup> An explicit consideration of the character of the electron density distribution in atoms, in particular its extension and asphericity (*e.g.*, lone pairs), is necessary in order to achieve the desirable level of accuracy. For this purpose, Stone proposed<sup>46,47</sup> a model of distributed multipoles, which enables determination of mono-, di-, quadrupole, *etc.* moments of atoms from the molecular wave function. Within the semiempirical methods based on the sp-basis, the quadrupole moment is the highest moment characterising a second-row element.<sup>48</sup> The original version of a common continuum model COSMO (Conductor-like Solvation Model) utilised only monopole and dipole moments of atoms, which gave satisfactory numerical results.<sup>8</sup> Later on,<sup>49</sup> the quadrupole moments were also included in the model.

According to the multi-centre model of point charges<sup>50</sup> also proposed for the semiempirical methods, an atom is represented by an atom core charge placed in the position of the atom nucleus surrounded by four pairs of charges, which mimic the native atomic orbitals.<sup>51</sup> The values of the charges are calculated based on the populations of the respective orbitals, and their distances from the atom nucleus depend on the contribution of the s-orbital into the respective sp<sup>n</sup>-hybrid orbital. The main idea behind this model is similar to that of the model of distributed multipoles, and the accuracy of the MEP calculated based on this model is higher

than those calculated within any scheme utilising point atomic charges (including those that use fitting to the MEP calculated directly from the electron density distribution). The contribution of higher electrical moments of atoms into the EP rapidly decreases with an increase in the distance; the contribution of quadrupole moments is as low as 1%–2% of the total EP at a distance of ~3.4 Å (which is the typical intermolecular distance in stacks of planar organic molecules). The contributions of quadrupole electrical moments become nevertheless substantial in crystals with short intermolecular contacts. However, the model cannot be applied to such systems, since the basic assumption of negligibly small intermolecular overlap of orbitals, which enables consideration of the intermolecular interactions within the classical theory, is then violated.<sup>52</sup>

Since the hydrogen atoms within the semiempirical calculations are assumed to possess only a 1s-orbital, they are represented in the multipole model as point charges. This representation is insufficient to correctly reproduce the MEP along the C–H direction; in order to reconcile the semiempirical results with the *ab initio* calculations [MP2/6–311+G\*\*, where 6–311+G\*\* is the Pople basis set extended with d- and p-polarisation functions with 1s-atomic orbitals approximated with six Gaussians and 2s- and 2p-orbitals approximated with five Gaussians grouped as (3,1,1)], additional point dipoles of 0.22 D<sup>52</sup> directed along the C–H bonds should be placed at the positions of all hydrogen atoms. As will be shown below, the contribution of the electrostatic interactions C–H...C into the total crystal lattice energy is small, but it has to be considered in simulations of crystal packing of aromatic hydrocarbons.<sup>53</sup>

Within a strict quantum-mechanical representation of a fragment of a crystal lattice by a cluster of *N* identical molecules composed of *M* atoms (the exchange interactions between the molecules are neglected), the following modification of the Fock matrix of a single molecule is necessary:<sup>23</sup>

$$F_{\mu\nu} = F_{\mu\nu}^0 + \left( \mu \left| \sum_{j=1}^M \sum_{i=2}^N -\frac{Z_j}{|r - R_j^i|} \right| \nu \right) + \frac{1}{2} \sum_{\lambda\sigma} P_{\lambda\sigma} \sum_{i=2}^N \left[ \left( \mu\nu | \lambda^i \sigma^i \right) + \left( \lambda\sigma | \mu^i \nu^i \right) \right], \quad (6)$$

where  $\mu$ ,  $\nu$ ,  $\lambda$  and  $\sigma$  are atomic orbitals, the superscript index *i* relates to the *i*th molecule in the cluster (*i* varies from 2 to *N*);  $Z_j$  is the nuclear charge of the *j*th atom;  $R_j^i$  is its radius-vector; *P* is the matrix of orders of the intramolecular bonds. The numerical solution of Eqn (6) represents a time-consuming task which requires calculation of numerous two-electron Coulomb integrals. The Coulomb integrals at long distances can be approximated with sufficient accuracy by two interacting multipoles, but overlapping charge distributions have to be taken into account at short distances.

Instead of Eqn (6), an approximate expression is often used, which is analogous to that used in many continuum models, *i.e.*,

$$F_{\mu\nu} = F_{\mu\nu}^0 + (\mu | U(r) | \nu), \quad (7)$$

where  $U(r)$  is the EP [see formula (5)].

The non-diagonal two-atom terms of the Hamiltonian are calculated within the semiempirical methods using empirical parameters; these terms remain constant upon modification of the Hamiltonian. Thus, the matrix element  $F_{\mu\nu}$  changes in the course of the iteration calculation only if both orbitals  $\varphi_\mu$  and  $\varphi_\nu$  belong to the same atom A.<sup>54</sup> The extension of  $U(r)$  in Eqn (7) into the Taylor series in the proximity of atom A indicates that  $U(A)$  contributes to  $F_{\mu\mu}$ ,  $U'(A)$  contributes to  $F_{\mu\nu}$  (where one of the atomic orbitals  $\mu$  or  $\nu$  is the s-orbital),  $U''(A)$  contributes to  $F_{\mu\mu}$  and  $F_{\mu\nu}$  (where both are the p-orbitals), *etc.* Higher-order derivatives can be neglected in the calculations, even neglect of the second derivative does not result in substantial errors.<sup>32,55</sup>

<sup>†</sup> DFT/TZVP and MP2/DZVP, where TZVP and DZVP are the basis sets with triply and doubly split valence atomic orbitals extended with d- and p-polarisation functions, MP2 is a method to account for the electron correlations within the approximation of the Müller–Plesset second-order perturbation theory.

Finally, we point to one fact that is almost ignored in the literature. Representation of the electrostatic contribution to the energy of the intermolecular interactions in the Coulomb form [see Eqn (4)] gives satisfactory results at large interatomic distances, but if the molecules are close to each other, the mutual repulsion of the electrons will be weaker than that predicted by the Coulomb law due to exchange and correlation interactions. It is well known from the practical use of semiempirical methods that the theoretical calculation of two-centre Coulomb integrals yields unsatisfactory results.<sup>56</sup> Thus, such integrals are determined using empirical equations which predict values much smaller than the theoretical ones at short distances. In particular, the Dewar–Sabelli–Klopman formula<sup>57,58</sup> is used for the calculation of two-centre integrals in the MNDO (Modified Neglect of Diatomic Overlap) family of methods

$$\gamma_{AB} = \left[ R_{AB}^2 + 0.25 \left( \gamma_{AA}^{-1} + \gamma_{BB}^{-1} \right)^2 \right]^{-1/2}, \quad (8)$$

where  $R_{AB}$  is the distance between atoms A and B. Thus, the modified potential determined according to the equation analogous to (8) rather than the Coulomb potential should be used for the calculation of the energy of interaction between the charge densities of molecules [see Eqn (4)]. Various types of potentials have been tested in calculations of the electronic structures of dimers of organic molecules.<sup>52</sup> In the case of the Coulomb potential, the intermolecular interactions appeared overestimated, whereas the modified potential well reproduced the results of the direct calculation of the electronic structure of molecular dimers, including ones with moderately strong H-bonds ( $O \cdots H$  and  $N \cdots H > 1.80$  Å).

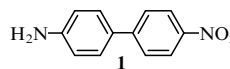
#### IV. Polarisation of molecules in crystals and the crystal lattice energy

As a rule, the intramolecular charge transfer and the dipole moment of a molecule increase on going from the gas phase to the crystal. In principle, the dipole moments of molecules in crystals can be determined experimentally by an analysis of the electron density distribution from X-ray diffraction data.<sup>59,60</sup> For simple molecules, this procedure yields results in quite good agreement with the HF calculations of crystals under periodic boundary conditions (taking into account that the Hartree–Fock dipole moments are typically overestimated by 12%–15%). Several examples are given in Table 1.

Nevertheless, in the case of large molecules, the results strongly depend on the method used for the analysis of X-ray diffraction data. For instance, high-precision diffraction data were collected<sup>67</sup> for *p*-nitroaniline and 4-amino-4'-nitrobiphenyl (**1**), which were further processed using the multipole model developed by Coppens.<sup>68</sup> Depending on the constraints imposed on the parameters  $\kappa$  and  $\kappa'$  of the multipole model (which define the degree of compression of the valence shell) during fitting, a large scatter in the values of dipole moments was observed for *p*-nitroaniline, whereas an unrealistically large value was obtained for compound **1** irrespective of the procedure applied. Probably, this poor reproducibility of the results is due to correlation between the parameters  $\kappa$  and  $\kappa'$  of neighbouring atoms, which results in incorrect assignment of the electron density in the proximity of one atom to another atom. Therefore, the results obtained using the EP can be compared with the experimental data and higher-level calculations only for simple molecules.

The molecular geometry of acetamide in crystal was calculated using the HF/4–21G method.<sup>69</sup> The potential  $U(r)$  was approximated by point Mulliken charges of 102 neighbouring molecules within a sphere of 10 Å, which were updated every SCF cycle. The account of  $U(r)$  lead to an increase in the charge transfer from the amino group to the carbonyl group, which was accompanied by shortening of the C–N bond (by 0.021 Å) and lengthening of the C=O bond (by 0.022 Å). According to the experimental data, the C=O bond length increases by 0.03 Å and the C–N bond length

**Table 1.** The dipole moments (D) of molecules in crystals according to X-ray diffraction measurements and quantum-chemical calculations under periodic boundary conditions (the CRYSTAL<sup>14</sup> code) and those based on the electrostatic potential.

| Compound                                                                           | Experiment and calculation | Isolated molecule in the crystal | Molecule in the crystal | Ref.   |
|------------------------------------------------------------------------------------|----------------------------|----------------------------------|-------------------------|--------|
| Formamide                                                                          | experiment                 | 3.7                              | 4.8                     | 61     |
|                                                                                    | CRYSTAL                    | 4.7 <sup>a</sup>                 | 6.7 <sup>a</sup>        | 62     |
|                                                                                    | SCMP-NDDO <sup>b</sup>     | 3.9                              | 5.7                     | 63     |
| Urea                                                                               | experiment                 | 3.8                              | 5.4, 4.2                | 64, 65 |
|                                                                                    | CRYSTAL                    | 5.1 <sup>a</sup>                 | 7.0 <sup>a</sup>        | 66     |
|                                                                                    | SCMP-NDDO <sup>b</sup>     | 4.5                              | 6.5                     | 63     |
| <i>p</i> -Nitroaniline                                                             | experiment                 | —                                | 2.4–16.1                | 67     |
|                                                                                    | CRYSTAL                    | 8.0 <sup>c</sup>                 | 13.3 <sup>d</sup>       | 67     |
|                                                                                    | AM1                        | 8.1                              | 10.8                    | 52     |
|  | experiment                 | —                                | 37.3–73.5               | 67     |
|                                                                                    | CRYSTAL                    | 9.2 <sup>c</sup>                 | 23.0 <sup>d</sup>       | 67     |

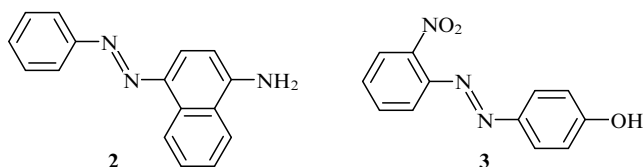
<sup>a</sup> The *ab initio* Hartree-Fock method with the 6–31G\*\* basis set. <sup>b</sup> The acronym stands for Self-Consistent Madelung Potential with Neglect of Diatomic Differential Overlap. <sup>c</sup> The *ab initio* DFT method with the Becke functional coupled with the Lee-Yang-Parr correlation functional (B3LYP) and the 6–311G\*\* basis set. <sup>d</sup> The *ab initio* Hartree-Fock method with the 6–21G\*\* basis set.

decreases by 0.043 Å on going from the gas phase<sup>70</sup> to the crystal.<sup>71</sup> Apparently, the effects of the crystal environment on the molecular geometry were underestimated in the aforementioned calculation. Probably, this is due to the fact that the model approximating the charge density by point charges is unable to correctly reproduce the effects of the intermolecular hydrogen bonds  $N-H \cdots O=C$ , which are present in the crystals of acetamide. It is of note that the maximum discrepancy between the theoretical and experimental data relates to the amino group. This indicates that, first, the neglect of the lone pairs of the oxygen atoms gives rise to underestimation of the strength of the H-bonds and, second, the representation of the hydrogen atoms of neighbouring molecules by point charges is an adequate approximation.

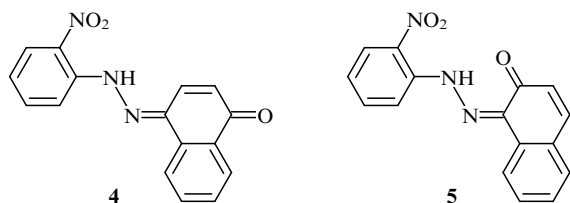
The SCMP-NDDO method, which features the AM1 parametrisation, accounts for the intermolecular van der Waals interactions based on the atom–atom potentials 6-exp and the Hamiltonian modified according to Eqn (6), was applied to 11 crystal structures formed by small polar organic molecules, including 8 compounds with intermolecular hydrogen bonds.<sup>63</sup> The results of crystal calculations for urea and formamide using this method and the HF method agree well both in terms of the absolute values and increases in the dipole moments due to crystal packing effects (see Table 1). For all 11 compounds, it was found that the increase in molecular dipole moments in the crystals was larger than in simulations of solvation in a polar solvent by the method of the self-consistent reaction field using an ellipsoidal cavity, *i.e.*, it appeared that the crystal lattice effects are stronger than the expected solvent influence.

The AM1 calculations for a sample of 79 organic crystal structures showed the mean increase in the molecular dipole moments in the respective crystals was 37%, but it varied significantly (from 14% to 100%) depending on the crystal packing motif.<sup>52</sup> A comparison of the EP effects with the solvent influence simulated by the COSMO method<sup>8</sup> demonstrated that the effect of the EP consideration exceeded the maximum possible solvent effect for 20% of the structures (half of which contained molecular ions), in an other 20% of cases, the EP effect was equivalent to that of a solvent with a dielectric permeability  $\epsilon > 10$ . The influence exerted by the crystal environment on the

packing motif can be traced for *p*-nitroaniline and *o*-methyl-*p*-nitroaniline as examples: both molecules in the isolated state are characterised by nearly identical dipole moments, but the EP induces a significant increase in the dipole moment for the former compound (see Table 1) and a decrease in the dipole moment by 1.1 D for the latter compound. For crystals containing two or more symmetrically independent molecules within the unit cell, the EP-based calculations make it possible to quantify the non-equivalency of the molecules. According to calculations performed for the crystal structures of 4-phenylazo-1-naphthylamine (**2**)<sup>72</sup> and 4-[(2-nitrophenyl)azo]phenol (**3**),<sup>73</sup> the dipole moments of molecules experiencing different crystal environments are also substantially different.



The crystal lattice effects on the electronic structures of azo dye molecules existing in the crystals in the quinonehydrazone form, 4-[(2-nitrophenyl)hydrazone]-4*H*-naphthalen-1-one (**4**)<sup>74</sup> and 1-[(2-nitrophenyl)hydrazone]-1*H*-naphthalen-2-one (**5**), were simulated using the EP.<sup>75</sup>



These molecules are characterised by rather large dipole moments (5.6 D and 6.8 D for compounds **4** and **5**, respectively) in the isolated state and form intermolecular hydrogen bonds C—H...O in the crystals. However the molecular dipole moments increase in the crystals by only 24% (**4**) and 22% (**5**).

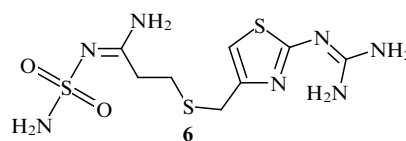
The intermolecular interactions lead to changes in the molecular polarisability. In a calculation performed for urea crystals, it was assumed that the potential is created only by molecules connected to the central molecule by hydrogen bonds.<sup>33</sup> Under this assumption, one of the components of the molecular quadratic hyperpolarisability tensor ( $\beta_{zzz}$ ) doubled nearly (from  $-44$  to  $-74$  a.u.). The EP approach was also utilised in an HF calculation for triaminotrinitrobenzene crystals.<sup>30</sup> This compound is of interest since its centrosymmetrical crystal can generate the second harmonics of laser light.<sup>76</sup> The calculations predicted a 3–4-fold enhancement of the components of the molecular tensor in the crystal; the non-linear optical properties of the crystal can be explained by violations of ordering in terms of the alternation of molecular layers in the crystal along the crystallographic direction *z*.

Applications of the atom–atom potentials method to the calculation of the crystal lattice energies was considered in detail elsewhere.<sup>77,78</sup> Here, we confine ourselves only to discussion of the role played by the electrostatic interactions. Since the empirical parameters of the potentials 6–12 and 6-exp are often determined by fitting to the experimental crystallographic and thermodynamical data, they implicitly include the mean effects of the electrostatic interactions. Some authors suggest (see, for example, Ref. 79) that it is unnecessary to additionally consider electrostatic interactions when these potentials are used. Indeed, the intermolecular interactions in crystals formed by low-polar molecules are quite successfully described based on such potentials. However, simulation of the crystal structures containing moderately strong intermolecular hydrogen bonds within this model required the introduction of six additional pairwise poten-

tials for the systems A...H—B.<sup>80</sup> It is quite possible that further extension of the range of H-bonded systems would require introduction of new types of pairwise interactions.

The explicit consideration of the electrostatic interactions seems more reasonable from the methodological viewpoint. For this purpose, the empirical parameters contained in the expression for the potential should be separated from the Coulomb contribution during their fitting to the experimental data<sup>81</sup> or determined using quantum-chemical calculations.<sup>82</sup> In order to calculate the electrostatic component, either the lone pairs have to be represented by supplementary point charges<sup>81</sup> or the multipole representation of the atomic charge densities should be used.<sup>83</sup> According to the calculations performed within the multipole model,<sup>84</sup> the ratio of the electrostatic and the van der Waals terms strongly depends on the nature of the intermolecular interactions in the crystal. In particular, in the crystal structure of benzene, the electrostatic contribution is as low as 14% of the total crystal lattice energy, whereas it amounts to 43% and 83% in the crystal structures of benzoquinone and uracil, respectively. In those calculations, the multipole moments of atoms were the same as in the isolated molecules, *i.e.*, their polarisation in the crystals was neglected.

This drawback was corrected in the aforementioned SCMP-NDDO method, which used no special parametrisation for the hydrogen bonds.<sup>63</sup> This method was applied to calculate the crystal lattice energies of 11 polar organic compounds forming intermolecular H-bonds; the mean relative error of the determined values was 7%, which is somewhat smaller than that obtained using the empirical potentials without explicit account for the electrostatic interactions ( $\sim 10\%$ , see Refs 79, 80). The SCMP-NDDO method was also used in a calculation of relative energies of conformational polymorphs of famotidine (**6**).<sup>85</sup>



The energy of an isolated molecule in the stable polymorph was higher than that of the metastable polymorph by 17.9 kJ mol<sup>-1</sup> due to sterical hindrance. However, the total energy of the molecule in the stable polymorph appears only 1.9 kJ mol<sup>-1</sup> higher than that in the metastable polymorph owing to the more efficient electrostatic interactions therein. These calculations agree with high accuracy with the fact that it is the metastable form of **6** that starts to crystallise first despite being unstable thermodynamically.<sup>86</sup>

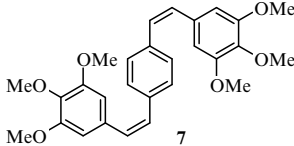
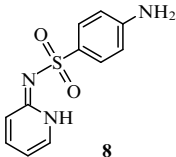
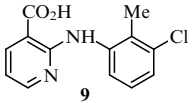
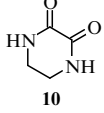
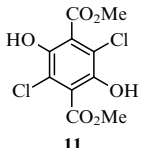
## V. Conformations of molecules in crystals

Conformations adopted by molecules of organic compounds often change upon transition from the gas phase or a solution into a crystal. Numerous examples of polymorphs formed by different conformers of a compound (so-called conformational polymorphism)<sup>87</sup> as well as the co-existence of several conformers in one crystal structure are known. Obviously, deviation of the molecular geometry in a crystal from the equilibrium geometry of the isolated molecule is caused by intermolecular interactions, including electrostatic ones.

An EP-based approach to the simulation of molecular conformations in crystals was applied for the first time to biphenyl. This example illustrates the importance of consideration of electrostatic interactions even for crystals formed by non-polar molecules. The biphenyl molecule is non-planar in the gas phase: the torsion angle between the planes of the phenyl rings  $\psi$  is 44(1)° according to electron diffraction data,<sup>88</sup> the energy barrier to planarisation is 8(2) kJ mol<sup>-1</sup>. In contrast, the molecule is planar in the crystal and occupies a special position on an inversion centre.<sup>89</sup> However a conformational analysis of the biphenyl



**Table 2.** Examples of calculations of molecular conformations in crystals based on the electrostatic potential.

| Compound                                                                              | Method                               | Comment                                                                                        | Ref.     |
|---------------------------------------------------------------------------------------|--------------------------------------|------------------------------------------------------------------------------------------------|----------|
| But-3-en-2-ol                                                                         | HF/4–21G, APC <sup>a</sup>           | a clathrate C <sub>4</sub> H <sub>8</sub> O · 2 C <sub>33</sub> H <sub>36</sub> O <sub>6</sub> | 94       |
| Glycine                                                                               | HF/6–31G, supermolecule <sup>b</sup> | three polymorphs with similar molecular conformations                                          | 95       |
|  7   | HF/4–21G, APC <sup>a</sup>           | <i>trans,trans</i> - and <i>cis,cis</i> -isomers                                               | 96       |
|  8   | HF/6–31G, APC <sup>a</sup>           | four conformational polymorphs                                                                 | 97       |
|  9   | HF/6–31G, APC <sup>a</sup>           | four polymorphs containing different tautomers and conformers                                  | 98       |
|  10  | HF/4–21G, APC <sup>a</sup>           | a change in the conformation of the ring in the crystal                                        | 99, 100  |
|  11 | HF/6–31G, supermolecule <sup>b</sup> | three polymorphs, one of them contains two crystallographically independent molecules          | 101, 102 |

<sup>a</sup> APC means atomic point charges determined according to the Mulliken or Hirshfeld prescription. <sup>b</sup> Supermolecule is a cluster composed of 15 molecules surrounded by atomic point charges.

moiety in 68 crystal structures revealed<sup>90</sup> that, despite the majority of molecules is grouped at around  $\psi = 40^\circ$ , the planar or nearly planar geometry occurs much more frequently than it being allowed by the Boltzmann distribution with the torsion potential of the isolated molecule. A study of the phonon spectrum of crystals of biphenyl showed that the observed planar geometry is a result of dynamical disorder,<sup>91</sup> the energy minimum corresponds to  $\psi = \pm 20^\circ$ , and the height of the energy barrier to planarisation is 3.4 kJ mol<sup>−1</sup>.

The quantum-chemical calculation of a crystal of biphenyl was performed using the HF/4–21G method; the coordination shell included 36 neighbouring molecules, their atoms were represented by point Mulliken charges.<sup>92</sup> We note that in this case (the absence of the lone pairs and short intermolecular contacts and the zero dipole moment of the molecule), this approximation is satisfactory. The calculation yielded  $\psi = 45.7^\circ$  and a planarisation barrier of 7.9 kJ mol<sup>−1</sup> for the isolated molecule, which is in good agreement with the experimental data. The barrier height and the torsion angle decreased to 3 kJ mol<sup>−1</sup> and 27°, respectively, following the introduction of the crystal EP into the calculations.

The biphenyl molecules in the crystal structure are packed in a herring-bone arrangement: the C–H bonds are approximately perpendicular to the planes of the phenyl groups of neighbouring molecules. The C–H··· $\pi$  interactions in the crystal structures of aromatic hydrocarbons are sometimes considered as a particular case of very weak hydrogen bonds,<sup>93</sup> which decrease the energy of the  $\pi$ -orbitals and, consequently, promote stronger  $\pi$ -delocalisation over the molecule. Similar packing motifs are observed in a number of other crystal structures containing the biphenyl fragment; the angle  $\psi$  exceeds 25° in none of these structures (see

Ref. 90). Thus, the simulation of the EP effects on the conformation of the biphenyl molecules established the reason for the planarisation of the biphenyl fragment for the whole class of similar compounds.

Other examples of application of the EP to simulations of molecular conformations in crystals are listed in Table 2.

Optimisation of the molecular geometry based on the atomic point charges led in some cases to results contradictory to the experimental crystallographic data. In particular, abnormally short intermolecular contacts were revealed in one out of four polymorphs of **8** and in two out of four polymorphs of **9**. The results were more accurate when a molecular cluster surrounded by point charges was used in the calculation. For instance, both methods were applied to polymorphs of glycine, and the deviations of the calculated torsion angles from the experimental values were 3–5 times larger in the calculation of a single molecule in the field of point charges than in the calculation of a molecular cluster. On the one hand, failures in the use of the model of atomic point charges can be due to the inadequacy of the model for the calculation of the EP in these systems, since all of them contain intermolecular hydrogen bonds. On the other hand, the use of a molecular cluster implicitly takes into account the effects of the van der Waals interactions on the molecular geometry, since too short distances between atoms of neighbouring molecules are avoided in the cluster calculations.

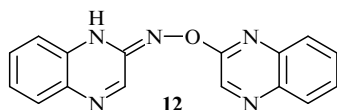
## VI. Crystal packing effects on the energy of electronic transitions

The first examples of the existence of organic compounds as crystalline forms with different colours were described in the



beginning of the 20th century.<sup>103</sup> At present, the Cambridge Structural Database<sup>104</sup> stores information on more than 50 families of differently coloured polymorphs and pseudopolymorphs, although solid-state spectral data have been reported for only a few representatives. Various reasons can be responsible for the differences in colours of molecular crystals. Firstly, the molecules in the crystals can adopt different conformations or exist as tautomeric forms which differ substantially in the degree of intramolecular conjugation. For instance, one of the aforementioned polymorphs of **11** is yellow, the second one is pale yellow, whereas the third one is colourless. The molecules in the yellow polymorph are nearly planar; the CO<sub>2</sub>Me and OH groups are turned by 68–83° and 32–51°, respectively, in the colourless polymorph due to intermolecular hydrogen bonds and they occupy intermediate positions in the pale yellow polymorph. Secondly, changes in the colour can be due to excitonic effects or intermolecular charge transfer.<sup>105</sup> Finally, by analogy with solvatochromic effects, the absorption bands in a crystal can shift due to polarisation of the molecule in the crystal environment. We consider this phenomenon in more detail below.

#### Compound 12

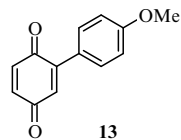
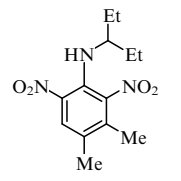
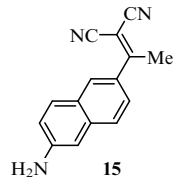
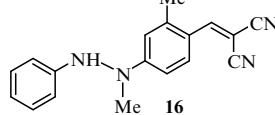


exists as orange and pale yellow polymorphs, in which the difference in the conformations of the molecules is not sufficiently large to explain the difference in colours. The effects of the EP on the electronic structure of the molecule were simulated using the SCMP-NDDO method. Only configurations produced upon

transfer of an electron from the highest occupied to the lowest unoccupied molecular orbitals were taken into account to calculate the excitation energy. According to the calculation,<sup>106</sup> crystals of the orange form of **12** are characterised by an excitation energy 1700 cm<sup>-1</sup> lower than that of the yellow form, which is the reason for the different colours of the polymorphs.

The INDO/S method has specially been optimised for calculations of spectra of organic molecules but it is less suitable to calculations of the ground states of molecules and the electron density distribution, in particular, than other semiempirical methods. In this respect, an alternative procedure was proposed,<sup>32</sup> in which the AM1 or PM3 method is used for the calculation of the EP, and the resultant potential is included in the INDO/S type Hamiltonian. The excitation energies for 16 groups of polymorphs and pseudopolymorphs were calculated within this approach.<sup>52</sup> For six groups, it was the EP effects that were shown to be responsible for the experimentally observed difference in colours, and a fair agreement between the calculated changes in the excitation energies and shifts of the absorption bands was observed for those compounds, the solid-state reflection spectra of which were available from the literature (Table 3). For four other compounds, the differences in the molecular geometries and the potential effects considered separately appeared small, but the difference in colours could be attributed to their joint influence. Finally, for the remaining six compounds, the calculations yielded identical excitation energies for different polymorphs. Apparently, the difference in colours in those cases should be attributed to another reason. We note however that the results of computation evidently contradicted the experimental data in none of the 16 cases. Within this approach,<sup>52</sup> bathochromic shifts of the absorption bands of quinacridone<sup>112, 113</sup> and indigo<sup>114, 115</sup> on going from solutions to the crystals can also be rationalised.

**Table 3.** Examples of compounds forming differently coloured polymorphs for which the excitation energies (cm<sup>-1</sup>) were calculated using the INDO/S method with the electrostatic potential.

| Compound                                                                                         | Colour of the polymorph | Experiment                                 | Calculation                                          |                                                      | Ref.     |
|--------------------------------------------------------------------------------------------------|-------------------------|--------------------------------------------|------------------------------------------------------|------------------------------------------------------|----------|
|                                                                                                  |                         |                                            | molecule in the crystal                              | isolated molecule                                    |          |
| <br><b>13</b> | red<br>yellow           | 19 190 <sup>a</sup><br>20 490 <sup>a</sup> | 31 220<br>33 118                                     | 32 013<br>32 734                                     | 107, 108 |
| <br><b>14</b> | orange<br>yellow        | 17 730 <sup>a</sup><br>19 190 <sup>a</sup> | 26 792<br>28 346                                     | 28 137<br>27 706                                     | 109      |
| <br><b>15</b> | red<br>yellow           | 15 500 <sup>b</sup><br>17 240 <sup>b</sup> | 26 273<br>28 599 <sup>c</sup><br>30 432 <sup>c</sup> | 29 339<br>29 720 <sup>c</sup><br>31 575 <sup>c</sup> | 110      |
| <br><b>16</b> | orange<br>yellow        | 17 210 <sup>b</sup><br>18 420 <sup>b</sup> | 28 456<br>28 998 <sup>c</sup><br>30 015 <sup>c</sup> | 29 423<br>28 430 <sup>c</sup><br>30 885 <sup>c</sup> | 111      |

<sup>a</sup> Position of the long-wavelength edge of the absorption band. <sup>b</sup> Position of the maximum of the fluorescence spectrum. <sup>c</sup> The crystal structure of the yellow polymorph contains two independent molecules.

The INDO/S method with included crystal EP was also applied to simulate the changes in dipole moments of the electronic transitions for crystals of certain amides, purines and pyrimidines with respect to the isolated molecules.<sup>55,116,117</sup> According to the calculations, a crystal-field-induced mixing of the  $n\pi^*$  and  $\pi\pi^*$  type excited states occurs, which gives rise to changes in the direction of the transition moments by  $10^\circ$  and even more. The calculations using the  $U(r)$  potential agree much better with the experimental spectra of the crystals than the respective calculations for the isolated molecules.

\* \* \*

Thus, the use of the crystal electrostatic potential in quantum-chemical calculations enables quite reliable determination of the crystal lattice energies and simulation of the geometry and electronic structure of molecules providing explanations of their changes on going from the isolated molecules to the crystals. The crystal lattice effects vary over a wide range depending on the packing motif and the character of the intermolecular interactions. This determines the difference in the properties of polymorph forms as well as variation of characteristics of crystallographically independent molecules experiencing different crystal environments. The systematic application of the EP-based calculations significantly extends the analytical potential of chemical crystallography as applied to molecular structures and makes it possible to step beyond a mere geometrical description.

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<sup>a</sup> — *Crystallogr. Rep. (Engl. Transl.)*

# Metal complexes with non-innocent ligands

K P Butin (deceased), E K Beloglazkina, N V Zyk

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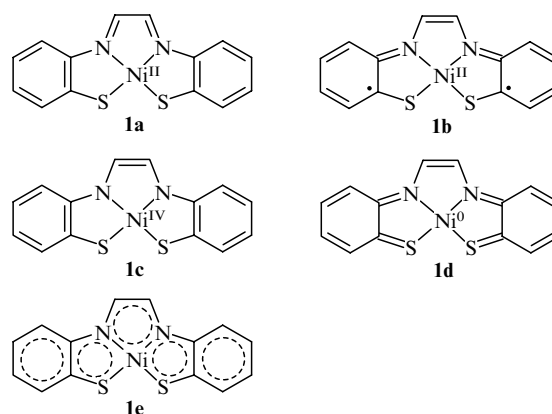
**Abstract.** The review summarises data on transition metal complexes with the so-called non-innocent ligands. The specific feature of these complexes is that the oxidation state of the central metal atom and the electronic structure of the ligands are impossible to determine *a priori* and unambiguously. The results of experimental studies (spectroscopic, electrochemical, X-ray diffraction) of complexes with various non-innocent ligands are analysed. Particular attention is given to their structures and redox properties. The bibliography includes 208 references.

## I. Introduction

Transition metal complexes with the so-called non-innocent ligands have been known in coordination chemistry since the 1960s, when square-planar dithiolene (enedithiol) compounds were synthesised.<sup>1</sup> However, the term ‘non-innocent’ gained wide acceptance only in the 1990s, when such complexes attracted considerable attention.

The term ‘non-innocent’ is generally used in jurisprudence to distinguish the verdicts ‘non-innocent’ and ‘innocent’. This term was introduced in chemistry by Jørgensen in 1966. According to the definition by Jørgensen, a ligand is innocent if it allows the unambiguous determination of the oxidation state of the central metal atom. This definition refers only to the ligand, but, in actuality, the innocent or non-innocent behaviour is related to the complex as a whole.<sup>2</sup>

An example of complexes with a non-innocent ligand is the neutral nickel complex with glyoxalbis(2-mercaptoanil) Ni(gma)<sub>2</sub> (**1**) characterised by the presence of an extensive system of conjugated  $\pi$  bonds. This complex can be considered as a 16-electron Ni<sup>II</sup> complex with diiminodithiolate (**1a**) or di(iminothiosemiquinonate) (**1b**), as a 14-electron Ni<sup>IV</sup> complex (**1c**) or, alternatively, as an 18-electron Ni<sup>0</sup> complex (**1d**).



Consequently, neither the oxidation state of the central metal atom nor the charges on the donor atoms of the ligand can be *a priori* precisely defined, and these structures are often described by formulae with delocalised bonds (**1e**), which means that complex **1** is non-innocent.<sup>3</sup>

A ligand (or ligands) in non-innocent complexes cannot be unambiguously described by the formula acceptable to the free ligand [in the above example, this is the formula of the doubly-charged glyoxalbis(2-thiolatoanil) anion]. The introduction of metal changes the ligand (for example, the free ligand is irreversibly reduced or oxidised, whereas these transformations in the complex are reversible). Earlier,<sup>3</sup> we proposed the term ‘non-indifferent ligand’, which, in our opinion, correctly reflects the heart of the problem. The characteristic feature of complexes with non-indifferent (non-innocent) ligands is the involvement of both the ligand and metal in many chemical and physical processes, which were earlier assigned (on the basis of the theoretical formalism) to only either the metal or ligand.

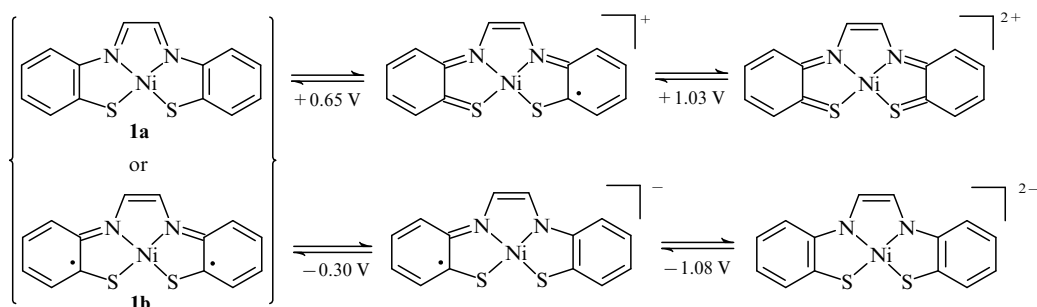
To bring the metal in the above-mentioned structures to one oxidation state (Ni<sup>2+</sup>), it is necessary to add two electrons to structure **1c** and abstract two electrons from structure **1d**. Consequently, ligand **1c** should exist as the doubly-charged anion, whereas ligand **1d** should occur as the doubly-charged cation of complex **1** provided that divalent nickel is retained in the structure. Therefore, if the ligand rather than the metal is reduced (oxidised), the ligand can have different structures in different states of the complex. These ligands are called ‘redox-non-innocent’.

K P Butin, E K Beloglazkina, N V Zyk Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax (7-095) 939 02 90, tel. (7-095) 939 40 20, e-mail: bel@org.chem.msu.ru (E K Beloglazkina), tel. (7-095) 939 46 52, e-mail: zyk@org.chem.msu.ru (N V Zyk)

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Scheme 1



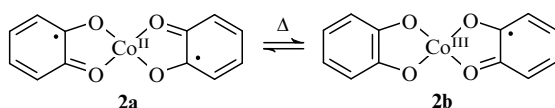
For example, two one-electron oxidation processes and two one-electron reduction processes in diiminodithiolate complexes occur, apparently, with the involvement of the ligand, whereas the divalent state of the metal remains unchanged (Scheme 1).<sup>3</sup>

In dithiolene complexes (and many other analogous complexes), the oxidation states of the metal and the ligand also could not be unambiguously determined, which results in confusion in the interpretation of electrochemical data (elucidation of whether the metal or ligand is subjected to oxidation and reduction) and UV-Vis spectroscopic data. The true nature of metals and ligands has been debated for decades.

After the synthesis and characterisation of first dithiolenes and metal dithiolenes, numerous other complexes exhibiting non-innocent behaviour were found. Pyrocatechol derivatives (catecholates) and other *ortho*-disubstituted benzene derivatives (*o*-phenylenediamines, *o*-aminophenols, *o*-aminothiophenols, *etc.*) belonging to the same structural type have received the most attention.

A reasonable question arises concerning the meaning of the term 'non-innocent'. Presently, this term is sometimes (incorrectly) used in the sense that a ligand in a complex is redox-active. Hence it follows that the term 'non-innocent ligand' is applicable, for example, to dithiolenes.

It should be noted that it is rather easy to determine which fragment of the molecule is involved in oxidation or reduction for complexes in which the frontier orbitals of the metal and the ligand differ substantially in energy. For example, the metal atom in  $[\text{Ru}(\text{bipy})_3]^{2+}$  (bipy is 2,2'-bipyridyl) is oxidised at the potential of +1.26 V, whereas a series of reduction steps involve the ligand, because the metal  $d(\pi)$  orbital (HOMO) and the ligand  $\pi^*$  orbital (LUMO) differ substantially in energy.<sup>4</sup> In contrast,  $[\text{Cr}(\text{bipy})_3]^{3+}$  is involved in a series of reduction reactions,<sup>5</sup> which are much more difficult to interpret, because the metal- and ligand-centred orbitals involved in redox processes are comparable in energy. In actuality, the metal atom of  $[\text{Cr}(\text{bipy})_3]^{3+}$  is reduced in the first step to form  $[\text{Cr}^{\text{II}}(\text{bipy})_3]^{2+}$ , and the successive two-electron reduction occurs at the  $\pi^*$  orbital of the ligand to give a species described as  $[\text{Cr}^{\text{II}}(\text{bipy})_2(\text{bipy}^{\cdot-})]^+$  {or as  $[\text{Cr}^{\text{III}}(\text{bipy})_2(\text{bipy}^{\cdot-})_2]^+$ . Therefore, the ligand is redox-active both in  $[\text{Ru}(\text{bipy})_3]^{2+}$  and  $[\text{Cr}^{\text{II}}(\text{bipy})_3]^{2+}$ , but the term 'non-innocent' is applicable only to the latter complex. Moreover, the difficulties of description of dithiolene complexes arise from strong mixing of the frontier orbitals of the ligand and metal rather than from the fact that the ligand is redox-active. Hence, it is difficult to draw conclusions about the oxidation states of the metal and the ligand in complexes. In some cases, the metal- and ligand-centred frontier orbitals can be so close in energy that so-called 'redox-isomeric' complexes appear. For example, Pierpont and Lange described<sup>6</sup> the cobalt dioxolene complex, which exists in either form **2a** or form **2b** depending on the temperature of the sample.



Consequently, the term 'non-innocent' refers to a combination of the metal and the ligand, *i.e.*, to the complex as a whole

rather than to the redox-active ligand by itself. Lever and co-authors<sup>7</sup> noted that the electron distribution in coordination compounds depends on the degree of mixing of the metal and ligand orbitals, which, in turn, is a function of energy, symmetry and overlap of the valence orbitals of the metal and ligand. This brings up questions about the true oxidation state of the central metal atom in these complexes and the electronic structures which correctly describe the complexes. These questions have been debated in the literature for more than four decades.<sup>6,8</sup>

When considering transition metal complexes with non-innocent ligands, the concept of the oxidation state of a metal in complexes should also be refined. It was suggested<sup>9</sup> that the formal oxidation state of a metal in mononuclear coordination compounds should be distinguished from the physical oxidation state. The former is generally determined as a charge remaining on the metal after removal of all ligands in the electronic configurations with complete shells, *i.e.*, with lone pairs, whereas the physical oxidation state is determined by the true electronic state of the metal atom. For example, iron in  $\text{Fe}^{\text{III}}$  complexes can exist in the high-, medium- or low-spin state. The electronic configuration of a metal in complexes can be determined by spectroscopy. Hence, Jørgensen<sup>10</sup> suggested the term 'spectroscopic oxidation state' to describe this situation.

In many cases, the formal and physical oxidation states are identical {for example, the physical and formal oxidation states of low-spin Co ( $d^6$ ) in the  $[\text{Co}(\text{NH}_3)_6]^{3+}$  complex ion is +3}. However, this is not always the case. The physical oxidation state differs from the formal oxidation state, for example, if an open-shell organic radical is coordinated to a transition metal ion. For instance, the formal oxidation state of iron in the O-coordinated iron complex with the phenoxyl radical is +4. However, Mössbauer and Raman spectroscopy demonstrated that the iron ion in this complex with the radical ligand is in the physical oxidation state of +3 and has the  $d^5$  configuration  $(\text{Ph}-\text{O}^{\cdot})\cdots\text{Fe}^{\text{III}}$ .<sup>9</sup> Evidently, the complex containing the  $\text{Ph}-\text{O}-\text{Fe}^{\text{IV}}$  fragment differs in its electronic structure from the complex with the  $(\text{Ph}-\text{O}^{\cdot})\cdots\text{Fe}^{\text{III}}$  fragment.<sup>†</sup>

The term 'physical oxidation state' is not commonly accepted. Moreover, the terms 'physical and formal oxidation states' are often used as synonyms. However, it is necessary to distinguish these terms in certain areas of coordination chemistry. In particular, it is worthwhile using the terms 'innocent' and 'non-innocent' as referring to the ligand only in combination with the term 'physical oxidation state', thus underlining that the ligands do not necessarily have closed shells.

Clear criteria for the assignment of ligands in non-innocent complexes to a particular oxidation state are presently available. Oxidation and reduction can be easily followed from structural changes in the ligand, in particular, from the changes in the bond lengths. For example, the length of the C–N single bond in *o*-phenylenediamine ligands<sup>12</sup> is  $\sim 1.46$  Å. In *o*-diiminoquinones, both C=N bond lengths are  $\sim 1.31$  Å, whereas these bond lengths in the *o*-diiminobenzosemiquinonate radical have an

<sup>†</sup> Mononuclear copper complexes with phenoxy radicals were found in the active sites of galactose oxidases.<sup>11</sup>

intermediate value of  $\sim 1.36 \text{ \AA}$  (these ligands are considered in more detail in Section II.2).

An analogous regularity was found for pyrocatechol and *o*-aminophenol complexes<sup>13,14</sup> and for *o*-aminothiophenol complexes.<sup>12</sup> Besides, the structures of the above-mentioned compounds are always characterised by the following feature: in aromatic ligands, which contain an even number of electrons and can exist as neutral molecules, singly-charged anions or doubly-charged anions depending on the degree of protonation, all six C–C bonds in the benzene ring are identical in length, whereas there are three alternating ‘short–long–short’ bonds and three adjacent long bonds in the six-membered rings of semiquinone and quinone.

To determine the electron density distribution in complexes with non-innocent ligands, various spectroscopic methods (UV-Vis, IR, Mössbauer, X-ray electron spectroscopy and ESR), electrochemical and spectroelectrochemical methods are widely used along with the structural criteria. The spectroscopic methods allow one to reveal the presence of radical species and spin-density localisation.

As mentioned above, oxidation or reduction of ligands rather than metals is very typical of complexes with non-innocent ligands (for details, see below). In redox reactions, such ligands can serve as an ‘electronic buffer’,<sup>15</sup> which reversibly accepts and donates electrons, whereas the oxidation state of the central metal atom remains unchanged.

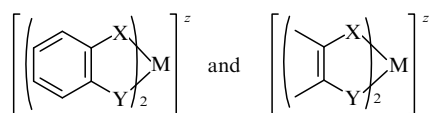
Below we consider complexes with various non-innocent ligands. Some widely known complexes with radical ligands, for example, complexes with a verdazyl radical, are beyond the scope of the present review. In such complexes, the ligand is unambiguously described as a radical (though delocalised) and the electronic structure and oxidation state of the metal are beyond doubt.

Several reviews have been devoted to various classes of non-innocent metal complexes: with oxygen-containing ligands based on pyrocatechols,<sup>1,16,17</sup> with dithiolene ligands,<sup>18</sup> with ligands based on aromatic diamines,<sup>19,20</sup> *p*-quinones,<sup>21</sup> corroles,<sup>22</sup> *etc.*<sup>23–25</sup> The present review summarises the results of investigations of complexes with non-innocent ligands carried out in the last decade, when the term ‘non-innocent’ has received wide recognition. Only the most important earlier studies are cited.

## II. Complexes with 1,2-disubstituted benzenes and ethylenes as ligands

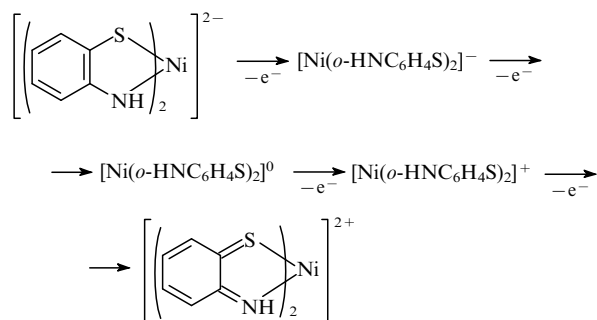
Dithiolenes, pyrocatechols, *o*-phenylenediamines, *o*-aminophenols and other analogous compounds belong to a well-known class of non-innocent ligands. The doubly deprotonated form of such ligands can be considered as a prototype of non-innocent ligands.

As early as the 1960s, Holm and co-authors (see, for example, Refs 26 and 27) noted that complexes belonging to the structural type



X, Y = O, NH, S; M = Ni, Pd, Pt.

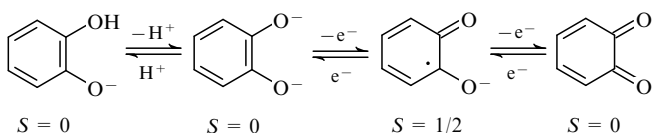
are readily subjected to chemical and electrochemical reversible one-electron oxidation and reduction. In early studies, the precise structures of most intermediates formed upon oxidation and reduction were not established. However, isoelectronic series of five compounds were proposed for their description, the *o*-quinoid structure being assigned to the ligand in the highest oxidised state based on ESR spectroscopic data.



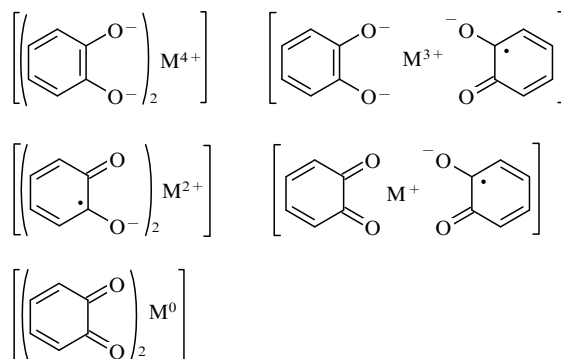
### 1. Complexes with pyrocatechol-based ligands

Complexes containing the deprotonated pyrocatechol fragment  $\sigma$ -bonded to a transition metal can exist as various electronic tautomers<sup>28–30</sup> due to the ease of electron transfer between the metal and the ligand.

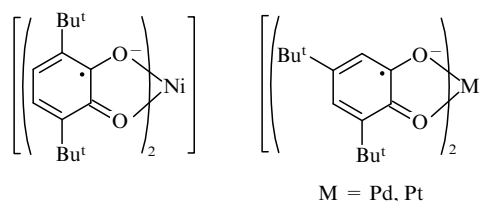
It was found<sup>12</sup> that *o*-catecholates in complexes can exist as aromatic closed-shell singly- or doubly-charged anions, even-electron neutral *o*-quinones or open-shell *o*-benzosemiquinone radicals ( $S = 1/2$ ).



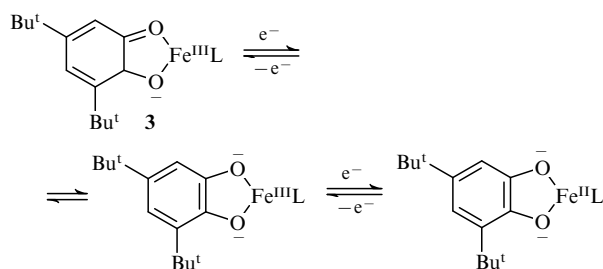
Correspondingly, a variable-valence transition metal atom can give a series of complexes with different forms of these ligands, which are described by the same empirical formula, but differ in the ligand structure and oxidation state of the central metal atom.



Pyrocatechol is the simplest representative of this class of ligands. Nickel,<sup>28,29</sup> palladium and platinum<sup>30</sup> complexes with ligands containing unsubstituted and 3,5- and 3,6-di-*tert*-butyl-substituted aromatic rings have square-planar structures and are diamagnetic. X-Ray diffraction study demonstrated that the structures of the above-mentioned three *tert*-butyl-substituted complexes correspond to the following formulae.



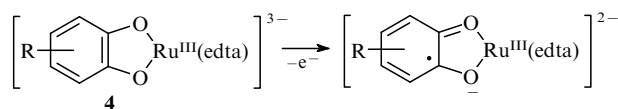
The non-innocent nature of the catecholate ligand allows the isolation of iron dioxolene complexes containing the ligand and metal atom in different oxidation states.<sup>31</sup>



L is a tetraazamacrocyclic ligand.

Iron complex **3** can serve as a structural model of the iron-containing enzyme nitrile hydratase.<sup>32</sup>

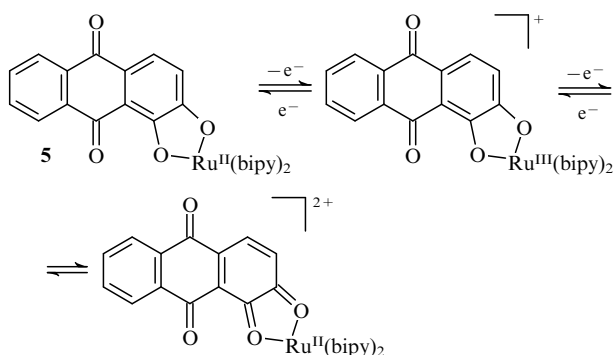
Free pyrocatechol is irreversibly oxidised by electrochemical methods at 0.3–0.6 V to give *o*-benzoquinone. The formation of the complex is accompanied by a substantial change in the redox characteristics. For example, oxidation of ruthenium complex **4** becomes reversible, occurs by a one-electron mechanism (at –0.6 to –0.5 V)<sup>33</sup> with the involvement of only the ligand and affords the semiquinone complex, *i.e.*, the addition of metal to the oxygen atoms of the ligand leads to a radical change in the nature of the ligand.



R = H, 4-CO<sub>2</sub>H, 3,5-(SO<sub>3</sub><sup>–</sup>)<sub>2</sub>.

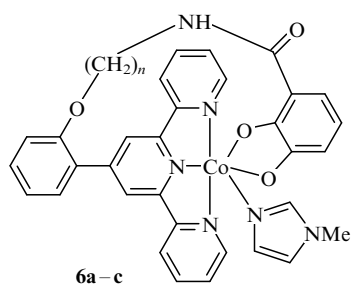
The Ru<sup>III</sup> complexes with L-DOPA, [Ru(edta)(L-DOPA)]Na<sub>3</sub> · 3 H<sub>2</sub>O and [Ru(edta)(L-DOPA)]Na<sub>4</sub> · 3 H<sub>2</sub>O behave analogously. Upon the complex formation, oxidation and reduction processes become reversible.<sup>34</sup>

Electrochemical oxidation of ruthenium(II) complex **5** with doubly deprotonated alizarine (1,2-dihydroxy-9,10-anthraquinone) containing the 2,2'-bipyridyl fragment involves successive one-electron oxidation of the metal atom and the ligand, both oxidation products (as salts) being isolated preparatively.<sup>35</sup>



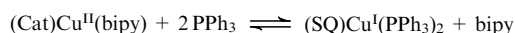
The structures of these complexes were confirmed by ZINDO calculations.

In a series of pentadentate ligands containing the terpyridyl fragment linked to the pyrocatechol fragment, which were synthesised in the study,<sup>36</sup> and their complexes with cobalt **6a–c**, the pyrocatechol fragment of the ligand also exists as the aromatic doubly-charged anion. Two of these complexes (**6a,b**) were characterised by X-ray diffraction. The authors hypothesised that two one-electron reduction steps in electrochemical redox reactions occur successively with the involvement of the terpyridyl fragment and the cobalt ion, whereas the pyrocatechol fragment of the ligand is oxidised.



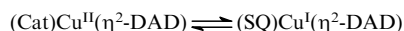
*n* = 4 (**a**), 5 (**b**), 6 (**c**).

For copper catecholate complexes, Abakumov *et al.*<sup>37</sup> demonstrated that reversible intramolecular electron transfer between the metal and the ligand can occur and it is induced by the replacement of the neutral ligand.

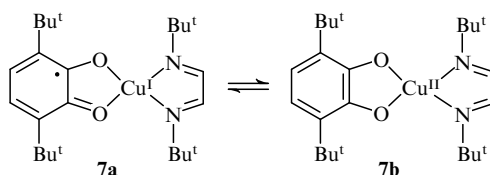


Cat is catecholate and SQ is semiquinone.

This reversible intramolecular metal–ligand electron transfer can occur also without changes in the composition of the coordination sphere about metal. For example, the reversible electron transfer in copper complexes with *N,N'*-disubstituted 1,4-diazabutadiene (DAD) is accompanied by a change in the geometry from square-planar (in the Cu<sup>II</sup> catecholate complex) to tetrahedral (in the Cu<sup>I</sup> semiquinone complex).<sup>38</sup>



Abakumov and Eremenko with co-workers<sup>39</sup> studied a copper complex containing simultaneously the di-*tert*-butyl-substituted catecholate and 1,4-diazabutadiene fragments. In solution, this neutral complex exists as an equilibrium mixture of two isomers, *viz.*, copper(I) semiquinonate **7a** and copper(II) catecholate **7b**.

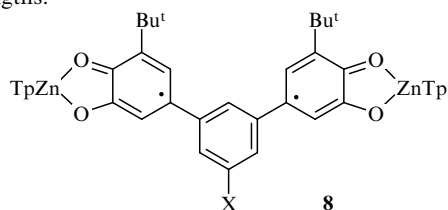


The addition of a neutral ligand (CO or ArNC) to a solution induces electron transfer from the catecholate fragment to Cu<sup>II</sup> giving rise to a complex containing an additional neutral ligand. In the case of carbon monoxide, this transformation is reversible, and the position of equilibrium strongly depends on the temperature. At 300 K, an equilibrium mixture of derivatives of molecules **7a** and **7** is present in solution, whereas almost exclusively the (SQ)Cu<sup>I</sup>(η<sup>1</sup>-DAD)CO complex exists at 200 K.

The electronic structures of the Cr<sup>III</sup> semiquinone complex [Cr(tren)(3,6-DTBSQ)]<sup>2+</sup> [tren is tris(2-aminoethyl)amine, and 3,6-DTBSQ is 3,6-di-*tert*-butylthiosemiquinone] and its catecholate analogue [Cr(tren)(3,6-DTBCat)]<sup>+</sup> containing the doubly-charged anionic 3,6-di-*tert*-butylthiocatecholate ligand 3,6-DTBCat<sup>40</sup> were studied by the DFT method. The calculations demonstrated that the Cr ion (*S* = 3/2) is antiferromagnetically coupled to the semiquinone radical (*S* = 1/2), so that the spin state *S* = 1 is the major one. Both complexes were also characterised by X-ray diffraction, and there is a good agreement between the structural data and the results of calculations. A calculation method proposed<sup>41</sup> for chromium complexes, in which chromium is bound only to electron-donating oxygen atoms, allows one to determine the oxidation state of the metal atom based on the sum of the Cr–O bond lengths.



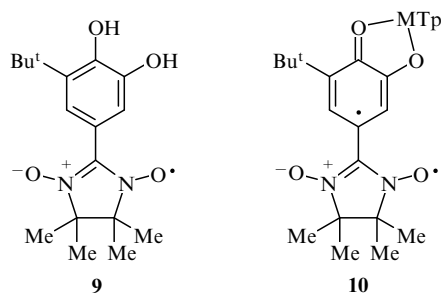
The ligands can include two *o*-semiquinone fragments (for example, in zinc complexes **8**).<sup>42</sup> All three known complexes were studied by X-ray diffraction, and the semiquinone structure of the ligand was confirmed by the characteristic C–C and C–O bond lengths.



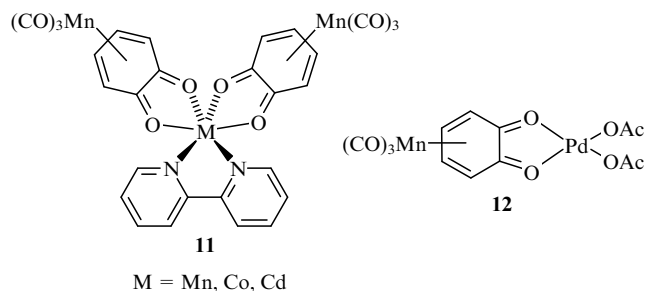
X = NMe<sub>2</sub>, Bu<sup>t</sup>, NO<sub>2</sub>;

Tp is hydrotris(3-methyl-5-isopropylphenylpyrazolyl)borate.

Ligand **9** containing both the potential semiquinone and nitronyl-nitroxide radical centres was synthesised.<sup>43</sup> In the ground state, Ni, Mn, Co, Cu and Zn complexes **10** with this ligand exist as singlet biradicals.

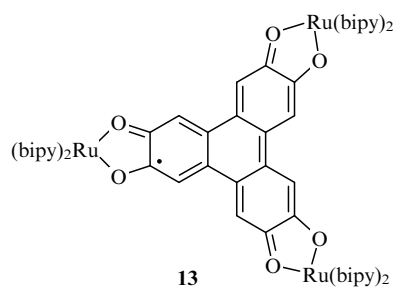


In complexes **11** and **12**, the oxygen-containing ligand (according to the results of the study<sup>44</sup>) exists as *o*-quinone, and the Mn(CO)<sub>3</sub> fragment serves as a 'reservoir' accepting electrons during oxidation of the ligand, thus being responsible for the electron density distribution between the metal and ligand.



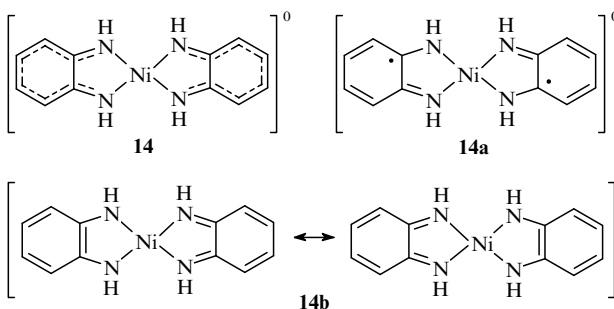
However, the structural study<sup>45</sup> demonstrated that the C–O bonds in complexes **11** and **12** (~1.29 Å) are longer than those in *o*-quinones (1.26–1.27 Å), *i.e.*, it cannot be stated that the structure of the ligand in these complexes precisely corresponds to *o*-quinone.

A comprehensive analysis of the literature data on polynuclear Ru<sup>II</sup> complexes with bridging dioxolene ligands and binuclear tris(pyrazolylborato)Mo(V) or Mo(VI) complexes with bridging bis-phenolate or bis-pyridyl ligands was presented in the review,<sup>1</sup> where the results of spectroscopic and spectroelectrochemical investigations of such complexes were discussed in detail, and the conclusion was drawn that there is a strong electron interaction between the metal ion and the bridging ligand. Complex **13** containing three coordinating catechol-type fragments in different oxidation states (one semiquinone fragment and two carbonyloxide fragments) in one ligand molecule is an interesting example cited in the review.<sup>1</sup>



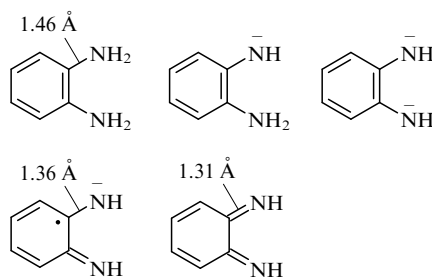
## 2. Complexes with *o*-phenylenediamine-type ligands and their deprotonated and oxidised forms

Nickel *o*-phenylenediamine complex **14** is among the first synthesised and structurally characterised complexes with non-innocent ligands. Once the oxidation state of the central metal atom higher than +2 has been rejected, two different descriptions of the electronic structure of this complex were proposed. Gray and co-authors<sup>46</sup> suggested that this compound is the Ni<sup>II</sup> d<sup>8</sup> complex with a singlet biradical (**14a**), whereas Holm and co-authors<sup>8,47</sup> described this compound by two resonance hybrids **14b**. Evidently, molecules **14a** and **14b** should differ in energy, and the question is which formula gives a more adequate description.



More recently, Abakumov *et al.*<sup>28</sup> and Pierpont with co-authors<sup>29,30</sup> have assigned the electronic structures of compound **14** and its palladium and platinum analogues to type **14a**, *i.e.*, to complexes with two intramolecular antiferromagnetically coupled iminosemiquinonate ligands, taking into account the available structural data.

Generally speaking, *o*-phenylenediamines form complexes of different structural types with transition metals (Fe, Ni, Pd, Pt, Co) depending on the oxidation state and protonation of the ligand. Complexes in which the ligands belong to the forms listed below were synthesised and characterised by X-ray diffraction and electrochemical methods.<sup>47–52</sup>

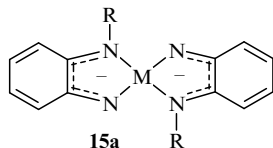


The structural changes observed in these complexes were analysed in the review.<sup>19</sup>

Eremenko and co-workers<sup>53–60</sup> described complexes of platinum-group metals (Pd and Pt) and Ni with ligands of the *o*-phenylenediamine series. The reactions of *o*-phenylenediamine<sup>53,54</sup> and its *N*-methyl<sup>55</sup> and *N*-phenyl derivatives<sup>53</sup> with alkaline solutions of K<sub>2</sub>MX<sub>4</sub> (M = Pt, Pd; X = Cl, NO<sub>3</sub>) initially

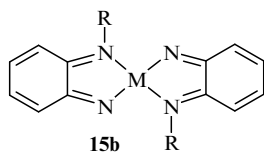


produce the tetraamine doubly-charged cationic complexes  $M(o\text{-NH}_2\text{C}_6\text{H}_4\text{NHR})\text{X}_2$ , which are transformed in the presence of atmospheric oxygen into mononuclear  $\text{Pt}^{\text{II}}$  or  $\text{Pd}^{\text{II}}$  bis(semiquinonedimine) complexes **15a**.



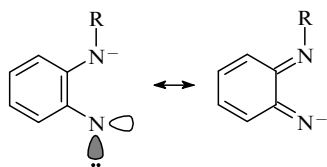
$M = \text{Pt}, \text{Pd}; R = \text{H}, \text{Me}, \text{Ph}$ .

In earlier studies,<sup>53, 54</sup> these compounds were considered as the  $M(o\text{-NC}_6\text{H}_4\text{NR})$  ( $R = \text{H}, \text{Me}, \text{Ph}$ ) complexes (**15b**) with anionic quinoneimine ligands.



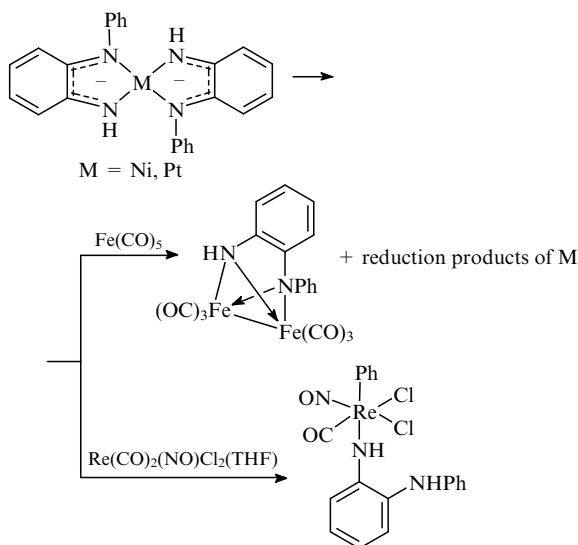
$M = \text{Pt}, \text{Pd}; R = \text{H}, \text{Me}, \text{Ph}$ .

The bidentate ligand, *viz.*, a *o*-phenylenediamine derivative, is described in terms of the nitrene-imide resonance.<sup>53</sup>

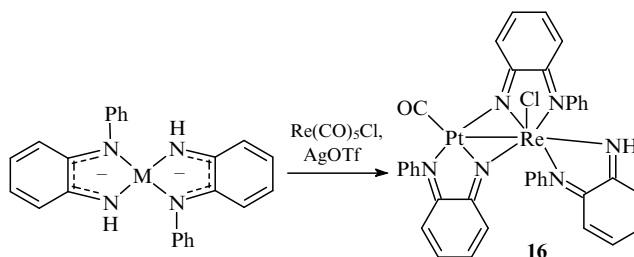


However, X-ray diffraction data<sup>53, 55</sup> are in better agreement with the semiquinone structure of the ligand [the C(ring)-N bond lengths are 1.335 and 1.352 Å, see above].

The reactions of the *o*-semiquinonedimine complexes  $M(o\text{-HNC}_6\text{H}_4\text{NPh})$  ( $M = \text{Ni}$  or  $\text{Pt}$ ) with carbonyl-containing iron and rhenium compounds are accompanied by reduction of the ligand to give Fe or Re phenylenediamide complexes.<sup>57</sup>

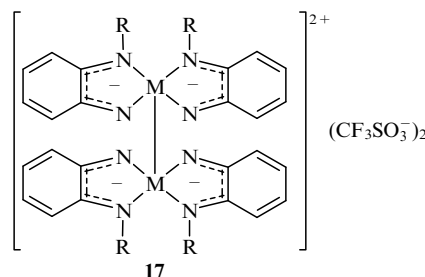


In the presence of silver triflate, the reaction yields heterobimetallic complex **16** containing an *o*-quinoneiminoimide-type ligand.<sup>57, 58</sup>



This deprotonated phenylenedimine ligand, but as a bridge, is present in the palladium complex generated in the reaction of the trinuclear complex  $\text{Pd}_3(\mu\text{-O}_2\text{CBu}^t)_6$  with *N*-Ph-*o*-phenylenediamine.<sup>58</sup>

Oxidation of  $\text{Pt}^{53, 59, 60}$  and  $\text{Pd}^{60}$  bis(semiquinonedimine) complexes with  $\text{AgOTf}$  affords binuclear  $\text{Pt}^{\text{III}}$  and  $\text{Pd}^{\text{III}}$  complexes **17**.

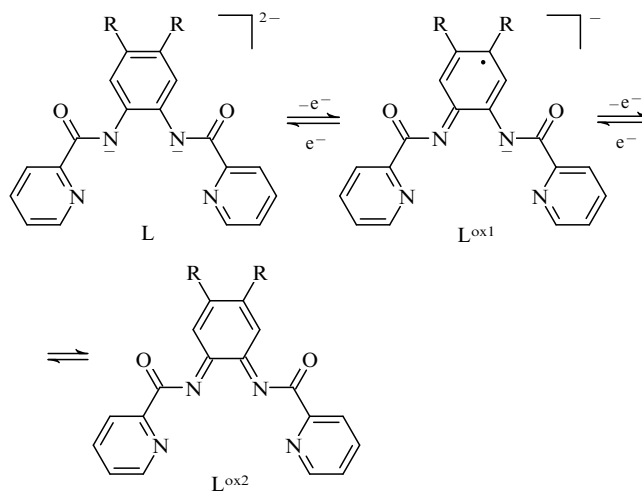


$M = \text{Pt}, \text{Pd}; R = \text{H}, \text{Ph}$ .

The structures of the binuclear complexes were established by spectroscopic and electrochemical methods and X-ray diffraction.

The reactions of  $\text{Ru}^{\text{III}}$  salts with *o*-phenylenediamine in the presence of an oxidant ( $\text{O}_2$  or  $\text{Hal}_2$ ) produced a series of  $\text{Ru}^{\text{II}}$  complexes with the *o*-benzoquinonedimine-type ligand, and the complexes were characterised by X-ray diffraction, electrochemical and spectroscopic methods.<sup>61</sup> In such complexes, the ligands are reduced in two one-electron steps to form ruthenium *o*-phenylenediamide complexes.

Ligands of the 1,2-bis(pyridine-2-carboxamido)benzene (bpb) series similar in electronic structure to *o*-phenylenediamine ligands also belong to the category of non-innocent ligands and can be involved in coordination compounds as doubly-charged anions ( $L$ ), one-electron oxidised radicals ( $L^{\text{ox1}}$ ) or two-electron oxidised diamagnetic iminoquinone species ( $L^{\text{ox2}}$ ).<sup>62, 63</sup>

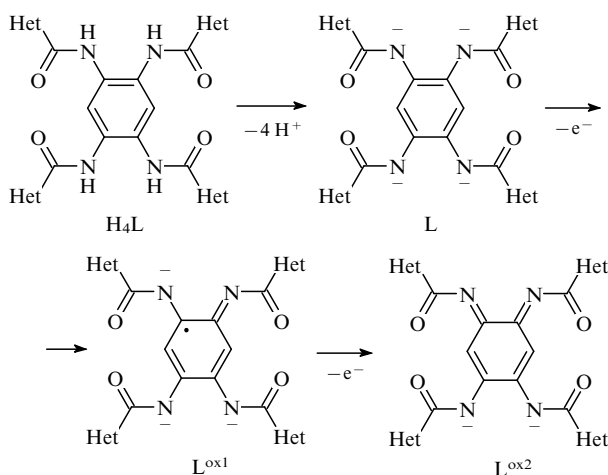


$R = \text{H}$  (bpb),  $\text{Cl}$  (bpc).

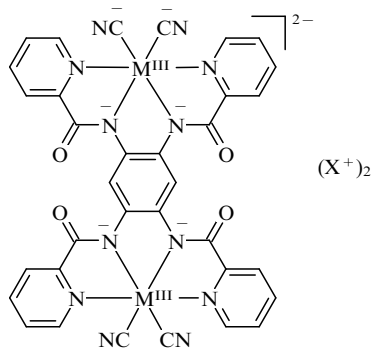
The anion L is coordinated to Fe<sup>III</sup> as a non-innocent ligand, because in a complex it can be oxidised to the paramagnetic  $\pi$ -radical cation and then to the diamagnetic neutral benzoquinone species.

Mononuclear iron and cobalt complexes with the bpb and bpc ligands were synthesised and characterised.<sup>62</sup> It was demonstrated that these ligands in coordination compounds can exist in radical one-electron and diamagnetic two-electron oxidised forms, L<sup>ox1</sup> and L<sup>ox2</sup>. These complexes were studied by X-ray diffraction, ESR and UV-Vis spectroscopy and electrochemical methods. Photolysis of the high-spin (Bu<sub>4</sub>N)[Fe<sup>III</sup>(bpb)(N<sub>3</sub>)<sub>2</sub>] complex and its (bpc)<sup>2-</sup> analogue in acetone at room temperature afforded the diamagnetic binuclear complex (Bu<sub>4</sub>N)[Fe<sup>IV</sup>( $\mu$ -N)(bpb)<sub>2</sub>(N<sub>3</sub>)<sub>2</sub>] analogous to the complex with (bpc)<sup>2-</sup>. However, photolysis in frozen acetonitrile produced a low-spin complex, whose structure was described as [Fe<sup>III</sup>(bpb<sup>ox2</sup>)(N)(N<sub>3</sub>)<sub>2</sub>]. The mononuclear complexes (Bu<sub>4</sub>N)[Fe<sup>III</sup>(bpb)(CN)<sub>2</sub>], (Et<sub>4</sub>N)[Co<sup>III</sup>(bpb)(CN)<sub>2</sub>] and Na[Co<sup>III</sup>(bpc)(CN)<sub>2</sub>] · 3 MeOH are chemically and electrochemically oxidised to the corresponding complexes L<sup>ox1</sup>. The oxidised form of the complex with the radical-anionic ligand can be isolated after preparative electrolysis. An analogous reaction was carried out by a chemical method.

The binuclear Co<sup>III</sup> and Fe<sup>III</sup> complexes with the non-innocent 1,2,4,5-tetrakis(2-pyridinecarboxamido)benzene ligands were documented.<sup>62–64</sup>



The general formula of the CN-containing complexes with an L-type ligand is as follows:



X = Na, NBu<sub>4</sub>.

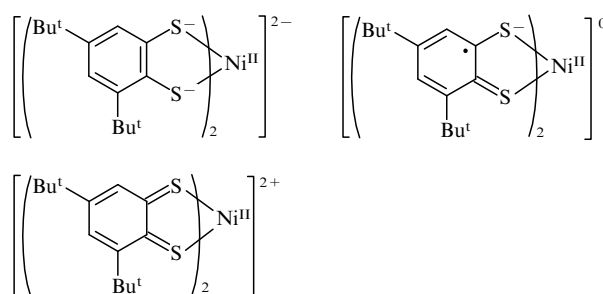
For iron complexes, the existence of the following five forms containing the central ligand and metal in different oxidation states was established: (1) doubly-charged anionic [Fe<sup>II</sup>L(CN)<sub>4</sub>]<sup>2-</sup>; (2) one-electron reduced mixed-valence [Fe<sup>III</sup>Fe<sup>II</sup>L(CN)<sub>4</sub>]<sup>3-</sup> with the diamagnetic L<sup>4-</sup> bridge; (3) completely reduced [Fe<sup>II</sup>L(CN)<sub>4</sub>]<sup>4-</sup>; (4) one-electron oxidised

[Fe<sup>III</sup>L<sup>ox1</sup>(CN)<sub>4</sub>]<sup>-</sup>; (5) completely oxidised [Fe<sup>IV</sup>L<sup>ox2</sup>(CN)<sub>4</sub>]. All forms were characterised by spectroscopic and electrochemical methods. The first and third forms were also studied by X-ray diffraction.<sup>64</sup> For cobalt complexes, three forms with different oxidation states of the ligand, [Co<sup>II</sup>L(CN)<sub>4</sub>]<sup>2-</sup> (*S* = 0), [Co<sup>II</sup>L<sup>ox1</sup>(CN)<sub>4</sub>]<sup>-</sup> (*S* = 1/2) and [Co<sup>II</sup>L<sup>ox2</sup>(CN)<sub>4</sub>] (*S* = 0), were investigated by X-ray diffraction.<sup>64</sup> It was concluded that the central 1,2,4,5-tetraaminobenzene fragment in the above-mentioned complexes can be oxidised in two reversible one-electron steps to paramagnetic (L<sup>ox1</sup>)<sup>3-</sup> and diamagnetic (L<sup>ox2</sup>)<sup>2-</sup> species.

### 3. Complexes of *o*-benzenedithiols and their deprotonated and oxidised forms

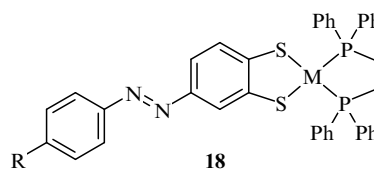
As early as the 1960s, it was found<sup>26,27</sup> that *o*-benzenedithiol complexes are readily involved in one-electron transfer reactions, the *o*-quinoid-type structure being assigned to the ligand in the highest oxidation state. However, although the existence of complexes with ligands in three oxidation levels has been rather easily established for *o*-catecholates, the situation for the corresponding *ortho*-dithio derivatives has remained unclear for a long time. For example, the existence of S,S-coordinated *o*-dithiobenzenesemiquinonate radical anions (rather than aromatic doubly-charged dithiolate anions) has been proposed for many complexes,<sup>65,66</sup> but this fact has not been supported by experimental evidence. Later on, the presence of such radicals was confirmed for the paramagnetic square-planar [Pd(bipy)(L<sup>Bu</sup>)]<sup>+</sup> complex (where L<sup>Bu</sup> is 3,5-di-*tert*-butylbenzene-1,2-dithiol)<sup>67</sup> by UV-Vis and ESR spectroscopy.

The nickel complex in which the metal is coordinated by two ligands with the molecular formula C<sub>14</sub>H<sub>20</sub>S<sub>2</sub>,<sup>68</sup> exists in three different forms, anionic, neutral and cationic, and the ligand exists as the dithiolate anion, the dithiosemiquinone radical and dithioquinone, respectively.

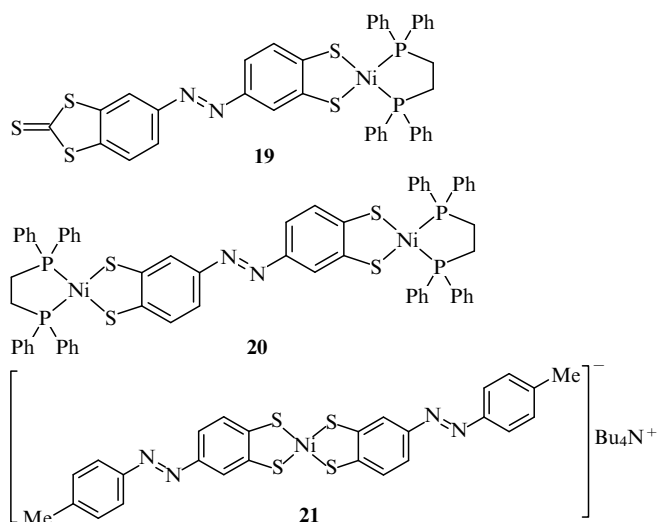


Recently, DFT calculations have convincingly demonstrated<sup>69</sup> that the spectroscopic oxidation state of the nickel atom in the diamagnetic square-planar NiL<sub>2</sub> complex (L is unsubstituted *o*-benzenedithiol) is +2 (d<sup>8</sup>), and both ligands are present as *o*-dithiobenzenesemiquinonates(1<sup>-</sup>). The Fe<sup>III</sup> and Fe<sup>IV</sup> complexes containing the *o*-benzenedithiolate ligands as doubly-charged anions were also studied by X-ray diffraction.<sup>70</sup> These results and the data published in the literature<sup>71</sup> have made it possible to propose structural criteria for assigning such ligands in complexes to a particular oxidation state.

The synthesis of a series of azo-coupled metal dithiolenes **18–20** containing Ni<sup>II</sup>, Pd<sup>II</sup> and Pt<sup>II</sup> and bis(diphenylphosphino)ethane (dppe) as an additional ligand and the synthesis of anionic nickel complex **21** were documented.<sup>72</sup>



M = Ni, Pd, Pt; R = H, Me, Cl, OMe.



All these complexes were studied by X-ray diffraction.<sup>65, 73, 74</sup> These complexes were electrochemically reduced. In the study,<sup>72</sup> it was hypothesised that the metal atom in the nickel complexes undergoes reversible one-electron reduction, whereas reduction of the platinum and palladium complexes is a reversible two-electron process, though it also involves the metal atom.

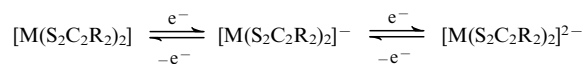
The electronic structures of the bis(*o*-benzenedithiolato)Au(III) anion and its neutral one-electron oxidised form were determined.<sup>65</sup> Earlier, the latter was described (based on poor-quality X-ray diffraction data) as an Au<sup>IV</sup> complex containing the central gold atom in the *d*<sup>7</sup> configuration.<sup>72</sup> Poor-quality X-ray diffraction data were also obtained for compounds containing the [AuL<sub>2</sub>]<sup>−</sup> anion (L is deprotonated *o*-benzenedithiol),<sup>75–79</sup> but these data did not provide unambiguous evidence for the true structure of the ligand in the complexes. More recently,<sup>74</sup> the neutral [AuL<sub>2</sub>] complex was demonstrated to be diamagnetic, and DFT calculations for the isolated molecule of this complex confirmed that the HOMO and LUMO are virtually purely bonding and antibonding combinations of the HOMO of the ligands, respectively.<sup>80</sup> This is possible only in the presence of the diamagnetic Au<sup>III</sup> ion in the *d*<sup>8</sup> electronic configuration, but this fact was not confirmed experimentally.

The square-planar diamagnetic Au<sup>III</sup> complexes with 3,6-di-*tert*-butylbenzene-1,2-dithiolate are oxidised with iodine in acetone to form neutral paramagnetic complexes of the corresponding *o*-dithiobenzosemiquinonate radical (the facts that the ligand

is oxidised and the reaction does not afford an Au<sup>IV</sup> complex were unambiguously established by Mössbauer, UV-Vis and ESR spectroscopy).<sup>65</sup> Analogous complexes containing the unsubstituted ligand (H<sub>2</sub>L is *o*-benzenedithiol), (NBu<sub>3</sub>H)[AuL<sub>2</sub>] and AuL<sub>2</sub>, were synthesised and characterised by X-ray diffraction. Taking into account the electronic structures of the paramagnetic neutral Au(L<sup>Bu</sup>)<sub>2</sub> and AuL<sub>2</sub> complexes, it was demonstrated<sup>65</sup> that these complexes contain the Au<sup>III</sup> ion (*d*<sup>8</sup>, *S* = 0) coordinated by two sulfur atoms of the *o*-dithiolate anion and the *o*-dithiobenzosemiquinonate(1<sup>−</sup>)  $\pi$ -radical, resulting in the ground state with *S* = 1/2. This fact was confirmed by the results of UV-Vis, IR and ESR spectroscopy.

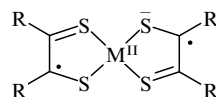
#### 4. Dithiolene complexes

Quantum-chemical calculations demonstrated that the HOMO of dithiolene complexes is localised virtually completely on the ligand; consequently, the ligand should be oxidised in these reactions.<sup>81</sup> Transition metal dithiolene complexes, like the above-described *o*-benzenedithiol complexes, are characterised by the existence of a series of forms related to each other by reversible one-electron oxidation and reduction steps (M = Ni, Pd or Pt).<sup>82–84</sup>

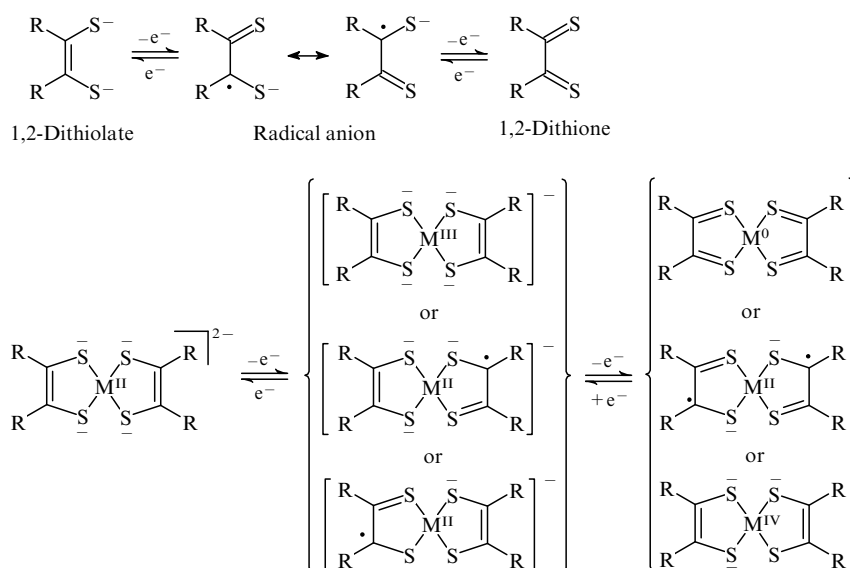


The end members of the series are diamagnetic, whereas the singly-charged anion is a radical. The existence of singly- and doubly-charged cations was also assumed, the latter cation containing M<sup>II</sup> coordinated by two 1,2-dithione-type ligands. However, these cations have not been detected. The oxidation states of the metals and ligands are presented in Scheme 2.<sup>85</sup>

The non-innocent nature of the dithiolene ligands has been studied in considerable detail.<sup>86–90</sup> The structural changes in nickel complexes resulting from the transformation from one oxidation state to another were discussed in the study.<sup>85</sup> Both the reduced (anionic dithiolate) and oxidised (neutral dithiolene) forms of this ligand give stable complexes with transition metals. The latter form is more adequately described as a complex containing two radical-anionic ligands rather than by two resonance structures.

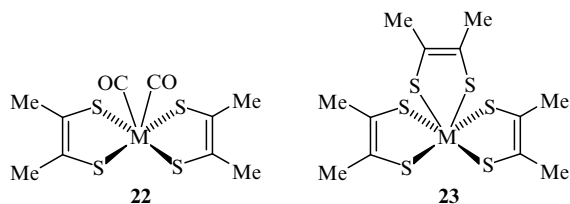


Scheme 2



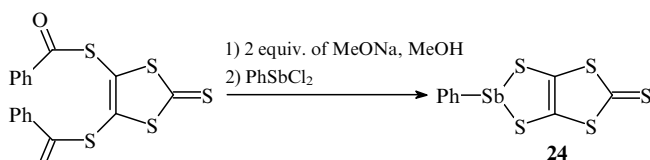
Different members of the redox series under consideration (primarily for  $M = \text{Ni}$ ) were either isolated or generated in solution by chemical or electrochemical reactions. For example, the  $[\text{Ni}\{\text{S}_2\text{C}_2(\text{CN})_2\}]^{2-}$  and  $[\text{Ni}\{\text{S}_2\text{C}_2(\text{CN})_2\}]^-$  complexes were characterised in early studies.<sup>91,92</sup> More recently,  $[\text{Ni}(\text{S}_2\text{C}_2\text{Et}_2)]^-$  ( $z = 0, 1-$ ),  $[\text{Ni}\{\text{S}_2\text{C}_2(\text{CF}_3)_2\}]^-$  ( $z = 0, 1-, 2-$ ) and  $[\text{Ni}(\text{S}_2\text{C}_2\text{Ph}_2)]^-$  ( $z = 0, 1-, 2-$ ) were isolated in individual form (see Ref. 85 and references cited therein).

Calculated data on the electronic structures of the complexes were confirmed by the results of ESR spectroscopy for molybdenum-containing compounds **22** and **23** and the results of electrochemical investigations on molybdenum and tungsten complexes.<sup>93,94</sup>



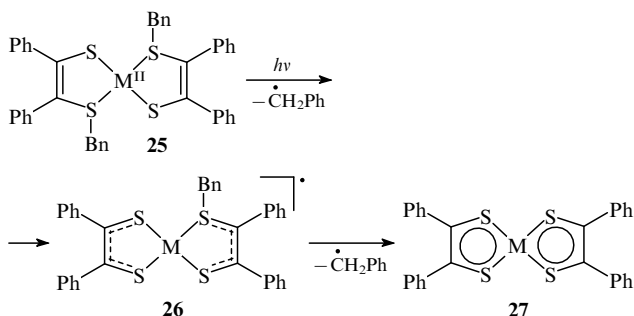
$M = \text{Mo}, \text{W}$ .

Neutral organoantimony dithiolene complex **24**<sup>81</sup> was synthesised by adding  $\text{PhSbCl}_2$  to  $\text{Na}_2(\text{dmit})$  (dmit is 4,5-dithiolato-1,3-dithiole-2-thione).



The complex was characterised by spectroscopy (NMR and IR) and X-ray diffraction.

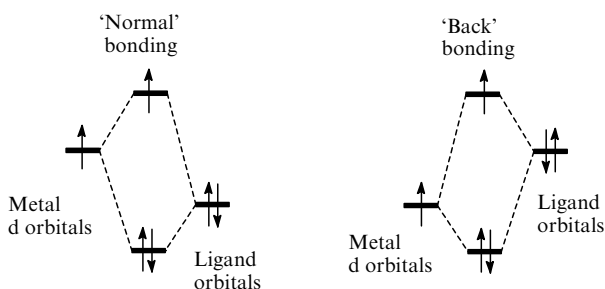
The dithione–dithiolate resonance cannot occur in nickel, palladium and platinum bis(*S*-benzyl-1,2-diphenylethylene-1,2-dithiolate) complexes **25**, and these compounds are ‘classical’ planar  $M^{\text{II}}$ -containing complexes.<sup>95</sup> However, irradiation of these complexes with visible light leads to successive elimination of both benzyl radicals from the ligand. Elimination of the first  $\text{CH}_2\text{Ph}^\bullet$  radical gives rise to radical complex **26**, in which 77%–94% of spin density is delocalised on the ligand depending on the nature of the metal. The latter radical complex decomposes in the dark to give the corresponding dithiolene complex **27** within approximately  $10^3$  s.



$M = \text{Ni}, \text{Pd}, \text{Pt}$ .

The spectroscopic [ESR, ENDOR, X-ray absorption spectroscopy, electron spin echo (ESE)] and calculated (DFT) data on nickel dithiolene complexes and their anionic species were summarised in the study.<sup>96</sup> According to these data, all nickel bis(dithiolene) complexes are characterised by back bonding, e.g., the energy of the valence orbitals of the ligands is higher than that of the d orbitals of the metal. A high energy of  $\pi$  orbitals of the ligand and good overlap of these orbitals with the Ni 3d

orbitals are responsible for the efficient ligand  $\rightarrow$  metal electron transfer.



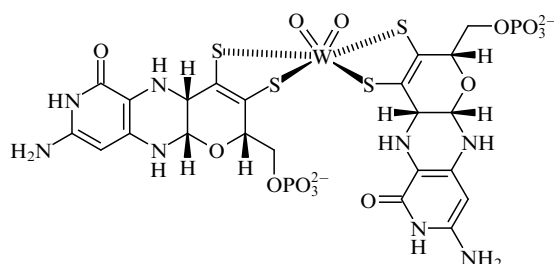
The lowest bonding molecular orbital of nickel complexes in all three oxidation states has more than 50% s-character; in the doubly-charged anionic complex, the LUMO is an antibonding combination of the Ni 3d<sub>xy</sub> orbital (~25%) and the b<sub>1g</sub>-symmetry S 3p<sub>x+y</sub> orbital (~75%). The singly-occupied molecular orbital (SOMO) of the singly-charged anionic complex is an antibonding combination of the Ni 3d<sub>xz</sub> orbital (~25%) and the b<sub>2g</sub>-symmetry S 3p<sub>z</sub> orbital (59%), whereas the LUMO is analogous to the corresponding orbital of the doubly-charged anionic complex. In the neutral complex, both the in-plane (b<sub>1g</sub>) and out-of-plane (b<sub>2g</sub>) orbitals are unoccupied and include ~20% of the Ni 3d orbital. On the whole, the singly-charged anionic complex is characterised by localisation of the unpaired electron predominantly on the sulfur atom.

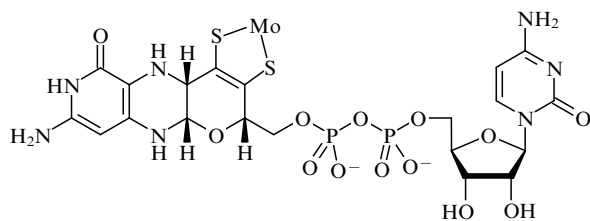
## 5. Magnetic properties of radical-ionic cyclopentadienyldithiolene complexes in the solid state

The ability of many non-innocent dithiolene square-planar  $[\text{M}^{\text{II}}(\text{S}_2\text{C}_2\text{R}_2)_2]^{2-}$  complexes to be reversibly oxidised in two steps, i.e., to exist in distinct oxidation states, allows the isolation of open-shell radical-anionic compounds (for example,  $[\text{Ni}\{\text{S}_2\text{C}_2(\text{CN})_2\}]^-$ ). In these compounds, efficient spin delocalisation over ligands is favourable for interactions in the solid state with a singlet–triplet, ferromagnetic or antiferromagnetic ground state. These complexes are of interest in materials science as potential solid materials with unique electronic properties, such as molecular metals, superconducting materials and magnetic crystals.<sup>18</sup>

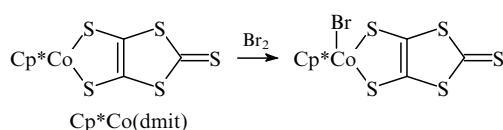
In 1986, Cassoux *et al.*<sup>97</sup> discovered superconductivity of mixed-valence salts containing  $[\text{Ni}(\text{dmit})_2]^-$ , which gave rise to an outburst of activity in the field of synthesis of square-planar dithiolene complexes (with various new dithiolate ligands, different metals, two different dithiolene ligands or tetrathiafulvalene-based dithiolenes), nonplanar  $\text{CpCo}(\text{mnt})$  (mnt is maleonitrile-2,3-dithiolate),  $\text{Cp}_2\text{Ti}(\text{bdt})$  (bdt is benzene-1,2-dithiolate) complexes and the wedge-shaped sandwich complex  $\text{Cp}_2\text{Nb}(\text{dmit})$ .<sup>18</sup>

Dithiolene complexes have attracted widespread attention due to their analogy with the so-called molybdo- and tungstoenzymes (cofactors of oxomolybdoenzymes).<sup>98</sup> Different steps of the catalytic cycle during redox reactions of these enzymes involve conformational changes, in which non-innocent dithiolene complexes play a key role. Examples of such compounds are the structures of W- and Mo-containing (fragment) cofactors of aldehyde oxidoreductases from bacteria *Picrococcus furiosus* and *Desulfovibrio gigas* with one and two dithiolene fragments, respectively.



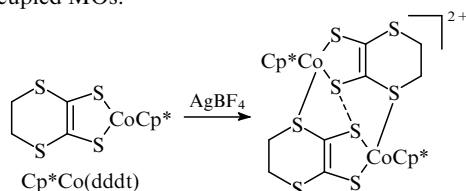


Based on the results of investigations of mixed complexes containing the dithiolene and Cp ligands, these complexes were classified into three groups.<sup>18</sup> The first group includes complexes generating radicals, in which the spin is completely or almost completely localised on the ligand. Examples are the trivalent cobalt complexes  $\text{CpCo(dmit)}$  and  $\text{Cp}^*\text{Co(dmit)}$ , where  $\text{Cp}^*$  is the pentamethylcyclopentadienyl anion. Oxidation of these diamagnetic complexes with bromine results in the formation of the bromide ion that is involved in the metal coordination sphere.



Studies by ESR demonstrated that the spin is localised predominantly on the dmit ligand and the paramagnetic  $\text{Cp}^*\text{Co(dmit)Br}$  complexes interact with the adjacent molecules *via*  $\text{S}\cdots\text{S}$  contacts to form homogeneous chains, which are adequately described by the Heisenberg antiferromagnetic chain model with large negative coupling between the radicals along the chain ( $J/k = -46.3 \text{ K}$  or  $32 \text{ cm}^{-1}$ ).

Upon oxidation of  $\text{Cp}^*\text{Co(dddt)}$  (dddt is 5,6-dihydro-1,4-dithiine-2,3-dithiolate) with  $\text{AgBF}_4$ , the  $\text{BF}_4^-$  anion is not coordinated, and the  $[\text{Cp}^*\text{Co(dddt)}]^+$  radical cation is unstable and is dimerised to the diamagnetic doubly-charged  $[\text{Cp}^*\text{Co(dddt)}]_2^{2+}$  cation. The sulfur atoms of the six-membered ring are involved in the coordination sphere of the adjacent cation to form a two-electron bond, *i.e.*, complete spin localisation on the dddt ligand leads to its coupling in the antibonding combination of two singly-occupied MOs.<sup>99</sup>

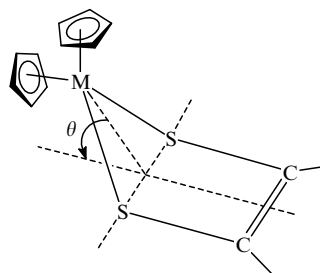


In both examples, intermolecular coupling occurs due to overlap of orbitals of different dithiolene fragments, and, if a covalent bond between the radicals is absent or this bonding can be precluded, the molecules possess properties of considerable interest in applied studies.

The second group includes complexes which form compounds containing an open-shell metal atom. Examples are the  $d^1$ -complexes  $\text{Cp}_2\text{V(dt)}$  and  $\text{Cp}_2\text{Nb(dt)}$  (dt is dithiolene). The  $d^0$ -complexes  $\text{Cp}_2\text{Ti(dt)}$  do not form stable radical ions. They are reduced at strongly negative potentials and are reversibly oxidised.<sup>100</sup> However, uranium can be transformed into the oxidation state  $\text{U}^V$ , and, although the neutral  $\text{Cp}_2\text{U(dddt)}$  complex does not form stable radical species, oxidation of  $[\text{U}^V(\text{cot})(\text{dddt})]$  (cot is cyclo-octatetraene) with  $\text{AgBF}_4$  affords the  $[\text{U}^V(\text{cot})(\text{dddt})]^-$  radical anion [salt with  $\text{Na(18-crown-6)(THF)}$ ]. The bond lengths in the dddt ligand of the radical anion are only slightly different from those in the starting doubly-charged anionic complex or in  $\text{Cp}_2\text{Ti(dddt)}$ , *i.e.*, the metal is subjected to oxidation to  $\text{U}^V$ . In the solid state, the spins are uncoupled.

Complexes of the third group, in which the unpaired electron is shared by the metal and the ligand, are intermediate between complexes of the first and second groups (an unpaired electron is

completely localised on either the ligand or the metal). Examples are molybdenum and tungsten  $d^1$ -complexes of the  $[\text{Cp}_2\text{M(dt)}_2]^+$  type. The  $\text{Cp}_2\text{Mo(dt)}$  ( $\text{Mo}^{\text{IV}}$ ,  $d^2$ ) complexes give reversible oxidation waves.<sup>101,102</sup> The  $\text{Cp}_2\text{Mo(dddt)}$  complex is oxidised by 7,7,8,8-tetracyanoquinodimethane (TCNQ), while  $\text{Cp}_2\text{Mo(dmit)}$  is oxidised by the strong acceptor,  $\text{TCNQF}_4$ , to form the corresponding radical-ionic salts  $\text{Cp}_2\text{Mo(dddt)}^+\text{TCNQ}^-$  and  $\text{Cp}_2\text{Mo(dmit)}^+\text{TCNQF}_4^-$ . Electrocrystallisation<sup>103</sup> afforded the  $\text{Cp}_2\text{Mo(dmit)}^+$  salts with different anions: monoatomic ( $\text{Br}^-$ ), tetrahedral ( $\text{BF}_4^-$ ,  $\text{ClO}_4^-$ ), octahedral ( $\text{PF}_6^-$ ,  $\text{AsF}_6^-$ ,  $\text{SbF}_6^-$ ) and more complex ( $\text{ReO(dmit)}_2^-$ ) anions. The most interesting result obtained in these investigations is the variability in the geometry of the  $d^1$ -radical cation and, particularly, in the puckering angle ( $\theta$ ) of the five-membered metallacycle with respect to the  $-\text{S}\cdots\text{S}-$  'hinge'.



The puckering angle varies from 0 to  $30^\circ$  depending on the nature of the ligand as exemplified by the  $\text{Cp}_2\text{Mo(dmit)}^+$  cation in Table 1 (see Ref. 18 and references cited therein).

**Table 1.** The puckering angle ( $\theta$ ) of the  $\text{MoS}_2\text{C}_2$  metallacycle and the C—S and C=C bond lengths in selected molybdenum and titanium complexes.

| Compound                                                                                | $\theta/\text{deg}$ | C—S / Å | C=C / Å |
|-----------------------------------------------------------------------------------------|---------------------|---------|---------|
| $\text{Cp}_2\text{Mo(dmit)}$                                                            | 4.2                 | 1.745   | 1.357   |
| $[\text{Cp}_2\text{Mo(dmit)}^+]\text{PF}_6^-$ (or $\text{AsF}_6^-$ , $\text{SbF}_6^-$ ) | 0.0                 | 1.691   | 1.41    |
| $[\text{Cp}_2\text{Mo(dmit)}^+][\text{ReO(dmit)}_2^-]$                                  | 5.6                 | 1.688   | 1.383   |
| $[\text{Cp}_2\text{Mo(dmit)}^+]\text{TCNQF}_4^-$                                        | 10.2                | 1.684   | 1.43    |
| $[\text{Cp}_2\text{Mo(dmit)}^+]\text{BF}_4^-$                                           | 23.21               | 1.718   | 1.360   |
| $[\text{Cp}_2\text{Mo(dmit)}^+]\text{Br}^-$                                             | 30.45               | 1.712   | 1.385   |
| $\text{Cp}_2\text{Ti(dt)}$                                                              | 43–51               |         |         |

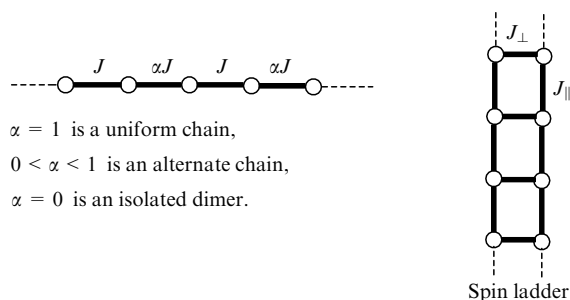
Similar puckering (even to a larger extent) was observed for the titanium  $d^0$ -dithiolene complexes (see Table 1). The reason is that puckering allows the free  $d^0$  orbital of the  $\text{Cp}_2\text{Ti}$  fragment to be mixed with the HOMO of dithiolene, resulting in stabilisation of the  $d^0$  system. This mixing is impossible at  $\theta = 0^\circ$  due to symmetry mismatch between the  $d^0$  orbital and the HOMO in this conformation. According to this theory, puckering for the  $d^2$  complexes  $\text{CpMo(dt)}$  is absent, which was confirmed experimentally.<sup>18</sup>

Great puckering was observed for 'heavier' complexes,<sup>18</sup> for example, upon the replacement of Mo with W, S with Se in the ligand or both elements simultaneously. This fact is consistent with the results of DFT calculations.<sup>104</sup> For example, electrocrystallisation of  $\text{Cp}_2\text{Mo(dsit)}$  and  $\text{Cp}_2\text{W(dmit)}$  (dsit is 1,3-dithiole-2-thione-4,5-diselenolate, a selenium analogue of dmit) in the presence of  $\text{AsF}_6^-$  affords isostructural salts with  $\theta = 0^\circ$ , whereas heavier  $\text{Cp}_2\text{W(dsit)}$  gives a radically different structure with  $\theta = 30.1^\circ$ .<sup>104</sup>

A strongly puckered conformation cannot exist in structurally rigid *ansa*-metallocene dithiolene complexes, and, hence, oxidation of the unpuckered  $d^2$  complexes  $\text{Me}_2\text{C}(\eta^5\text{-C}_5\text{H}_4)_2\text{Mo(dmit)}$  and  $\text{Me}_2\text{C}(\eta^5\text{-C}_5\text{H}_4)_2\text{W(dmit)}$  ( $\theta_{\text{Mo}} = 0.68^\circ$ ,  $\theta_{\text{W}} = 0.29^\circ$ ) in  $\text{TCNQF}_4$  salts results in weak puckering ( $\theta_{\text{Mo}} = 7.35^\circ$ ,  $\theta_{\text{W}} = 6.99^\circ$ ).<sup>105</sup>

An increase in the puckering angle is indicative of enhancement of interactions between the frontier orbitals of the metal-locene and dithiolate fragments, with the result that the unpaired electron is shared by the ligand and the metal (more precisely, by the  $\text{Cp}_2\text{M}$  fragment). Therefore, the non-innocent character is not an indication of only a redox-active ligand. If there is strong mixing of the ligand and metal orbitals, the non-innocent behaviour characterises the complex as a whole (oxidation states of the metal or the ligand are difficult to determine).

The formation of crystals of radical-cationic  $d^1$  complexes in the presence of various anions involves a fine balance between the degree of intramolecular puckering, intermolecular spin-spin coupling and the counterion size aimed at decreasing the crystal free energy. Variations in the spin density on the dithiolene fragment and the crystal structure of the  $\text{Cp}_2\text{M}(\text{dt})^+\text{X}^-$  salts would be expected to change the magnetic properties of the substance in the solid state, because the latter are controlled by the strength of the  $\text{dt}\cdots\text{dt}$  and  $\text{dt}\cdots\text{Cp}$  intermolecular interactions. For the complexes under consideration, the following two main structural motifs were suggested: diads, which are associated with each other to a greater or lesser degree, or extended three-dimensional structures. Below are shown the possible models of interactions between the diads: uniform ( $\alpha = 1$ ) and alternate ( $0 < \alpha < 1$ ) chains and the so-called 'spin ladders'.<sup>18</sup>



Each circle indicates a spin carrier, and each line corresponds to interactions;  $J$  and  $\alpha J$  characterise interactions between the radicals along the chain. For example, the radical cations in the isostructural  $[\text{Cp}_2\text{Mo}(\text{dddt})][\text{TCNQ}]$  and  $[\text{Cp}_2\text{W}(\text{dddt})][\text{TCNQ}]$  complexes are actually arranged as diads with short  $\text{S}\cdots\text{S}$  contacts. These diads are not isolated from each other, but form alternate chains ( $0 < \alpha < 1$ ). The alternate chains are characterised by the following parameters:  $J_{\text{Mo}}/k = -26 \text{ K}$  ( $18 \text{ cm}^{-1}$ ),  $\alpha_{\text{Mo}} = 0.0\text{--}0.2$ ,  $J_{\text{W}}/k = -16 \text{ K}$  ( $11 \text{ cm}^{-1}$ ),  $\alpha_{\text{W}} = 0.5\text{--}0.6$ . Interactions between the molybdenum diads are stronger than those between the tungsten diads, which is attributed to a greater localisation of the spin on the metal in the tungsten complex. The interaction is antiferromagnetic ( $J < 0$ ) due to direct exchange interaction between SOMOs.

The model of a uniform chain ( $\alpha = 1$ ) is better applicable to  $[\text{Cp}_2\text{Mo}(\text{dsit})][\text{TCNQF}_4]$ , whereas  $[\text{Cp}_2\text{W}(\text{dsit})][\text{TCNQF}_4]$  is more adequately described by an alternate chain with  $\alpha = 0.5$ . Examples of molecular spin ladders are  $[\text{Cp}_2\text{Mo}(\text{dmid})][\text{TCNQF}_4]$  (dmid is 1,3-dithiol-2-one-4,5-dithiolate)<sup>106</sup> and  $[\text{Cp}_2\text{W}(\text{dsit})]\text{AsF}_6$ .<sup>104</sup> In these salts, the diads formed by two organometallic cations are arranged one above another to form a ladder-like system ( $|J_{\perp}| > |J_{\parallel}|$ ). In this case, stronger intermolecular interactions also occur in the molybdenum compounds, because the SOMO in molybdenum salts is localised to a larger degree on the dithiolene fragment compared to the tungsten complexes.

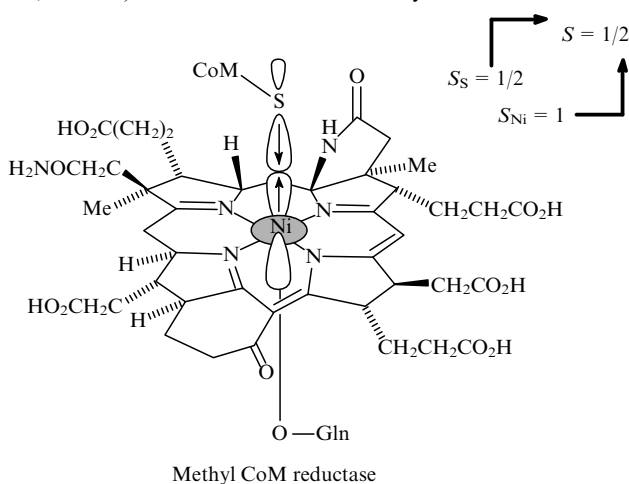
## 6. Non-innocent behaviour of thiolate ions

The results of experimental and calculated studies suggest that the HOMO of many metal thiolates is centred on the sulfur atom and has the character of its  $p$  orbital (see Ref. 107 and references cited therein). Hence, many reactions of transition metal thiolates, including redox reactions, would be expected to occur at the

sulfur atom. Oxidation of thiolate complexes gives rise to thiolate radicals.

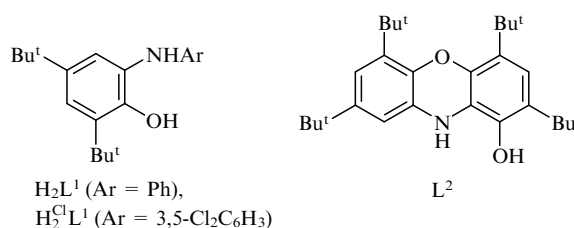
The oxidation states of the Ni cofactor  $\text{F}_{430}$  in methyl coenzyme M reductase were studied<sup>108</sup> by magnetic circular dichroism, X-ray absorption spectroscopy and DFT calculations, and it was hypothesised that the oxidised state of the enzyme containing the Ni-SR bond can formally be described as a  $\text{Ni}^{\text{II}}$  complex with the thiyl radical ( $^{\bullet}\text{SCoM}$ , CoM is the coenzyme M).

This state can alternatively be described as  $\text{Ni}^{\text{III}}$  thiolate, but this description is less probable. Earlier, an analogous non-innocent behaviour of sulfur-containing ligands (S-centred radical, thiolate) was assumed in biochemistry.<sup>109</sup>



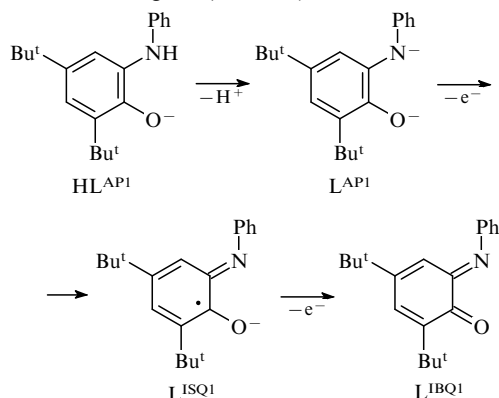
## 7. Complexes of *o*-aminophenols

Like other compounds belonging to the  $o\text{-XC}_6\text{H}_4\text{Y}$  structural type (X, Y = O, S or NH), *o*-aminothiophenols are classical non-innocent ligands. Ligands in complexes with V, Cr, Fe and Co and the corresponding catecholate, *o*-phenylenediamine and *o*-benzenedithiolate complexes can be assigned to a particular oxidation state on the basis of the structural criteria proposed in the study.<sup>110</sup> Complexes of *o*-aminophenol and its substituted analogues  $\text{H}_2\text{L}^1$  (see Refs 9 and 110) and  $\text{L}^2$  (see Refs 111 and 112) with  $\text{Fe}^{\text{III}}$ ,  $\text{Ni}^{\text{II}}$ ,  $\text{Co}^{\text{III}}$ ,  $\text{Pd}^{\text{II}}$  and  $\text{Cu}^{\text{II}}$  were documented. In these complexes, the ligand is present as the singly-charged anionic *o*-iminosemiquinone radical.



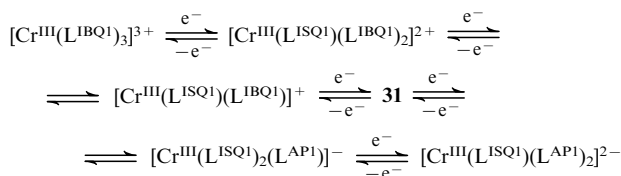
The  $\text{Co}^{\text{III}}(\text{L}^{\text{ISQ}1})_3$  (**28**),  $[\text{Cu}(\text{dmtacn})\text{L}^{\text{ISQ}1}]\text{PF}_6$  (**29**),  $\text{Cu}(\text{L}^{\text{ISQ}1})_2$  (**30**),  $\text{Ni}(\text{L}^{\text{ISQ}1})_2$ ,  $\text{Ni}(\text{ClL}^{\text{ISQ}1})_2$  and  $\text{Pd}(\text{L}^{\text{ISQ}1})_2$  compounds ( $\text{L}^{\text{ISQ}1}$  and  $\text{ClL}^{\text{ISQ}1}$  are  $\text{L}^1$  and  $\text{ClL}^1$ , respectively, in the semiquinone form, dmtacn is 1,4-dimethyl-1,4,7-triazacyclononane) were studied by X-ray diffraction.<sup>9</sup> The central metal atoms in copper complex **30** and divalent nickel and palladium complexes are in a square-planar environment. The ground state of complex **29** is  $S = 1$ , which is associated with the strong antiferromagnetic coupling between the  $\text{Cu}^{\text{II}} d_{x^2-y^2}$  orbital and the  $\pi$  orbital of the radical ligand. Complex **28** contains three virtually orthogonal semiquinone ligands  $\text{L}^{\text{ISQ}1}$ , and its ground spin state is  $S = 3/2$ . Other complexes are singlet biradicals, the central divalent metal atoms in these complexes have the  $d^8$  configuration, and the complexes are diamagnetic. A detailed study of electrochemical oxidation and reduction of all five complexes revealed a series of reversible one-electron steps, all processes occurring at the ligand.

For the HL<sup>1</sup> ligand (Ar = Ph)<sup>110</sup>

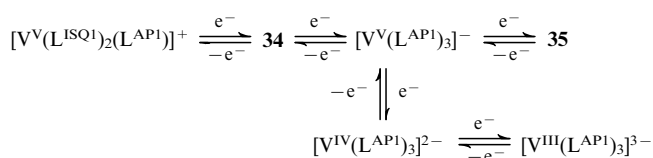


complexes with  $\text{Cr}^{\text{III}}(\text{L}^{\text{ISQ1}})_3$  (**31**),  $\text{Co}^{\text{III}}(\text{L}^{\text{ISQ1}})_3$  (**32**) and  $\text{Fe}^{\text{III}}(\text{L}^{\text{ISQ1}})_3$  (**33**) and a series of vanadium complexes, including  $\text{V}^{\text{V}}\text{L}^{\text{ISQ1}}(\text{L}^{\text{API}})_2$  (**34**) and  $\text{V}^{\text{V}}(\text{L}^{\text{API}})_2(\text{HL}^{\text{API}})$  (**35**), were described. All five compounds **31**–**35** were characterised by X-ray diffraction.

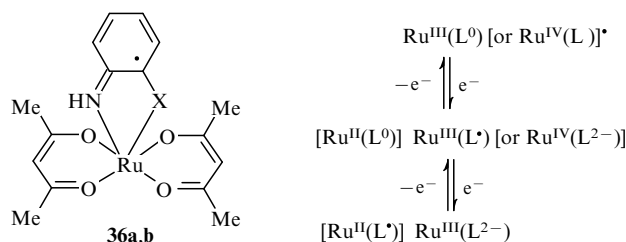
The electrochemical behaviour of the above-mentioned complexes was accounted for by redox processes involving both the metal and the ligand depending on the nature of the metal in the complex. For example, all redox processes in chromium complex **31** involve exclusively the ligand.



By contrast, the metal atom in vanadium complex **34** is reduced in the second and third steps, and, in addition, highly oxidised members of the redox series are electrochemically inaccessible.

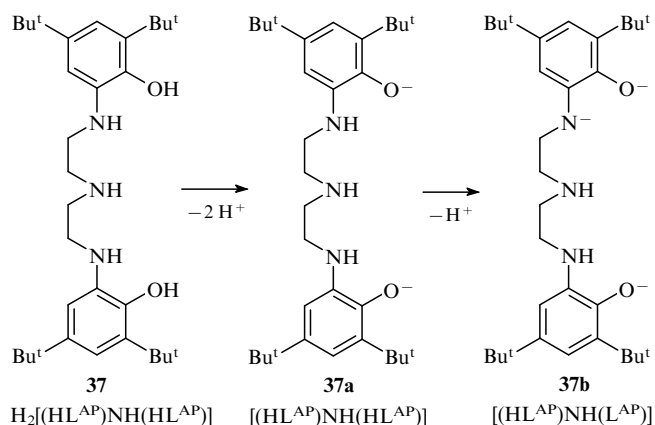


The diamagnetic  $\text{LRu}^{\text{II}}(\text{acac})_2$  complexes (**36a,b**) [**L** is *o*-iminoquinone (**36a**) or *o*-iminothiosemiquinone (**36b**); compound **36a** was characterised by X-ray diffraction<sup>113</sup>] are irreversibly oxidised or reduced by electrochemical methods to form paramagnetic singly-charged cations and anions. Electrochemical, calculated and spectroscopic data demonstrated that the ligand is subjected to oxidation and reduction (below the acac ligands are omitted for simplicity; possible alternative formulae of the compounds are given in parentheses).


$$X = O(\mathbf{a}), S(\mathbf{b}).$$

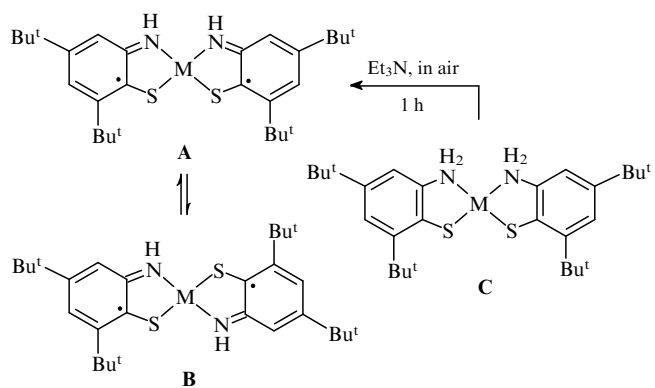
*N,N'*-Bis[2-(4,6-di-*tert*-butyl)hydroxyphenyl]diethylenetriamine **37** was studied in complexation reactions with first-row transition metals (vanadium, chromium, iron and cobalt).<sup>110</sup> The resulting

complexes containing ligands in the above-mentioned three forms were studied in detail by electrochemical and spectroelectrochemical methods. The vanadium complex  $V^{VO}[(HL^{AP})NH(L^{AP})]$  with the triply-charged anion **37b** as the ligand was studied by X-ray diffraction.



## 8. Complexes of *o*-aminothiophenols and their selenium- and tellurium-containing analogues

Neutral square-planar  $\text{Ni}^{\text{II}}$ ,  $\text{Pd}^{\text{II}}$  and  $\text{Pt}^{\text{II}}$  bis(*o*-iminothioseminquinonate) complexes were synthesised and characterised. Being singlet biradicals, these complexes are diamagnetic. The reaction of *o*-aminothiophenols with  $\text{M}^{2+}$  salts in ethanol or acetonitrile in air produced both complexes with ligands containing the unsubstituted benzene ring<sup>46, 114–116</sup> and black-blue complexes based on 6-amino-2,4-di-*tert*-butylthiophenol.<sup>12, 117</sup> The structures of all the complexes synthesised were confirmed by NMR, UV-Vis and ESR spectroscopy and, in most cases, by X-ray diffraction analysis. The NMR spectra suggest that the *cis* and *trans* forms **A** and **B** of the complexes with di-*tert*-butyl-substituted ligands are in rapid equilibrium in solution.


$$\text{M} = \text{Ni}^{\text{II}}, \text{Pd}^{\text{II}}, \text{Pt}^{\text{II}} (\text{A}, \text{B}); \text{M} = \text{Ni}^{\text{II}}, \text{Pd}^{\text{II}} (\text{C}).$$

Both the *cis* and *trans* forms of the complexes were isolated and studied by X-ray diffraction analysis. The *cis*–*trans* transformation is fast in the case of Ni and slow in the case of Pt, whereas the rate of this transformation in the case of Pd is intermediate. It should be noted that the beige-yellow ‘classical’ complex **C** is derived from *o*-aminothiophenols and  $M^{2+}$  salts under inert atmosphere.

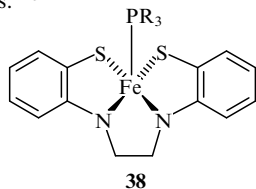
Spectroelectrochemical and electrochemical studies of the complexes **A** and **B** revealed a usual electron-transfer series, in which a singly-charged cation, a neutral species and singly- or doubly-charged anions were identified.<sup>13</sup> The ESR spectra of singly-charged cations of the nickel and platinum complexes confirmed that only the ligand is oxidised to form  $[\text{M}^{\text{II}}(\text{L}^{\text{ISQ}})(\text{L}^{\text{IBQ}})]^+$ , where  $\text{L}^{\text{IBQ}}$  is *o*-iminothioquinone. In contrast, the structures of the complexes for the corresponding singly-charged anions are most adequately described by the  $[\text{M}^{\text{II}}(\text{L}^{\text{ISQ}})$ .

$(L^{AP})^-$  and  $[M^I(L^{ISQ})_2]^-$  resonance structures, the contribution of the latter being considerable ( $L^{AP}$  is the doubly-charged *o*-imidothiophenolate anion).

The *o*-iminothiosemiquinonate radical is characterised by two intense  $\pi-\pi^*$ -charge transfer bands in the visible region of the UV-Vis spectra at  $\sim 640$  and  $560$  nm and by an intense ligand–ligand charge transfer band at the boundary between the visible and near-IR regions at  $730-840$  nm in the IR spectra.<sup>12</sup>

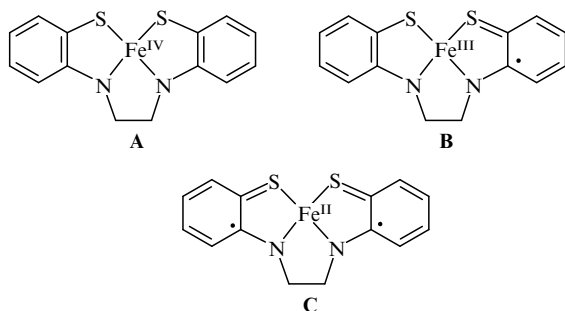
Analysis of the literature data on the geometric features of 120 complexes containing *o*-aminothiophenolate-type ligands<sup>12</sup> made it possible to propose criteria for the determination of the degree of protonation and oxidation of the ligands in these complexes. As in the *o*-phenylenediamine and *o*-catecholate complexes, the C–N and C–S bond lengths and the C=C bond lengths in the benzene ring are very characteristic. The bond lengths in the ligand are virtually independent of the nature of the coordinated metal. The radical form ( $L^{ISQ}$ ) of non-innocent *o*-aminothiophenolates is the major one in coordination compounds.

In 1997, a series of complexes **38** containing five-coordinate iron atoms and *o*-amidothiophenolate ligands were synthesised and characterised by X-ray diffraction and spectroscopic methods.<sup>118</sup>



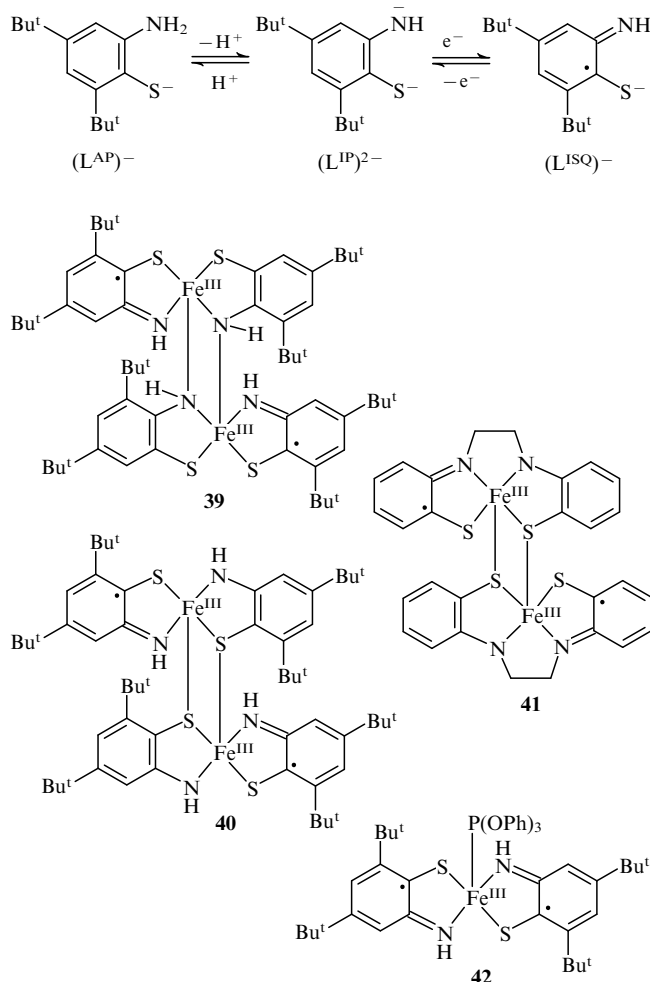
R = Me, Et, Pr<sup>n</sup>, Bu<sup>n</sup>, Ph, cyclo-C<sub>6</sub>H<sub>11</sub>, OMe, OPh.

In the study,<sup>118</sup> the ligand was considered as the redox-innocent quadruply-charged 1,2-ethanediamido-*N,N'*-bis(2-benzenethiolate)<sup>4-</sup> anion, and the complex as a whole was described as an Fe<sup>IV</sup> complex ( $S = 1$ ) (**A**). This structure is consistent with the magnetic moment of  $2.76 \mu_B$  observed for this complex at room temperature and the data from cyclic voltammetry (reversible reduction of the complex at  $+0.04$  and  $-0.86$  V, which were assigned to the Fe<sup>IV</sup>/Fe<sup>III</sup> (**A/B**) and Fe<sup>III</sup>/Fe<sup>II</sup> (**B/C**) transitions, respectively) and Mössbauer spectroscopy, although a complete analysis of the latter spectrum was lacking.



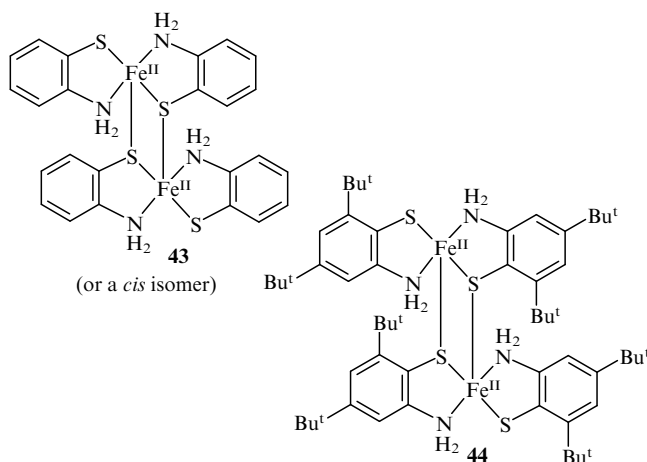
However, the studies<sup>12, 119</sup> cast doubt on this description of the structures. In the study,<sup>119</sup> it was demonstrated that the bond lengths in this class of complexes determined by X-ray diffraction analysis are typical of complexes of the *o*-iminothiosemiquinonate radical, the physical oxidation state of iron in the complex is  $+2$  (structure **C**), and the spin  $S = 1$  observed for the ground state of the complex is attributed to strong intramolecular antiferromagnetic coupling between two organic radicals and the low-spin iron ion. Analysis of the spin-Hamiltonian<sup>12</sup> confirmed this assumption. Ghosh *et al.*<sup>119</sup> reproduced the experiment performed earlier by Sellmann *et al.*<sup>118</sup> and demonstrated that only the freshly prepared complex had the magnetic moment of  $2.76 \mu_B$ , whereas this value decreased to  $0.6 \mu_B$  after two crystallisations.

Analogous iron complexes containing the di-*tert*-butyl-substituted *o*-iminothiosemiquinonate fragments were described in the study.<sup>119</sup> The binuclear  $(\mu-NH, NH)[Fe^{III}L^{IP}L^{ISQ}]_2$  (**39**) and  $(\mu-S, S)[Fe^{III}L^{IP}L^{ISQ}]_2$  complexes (**40** and **41**) and the mononuclear  $Fe^{III}(L^{ISQ})_2[P(OPh)_3]$  complex (**42**) were synthesised and characterised by X-ray diffraction analysis.

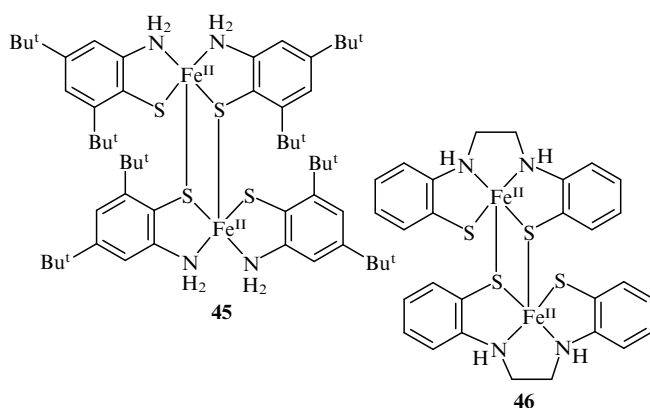


The oxidation state of the ligands was established by X-ray diffraction and ESR, UV-Vis and Mössbauer spectroscopy.

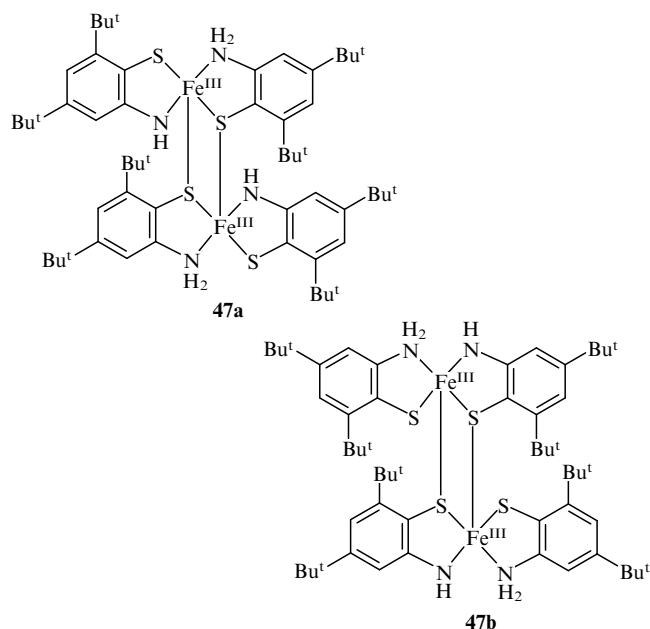
Dimeric complexes **43–46** were synthesised under inert atmosphere in a neutral medium, *i.e.*, under conditions precluding deprotonation.<sup>120</sup>







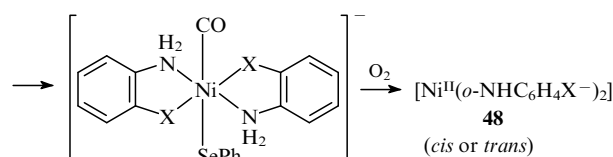
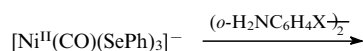
Complexes **43–45** are sensitive to atmospheric oxygen and moisture and are transformed into the  $[\text{Fe}(\text{L}^{\text{ABT}})_2\text{L}^{\text{ISQ}}]$  complex ( $\text{L}^{\text{ABT}}$  is the *o*-aminobenzothiolate anion) in the presence of traces of oxygen. The latter complex is characterised by the ground spin state  $S = 3/2$ . Dimers **47a,b** are produced in the presence of  $\text{Et}_3\text{N}$  and traces of  $\text{O}_2$ .



The structures of compounds **44**, **46** and **47a** were determined by X-ray diffraction. Mössbauer spectra of compounds **43–45** unambiguously established the presence of the high-spin iron ion, whereas both medium-spin Fe ions ( $S_{\text{Fe}} = 3/2$ ) in dimers **47a,b** are antiferromagnetically coupled, resulting in the ground state  $S = 0$ .

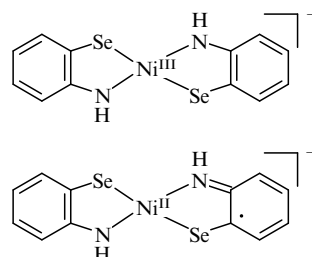
Di- and trivalent cobalt complexes with the same ligands as in complexes **31–35** and **39–47** were documented.<sup>121</sup> In all the complexes synthesised, the ligands are redox-non-innocent, but oxidation and reduction of either the metal or ligand depend on the state (anionic, radical-anionic or neutral) of the ligand and the oxidation state of the central metal atom in the starting complex.

In 2003, selenium- and tellurium-containing ligands (analogues of *o*-aminothiophenol) were synthesised and their complexes with nickel **48** were prepared by the oxidative addition of 2-aminophenyl dichalcogenides to the  $[\text{Ni}(\text{CO})(\text{SePh})_3]^-$  anion.<sup>122</sup>

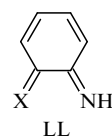


$\text{X} = \text{Se}, \text{Te}$

The *trans*- $[\text{Ni}(\text{SeC}_6\text{H}_4\text{NH-}o)_2]^-$  and *cis*- $[\text{Ni}(\text{TeC}_6\text{H}_4\text{NH-}o)_2]^-$  complexes [as salts with the  $(\text{PPh}_3)_2\text{N}^+$  cation] were studied by X-ray diffraction. All complexes were also characterised by X-ray electron spectroscopy and DFT calculations. It was concluded that the singly-charged  $[\text{Ni}(\text{SeC}_6\text{H}_4\text{NH-}o)_2]^-$  and  $[\text{Ni}(\text{TeC}_6\text{H}_4\text{NH-}o)_2]^-$  anions are most adequately described as resonance hybrids of nickel(III) bis[*o*-amidochalcogenolate(2-)] and nickel(II) bis[*o*-iminochalcogenobenzosemiquinonate(1-)].



The delocalisation of the metal d-electrons in ruthenium bis(bipyridyl) complexes with redox-active quinoid ligands  $\text{Ru}(\text{bipy})_2\text{LL}$  was calculated.<sup>123</sup>



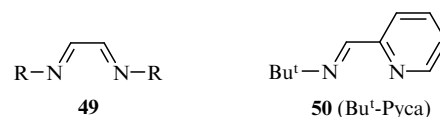
$\text{X} = \text{NH}, \text{O}, \text{S}$ .

The results of calculations confirmed by UV-Vis spectra of the compounds synthesised demonstrate that the degree of coupling between the  $\pi$ -orbitals of ruthenium and the LL ligand increases in the series  $\text{NH} < \text{O} < \text{S}$ .

### III. Complexes with diimine-containing ligands

#### 1. Complexes of $\alpha$ -diimines and their phosphorus analogues, 2,2'-biphosphines

Complexes of 1,2-diketone derivatives (**49**) and complexes with ligands in which the diimine fragment is involved in the heterocyclic system (**50**, bipy, etc.) are assigned to this structural type.

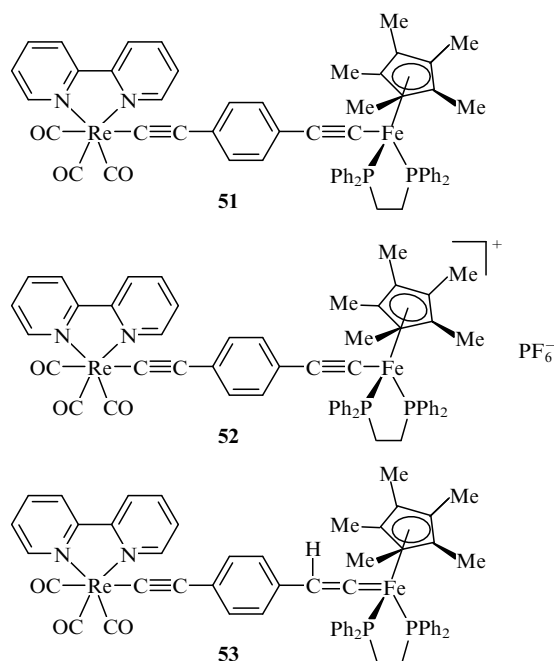


$\text{R} = \text{Alk}, \text{Ar}$ .

Complexes of 1,4-disubstituted 1,4-diazabutadienes **49** ( $\text{R} = \text{Bu}^t$ ,  $\text{cyclo-C}_6\text{H}_{11}$ ,  $4\text{-MeC}_6\text{H}_4$  and  $2,6\text{-Me}_2\text{C}_6\text{H}_3$ ) with  $\text{PtMe}_2$ ,  $\text{PtMe}_4$  and  $\text{PtMes}_2$  were studied by spectroscopic methods and DFT calculations.<sup>124</sup> These data suggest considerable metal  $\rightarrow$  ligand charge transfer. The results of spectroelectrochemical studies are consistent with reversible oxidation of the ligand to form the  $[\text{Pt}^{\text{II}}\text{L}]^+$  or  $[\text{Pt}^{\text{IV}}\text{L}]^+$  complexes. The reduction of analogous rhenium,<sup>125</sup> ruthenium, osmium, iridium and rhodium<sup>126</sup> complexes is also most adequately described as the reduction of the ligand to form the radical anion.

In complexes **6a–c** containing the terpyridyl fragment in the ligand (see Section II.1), the diimine fragment also undergoes one-electron reduction in the first step.<sup>24</sup>

Heteronuclear alkynyl-bridged complex **51** and its analogue **52** with oxidised iron (from Fe<sup>II</sup> to Fe<sup>III</sup>) were synthesised and characterised by X-ray diffraction.<sup>127</sup>



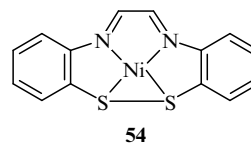
Vinylidene complex **53** was also documented.<sup>127</sup> This complex is reversibly oxidised at  $-0.19$  V and quasireversibly reduced at  $-1.49$  V. Electrochemical data and results of DFT calculations suggest that the LUMO of the complex is localised predominantly on the  $\pi^*$  orbital of the bipyridyl ligand, whereas the HOMO has the character of the iron(II) d orbital.

Phosphorus analogues of  $\alpha$ -diimines, in particular, 2,2'-biphosphines, can also be considered as non-innocent ligands. For example, 4,4',5,5'-tetramethyl-2,2'-biphosphine (tmbp) is reduced with potassium mirror to the planar radical anion (studied by X-ray diffraction analysis as a lithium salt), in which the unpaired electron (DFT calculations) is delocalised over the PCCP fragment with a large contribution of the phosphorus  $p_\pi$  orbitals.<sup>128</sup> Electrochemical reduction of the Ni<sup>0</sup>(tmbp)<sub>2</sub> complex afforded a 19-electron complex studied by X-ray diffraction. These data are consistent with the results of DFT calculations, which demonstrated that the unpaired electron in the Ni<sup>0</sup>(bp)<sub>2</sub><sup>•-</sup> complex (bp is 2,2'-biphosphine) is delocalised primarily on the ligand.<sup>128</sup> The calculations showed also that the metal–ligand back bonding in Ni<sup>0</sup>(bp)<sub>2</sub> makes a considerable contribution to the metal–ligand bonding.

## 2. Complexes with ligands of the glyoxalbis(2-mercaptoanil) series

Oxidation and reduction of compounds with ligands of the glyoxalbis(2-mercaptoanil) series, which combine the  $\alpha$ -diimine and *o*-aminothiophenol fragments, were studied for the first time by Holm and co-workers<sup>26,129</sup> in 1960s. They demonstrated that the Ni(gma)<sub>2</sub> compound (**1**), analogously to the N<sub>2</sub>S<sub>2</sub> complexes with ligands of the *o*-disubstituted benzene series, is the central member of the electron-transfer series, the final oxidation product being a quinone complex. Holm and co-workers also described the chemical reduction of Ni(gma)<sub>2</sub> with sodium amalgam to the anionic Ni(gma)<sub>2</sub><sup>•-</sup> species. The radical character of the latter was demonstrated by ESR spectroscopy. When discussing the electron distribution in the starting complex and the degree of mixing of the metal and ligand orbitals, the authors considered the delocalised ground state and did not draw an unambiguous conclusion about localisation of the unpaired electron (on either the metal or the ligand) in the reduced radical-anionic form of the complex.

Complex **1** and other Ni<sup>II</sup> diiminodithiolate and diiminodisulfide N<sub>2</sub>S<sub>2</sub> complexes of this type, *i.e.*, with complete  $\pi$ -conjugation between all four donor centres, were synthesised.<sup>3</sup> These complexes were studied by <sup>1</sup>H NMR, ESR and UV spectroscopy, mass spectrometry and electrochemical methods. In solutions of complex **1** in DMF, the ESR signal first appears and then attenuates with time, which is accompanied by an analogous change in the intensity of the absorption band at 931 nm. The electrochemical behaviour also varies with time. After storage of compound **1** in solution for 5 h, the cyclic voltammogram becomes similar to the curve measured for the corresponding diiminodisulfide complex **54**.

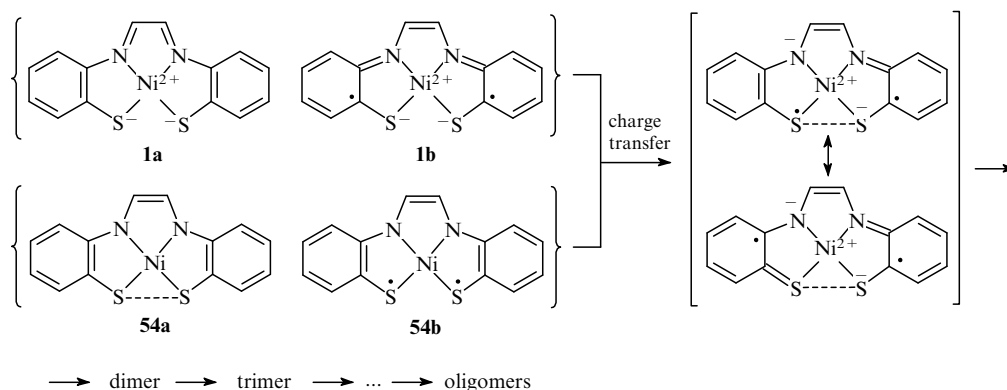


The results of this study suggest that non-innocent compounds of the glyoxalbis(2-mercaptoanil)nickel(II) type were synthesised as classical diiminodithiolate structures, but then the ligands were transformed successively (rapidly in solution and slowly in the solid state) into the *o*-iminothiosemiquinonate biradicals and oligomeric structures, the latter remaining unchanged over a long period of time (Scheme 3).

## 3. Complexes of pyridine-2,6-dialdimine and its derivatives

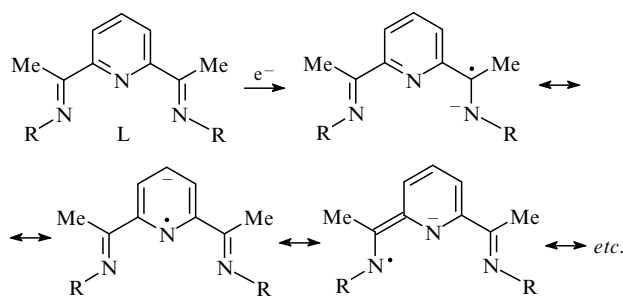
Most complexes with this ligand were described as the five-coordinate [M<sup>II</sup>X<sub>2</sub>L<sup>0</sup>] complexes or the six-coordinate [M<sup>II</sup>L<sub>2</sub><sup>0</sup>]X<sub>2</sub> complexes (M = Mn, Fe, Co, Ni, Cu, Zn or Cd; X = Cl or Br) containing one or two neutral tridentate ligands; and the ligands were always described as redox-innocent.<sup>130–134</sup> However, more recent studies by electrochemical methods and NMR, ESR and

Scheme 3



Mössbauer spectroscopy demonstrated that pyridine-2,6-dialdimines are non-innocent ligands, which can be coordinated to a transition metal ion as the neutral ligand  $L^0$  or the radical anionic ligand  $L^{-\bullet}$ .<sup>134</sup> This was suggested earlier by Toma and co-workers,<sup>130, 131</sup> but has not been strictly proved.

Metal complexes with pyridine-2,6-dialdimine with the general formula  $[M^{II}L_2](PF_6)_n$  ( $M = Mn, Fe, Co, Ni, Cu$  or  $Zn$ ) are reversibly reduced to  $[ML_2]^+$  and  $[ML_2]^0$ .<sup>135</sup> X-ray diffraction study of  $[MnL_2]PF_6$  and  $[CoL_2]PF_6$  demonstrated that the former complex is  $[Mn^{III}(L^{-\bullet})_2]PF_6$  (reduction of the ligand), whereas the latter complex is  $[Co^IL_2]PF_6$  (reduction of the metal).



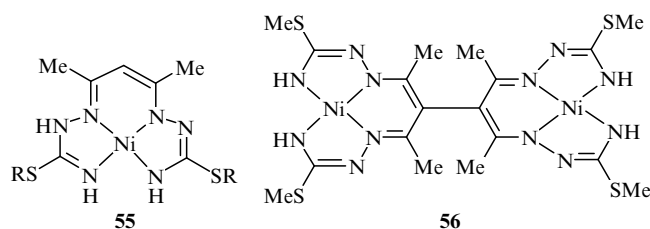
$R = 4\text{-MeOC}_6\text{H}_4$ .

#### 4. Complexes with pentane-2,4-dionebis(2-alkylisothiosemicarbazone)-type ligands

Template condensation of pentane-2,4-dione with *S*-alkylisothiosemicarbazide hydrochloride in the presence of divalent metal ions ( $Ni$ ,<sup>136, 137</sup>  $Co$ ,<sup>138</sup>  $Fe$ <sup>139–141</sup>) affords complexes containing pentane-2,4-dionebis(2-alkylisothiosemicarbazone) ( $H_3L$ ) as the ligand (Scheme 4).

This ligand exhibits a complex coordination behaviour towards transition metals, because it, first, can exist in different protonated forms,  $(H_3L)^0$ ,  $(H_2L)^-$ ,  $(HL)^{2-}$  and  $(L)^{3-}$ , and, second, can undergo two-electron oxidation also to two different protonated forms,  $(HL)^0$  and  $(L)^-$ .

Mono- and binuclear nickel complexes with the non-innocent pentane-2,4-dionebis(2-alkylisothiosemicarbazone) ligands exist in two forms containing the ligand in different oxidation states,<sup>142</sup> viz., the red-brown  $Ni^{II}(HL)$  complexes **55** sensitive to oxidation with atmospheric oxygen and the paramagnetic black-green oxidised  $Ni(L-L)Ni$  complexes **56** (in this formula, the nickel atom is in the formally trivalent oxidation state; however, in the real complex studied by X-ray diffraction, the ligand is apparently oxidised and the nickel atom is reduced to the oxidation state of +2).

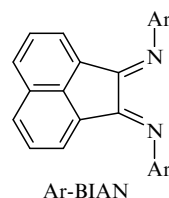


$R = Me, n\text{-dodecyl}$ .

Both oxidation and reduction of the dinuclear complex occur with the involvement of the ligand and with retention of the oxidation state of the nickel atoms.

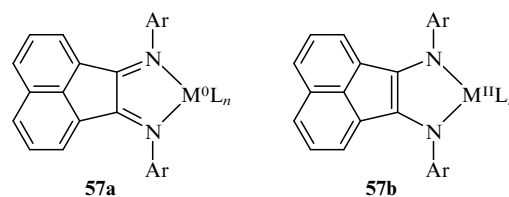
#### 5. Complexes of bis(arylimino)acenaphthenes

In recent years, bis(arylimino)acenaphthenes (Ar-BIAN) have attracted considerable attention. Their complexes with transition metals can serve as catalysts for some reactions of organic compounds.<sup>143–151</sup>

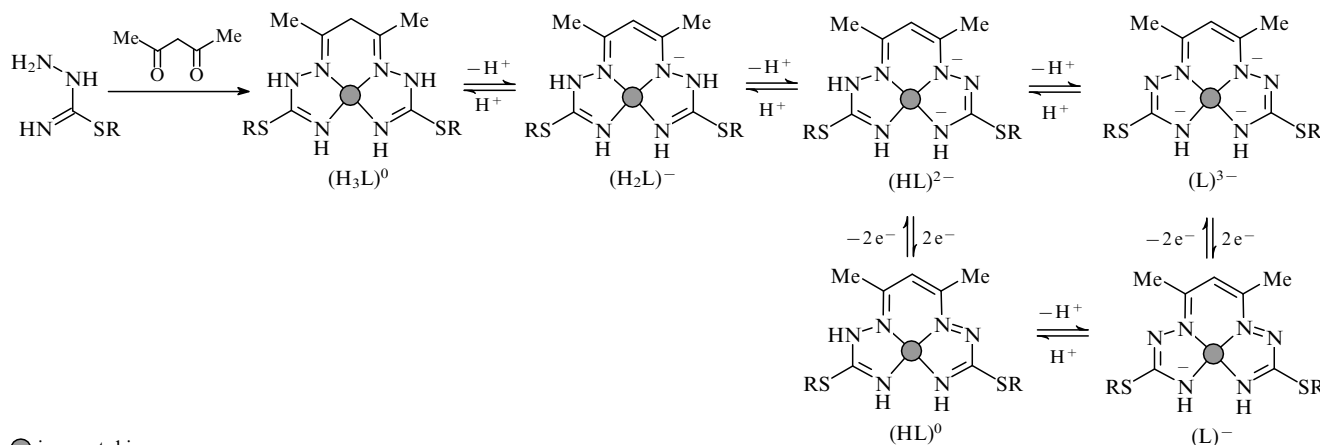


Compared to other diimine ligands, BIAN derivatives are more rigid molecules (due to the presence of the naphthalene fragment), and this rigidity provides, first, the directionality of the lone electron pairs of the nitrogen atoms favourable for coordination and, second, almost complete inertness to hydrolysis and cleavage of the central C–C bond.<sup>151</sup> (Hydrolysis presents a serious problem in reactions with the use of most diimine ligands as catalysts.)

The neutral  $(Ar-BIAN)ML_n$  complex can *a priori* be represented as a compound of either zero-valent metal **57a** or divalent metal **57b**, i.e., this complex is non-innocent.

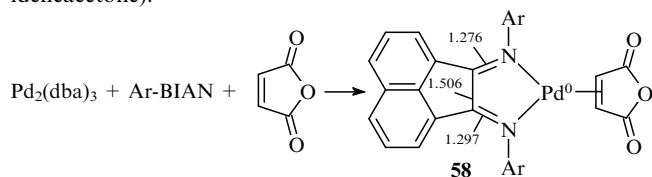


Scheme 4

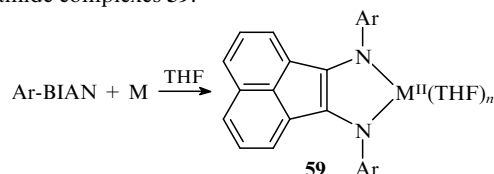


● is a metal ion.

The reactions of Ar-BIAN with zero-valent transition metals generally give rise to diimine structures. An example is palladium complex **58**<sup>146</sup> (the bond lengths are given in Å; dba is dibenzylideneacetone).



Alkali and alkaline-earth metals react with Ar-BIAN to give diamide complexes **59**.<sup>144, 147</sup>

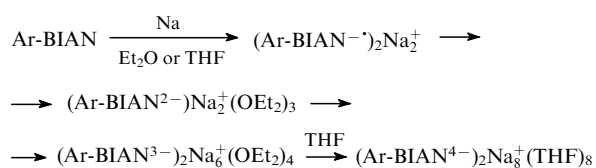


Ar = 2,6-Pr<sub>2</sub>C<sub>6</sub>H<sub>3</sub>; M = Mg, Ca.

| M  | C–N / Å      | C=C / Å |
|----|--------------|---------|
| Mg | 1.401, 1.408 | 1.389   |
| Ca | 1.391, 1.402 | 1.409   |

Complexes with Ar-BIAN are very easily reduced, the ligand being subjected to reduction<sup>148–150</sup> and reduction occurring at much less negative potentials than for other diimine ligands. For example, electrochemical studies demonstrated that Re<sup>I</sup>(Ph-BIAN)(CO)<sub>3</sub>Cl is reduced at potentials (–0.65 V), which are 1 V less negative compared to Re<sup>I</sup>(bipy)(CO)<sub>3</sub>Cl (–1.64 V).<sup>150</sup> This is evidence that the  $\pi$ -acceptor properties of Ar-BIAN are much stronger than those of other diimines.

Chemical reduction of free 2,6-Pr<sub>2</sub>C<sub>6</sub>H<sub>3</sub>-BIAN with Na or Li in ethereal solvents involves the successive formation of the radical anion, the doubly-charged anion, the triply-charged radical anion and, finally, the quadruply-charged anion, which were isolated and studied by UV-Vis spectroscopy and X-ray diffraction.<sup>151, 152</sup> The singly-, triply-, and quadruply-charged anions have dimeric structures.

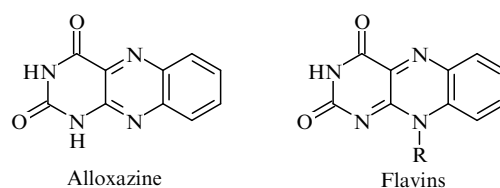
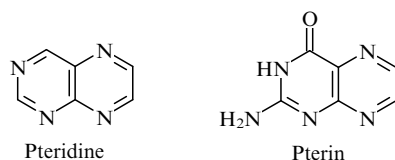


During reduction, the first two electrons are transferred to the diazadiene fragment, and the next two electrons are transferred to the  $\pi$ -system of the naphthalene moiety.<sup>152</sup>

Undoubtedly, the possibility of four-electron reduction indicates that two almost degenerate LUMOs of Ar-BIAN are very low-lying.

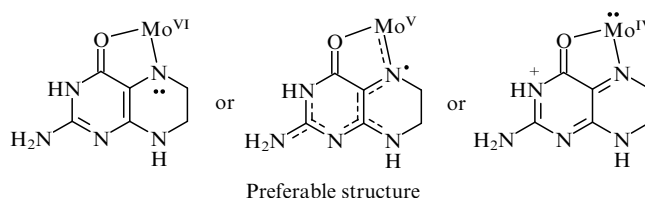
#### IV. Pterin complexes

Yet another group of non-innocent nitrogen-containing ligands includes pterins, pteridines and structurally related alloxazines and flavins. In complexes with these ligands, there is a strong interaction between the transition metal ion and the ligand.<sup>153</sup>



Since the degree of electron delocalisation between the metal and the coordinated pterin varies in different complexes, the problem is to determine the formal oxidation states of the metal and the pterin in each particular complex. Evidently, the molecules of pterin, pteridine and their analogues are redox-active, and generally their coordination to transition metals results in a high degree of electron delocalisation between the metal and the ligand.<sup>153</sup> As in the case of other non-innocent ligands, it is most convenient to determine the redox characteristics of transition metals and ligands in metal pterin and metal pteridine complexes by X-ray diffraction and UV-Vis spectroscopy in the visible range. For molybdenum complexes with pterin ligands, the structural criteria for this assignment were reported in the studies.<sup>154, 155</sup>

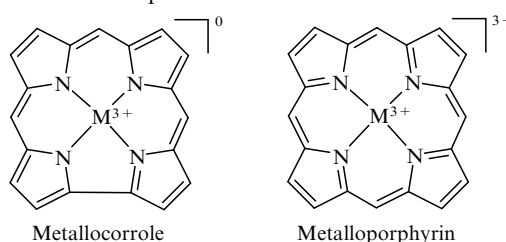
In particular, UV-Vis and photoelectron spectroscopy demonstrated that the Mo<sup>V</sup>(H<sub>3</sub>pterin<sup>•</sup>) structure is preferable for the molybdenum complex with tetrahydropterin (a fragment of the complex is shown).<sup>153</sup>

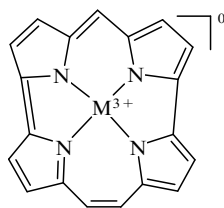


The redox-resonance of analogous structures was suggested in the study<sup>156</sup> for the structures of molybdenum complexes with reduced pterin and flavin. A considerable metal  $\rightarrow$  ligand charge transfer and stabilisation of ruthenium, copper and rhenium complexes with the reduced ligand were established by cyclic voltammetry and UV-Vis spectroscopy in the visible region.<sup>157</sup> Iridium,<sup>158</sup> copper,<sup>159–162</sup> iron(II),<sup>160</sup> cobalt(II)<sup>160</sup> and zinc<sup>161</sup> complexes with pterin and pteridine were studied by spectroscopic and electrochemical methods and characterised by X-ray diffraction.

#### V. Porphyrins, corroles and isocorroles

Porphyrins and corroles stabilise high-valence states of coordinated metal atoms. Studies by Raman spectroscopy and DFT calculations demonstrated that the valence orbitals of corroles are qualitatively similar to those of porphyrins.<sup>163</sup> Isocorroles, as a whole, are also similar to corroles, but their ground states differ in symmetry (<sup>2</sup>A'' for corroles and <sup>2</sup>A' for isocorroles), resulting in different  $d_{\pi}-p_{\pi}$  metal–ligand interactions.<sup>163, 164</sup> Porphyrins, corroles and isocorroles can exist in two oxidised radical-cationic forms, which are very similar in energy. For copper corrole and isocorrole complexes, the Cu<sup>II</sup>  $\pi$ -radical cation has a slightly higher energy than the diamagnetic Cu<sup>III</sup> d<sup>8</sup> complex. In contrast, for the nickel complexes, the low-spin Ni<sup>II</sup>-containing  $\pi$ -radical cation has a lower energy than the state with Ni<sup>III</sup>, which is consistent with experimental data.<sup>163</sup>



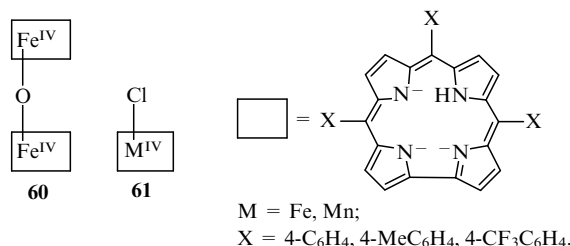


Metalloisocorrole

Iron-containing metalloporphyrin radical cations are postulated as intermediates in processes catalysed by natural peroxidases, catalases and their synthetic analogues.<sup>165</sup> Formally, the oxidation state of iron in these intermediates is +5. However, it is better to consider the intermediates as Fe<sup>IV</sup>-oxo porphyrin  $\pi$ -radical cations.<sup>166</sup>

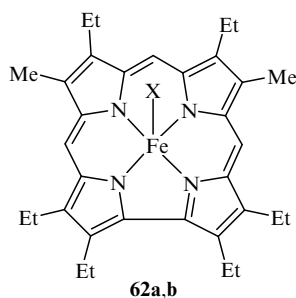
It was demonstrated<sup>167</sup> that one-electron reduction of Au<sup>III</sup> complexes with substituted porphyrin ligands occurs in different ways depending on the nature of the substituent in the  $\beta$  positions of the pyrrole fragments of the macrocycle. If the porphyrin moiety contains the electron-donating 3,5-di-*tert*-butylbenzene substituents, the metal atom is reduced to give Au<sup>I</sup> porphyrin. If the ligand contains the electron-withdrawing NO<sub>2</sub> groups, reduction affords the Au<sup>III</sup> complex with the porphyrin  $\pi$ -radical cation.

The Fe<sup>IV</sup> and Mn<sup>IV</sup> triarylcorrole complexes (**60** and **61**) were characterised in the study.<sup>168</sup>



The first oxidation potentials of complexes **61** are higher than that of the corresponding oxo dimer **60**, which confirms the higher oxidation state of the corrole ligand in complexes **61** (the ligand is already oxidised to a radical-like state).<sup>168</sup> This conclusion agrees with the hypothesis proposed by Walker and co-workers<sup>169</sup> that the iron ion in chloro(octaalkylcorrolato)iron(IV) complexes has an intermediate spin ( $S = 3/2$ ) and is antiferromagnetically coupled to the corrole  $\pi$ -radical. Calculations by the DFT method demonstrated that this coupling results from interaction between the metal  $d_{z^2}$  orbital and the  $b_1$ -symmetry  $\pi$  orbital of the corrole. By contrast, the corrole ligand in dimer **60** is not, apparently, a radical.

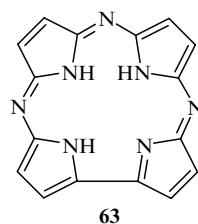
Two iron octaalkylcorrolate complexes **62a,b** with axial ligands were studied by <sup>1</sup>H NMR and Mössbauer spectroscopy. The temperature dependence of the magnetic susceptibility of these complexes was studied<sup>170</sup> to determine the true electronic configuration of the anionic iron corrolates, *e.g.*, to determine whether they are Fe<sup>IV</sup> corrolates(3<sup>-</sup>) or Fe<sup>III</sup>-corrolates(2<sup>-</sup>) with antiferromagnetic coupling of the electrons of the iron ion to



the electrons of the macrocyclic ligand. In both cases, the total spin is 1.

Magnetic susceptibility measurements and results of DFT calculations provided evidence for the non-innocent properties of the macrocyclic corrolate ligand in chlorine-containing complex **62a**. As for phenylcorrolate complex **62b**, no unambiguous conclusion has been drawn. However, it has been hypothesised that the corrolate in both complexes behaves as a non-innocent ligand, but this behaviour is much more pronounced in the chlorine-containing complex.

In contrast, calculations for the Fe<sup>IV</sup> and Mn<sup>IV</sup> complexes with corrolazine (**63**)



demonstrated<sup>171</sup> that this ligand is much more similar to classical ligands and stabilises a 'more pure' high-valence state of the transition metal ion.

The Cu<sup>II</sup> and Fe<sup>III</sup> complexes with  $\beta$ -octafluorocorrole ligands were synthesised and characterised in the study.<sup>171</sup> Study by NMR spectroscopy and DFT calculations showed that the radical character of the electron-deficient fluorine-containing corrole ligand in the LFeCl complex is much less pronounced than that in the complex with the corresponding nonfluorinated ligand. It was shown that the copper complex with octafluorocorrole can exist in a thermally accessible paramagnetic excited state, in which the ligand is present as a radical.

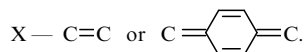
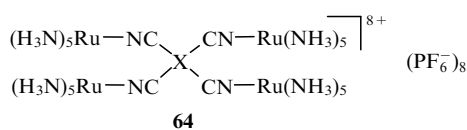
X-ray diffraction studies<sup>172–177</sup> of metalloporphyrins (M = Zn, Cu, Mg, Fe) revealed considerable bond length alternation in the 16-membered ring of the porphyrin ligands. The structural data, results of various spectroscopic studies<sup>163, 169</sup> and DFT calculations led the authors<sup>170</sup> to the conclusion that the real structures of these complexes are similar to those of lower-valence metal complexes with a  $\pi$ -radical-cationic ligand, *i.e.*, porphyrins and corroles are typical non-innocent ligands (it should be remembered that numerous valence-tautomeric electron distributions can be displayed for high-valence transition metal complexes with porphyrin and corrole ligands).

Simple rules, which allow one to predict whether the spin density is localised on the metal or the ligand in iron complexes with aromatic macrocycles (porphyrins, corroles and chlorins), were formulated<sup>178</sup> using the results of pulse spectroscopy (ESR, ESE, ENDOR).

## VI. Tetracyanoethylene, tetracyanoquinodimethane and tetraiminoethylene complexes

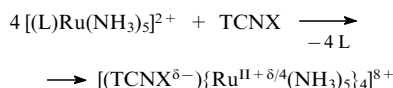
The tetracyanoethylene (TCNE) and 7,7,8,8-tetracyanoquinodimethane (general notation is TCNX) molecules are (see the study<sup>179</sup>) 'the least innocent' organic ligands, because their  $\pi^*$  orbitals are very low-lying. Generally, reactions of easily reducible tetracyanoethylene and 7,7,8,8-tetracyanoquinodimethane with transition metal salts produce mono-, di-, tri- or tetranuclear complexes of the TCNX<sup>•-</sup> radical anions and doubly-charged TCNX<sup>2-</sup> anions,  $\pi$  complexes with coordination at the C=C bond or ion-pair TCNX<sup>•-</sup>(ML<sub>n</sub><sup>+</sup>) compounds without direct coordination.<sup>180</sup>

## The tetranuclear ruthenium complexes with TCNX (64)



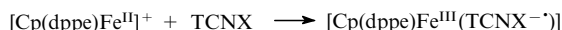
were characterised in the studies.<sup>40,181</sup> These complexes were described as completely delocalised symmetrical  $\pi$  systems with the partially reduced ligand and the partially oxidised metal atoms.

These compounds were studied by ESR, NMR and IR spectroscopy and cyclic voltammetry. It is unusual that the first reduction potentials of the tetranuclear complexes are more negative than that of the free ligand (an analogous phenomenon is observed also for the iron complexes with TCNX).<sup>40</sup> This fact is attributable to considerable metal  $\rightarrow$  ligand charge transfer in the resulting complex ( $0 \leq \delta \leq 2$ ).



In the analogous complexes with 1,2,4,5-tetracyanobenzene and 2,3,5,6-tetracyanopyrazine, which were synthesised and described in this study,<sup>40</sup> the degree of metal  $\rightarrow$  ligand charge transfer is much smaller.

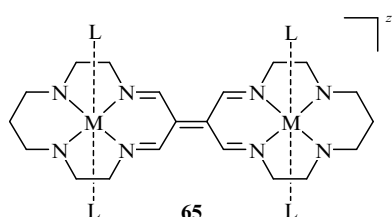
The ruthenium complexes with TCNX were characterised also in the studies.<sup>182–185</sup> Analogous conclusions about the metal  $\rightarrow$  ligand charge transfer were drawn on the basis of the results of ESR and IR spectroscopy and electrochemical studies of discrete manganese,<sup>40,184–186</sup> osmium,<sup>187</sup> rhenium<sup>188</sup> and iron<sup>189</sup> complexes. It was hypothesised<sup>189</sup> that the reaction of the  $\text{Fe}^{\text{II}}$  cyclopentadienyl complex with TCNX afforded the radical-anionic iron(III) complex.



Then the ligand is presumably reduced to the doubly-charged anion.

In the present review, we restrict ourselves to the discussion of discrete tetracyanoethylene and tetracyanoquinodimethane complexes. However, a large number of analogous coordination polymers, in which the TCNX ligands serve as bridges, have also been described.<sup>179</sup>

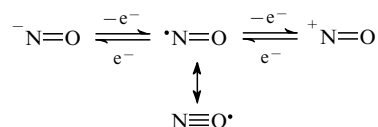
The ground electronic state of related complexes **65** with four imino groups has been described earlier<sup>190–194</sup> as a mixed-valence form, in which one metal atom has the oxidation state of +2, whereas another metal atom is in the oxidation state of +3. However, UV-Vis spectroscopy and semiempirical quantum-chemical calculations provided evidence that such nickel complexes are more adequately described as an identical pair of  $\text{Ni}^{\text{II}}$  centres linked *via* a bridging radical-anionic ligand.<sup>195</sup>



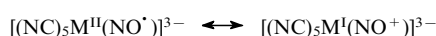
$\text{M} = \text{Ni}, \text{Fe}, \text{Ru}; \text{L} = \text{Hal}^- \text{ or a solvent molecule.}$

## VII. Complexes with nitrogen(II) oxide

The NO species is a typical non-innocent ligand,<sup>196</sup> because it can exist in three forms: diamagnetic  $\pi$ -acceptor cationic, paramagnetic neutral radical and diamagnetic anionic.



The  $[(\text{NC})_5\text{M}(\text{NO})]^{3-}$  complexes ( $\text{M} = \text{Fe}, \text{Ru}, \text{Os}$ ) with  $\text{NO}^\bullet$  as ligands were synthesised and studied by ESR<sup>197–201</sup> and IR<sup>202</sup> spectroscopy, electrochemical methods<sup>202</sup> and DFT calculations.<sup>201</sup> The calculations demonstrated that the spin density is localised predominantly on the nitrosyl fragment of the molecule, and the electronic structures of these complexes are adequately described as a resonance hybrid of two structures, the contribution of the second structure being insignificant.

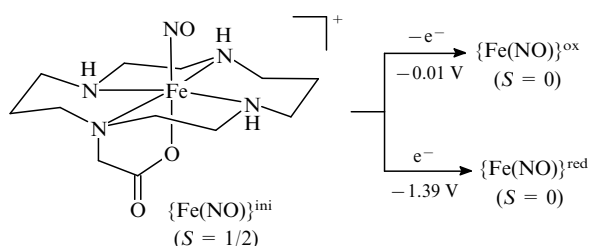


The binuclear ruthenium complex  $[(\text{NC})\text{Ru}(\text{py})_4(\text{CN})\cdot\text{Ru}(\text{py})_4(\text{NO})](\text{PF}_6)_3$  was synthesised and studied by spectroscopic and electrochemical methods,<sup>203</sup> which revealed a considerable charge transfer from the ruthenium ion, so that the  $\{\text{Ru}^{\text{II}}-\text{NO}^\bullet\}$  resonance structure makes a large contribution to the structure of the complex.

The five-coordinate  $[\text{Fe}(\text{OEP})(\text{NO})]\text{ClO}_4$  complex and the six-coordinate  $[\text{Fe}(\text{OEP})(\text{im})(\text{NO})]\text{ClO}_4$  complex (im is imidazole, OEP is octaethylporphyrin) were synthesised and characterised by X-ray diffraction and spectrophotometry.<sup>204</sup> Mössbauer spectroscopy provided evidence that the oxidation state of iron in the five-coordinate complex is higher than +3. However, the IR spectroscopic data are inconsistent with such a large charge transfer to NO.

The results of X-ray diffraction study and the data from Mössbauer and ESR spectroscopy for the neutral paramagnetic binuclear iron complexes  $[\text{Fe}_2(\mu_2\text{-SR})_2(\text{NO})_4] \cdot n\text{H}_2\text{O}$  ( $n = 1$  or  $2$ ; R is 5-amino-1,2,4-triazol-3-yl, 1,2,4-triazol-2-yl, 1-methyltetrazol-5-yl, benzotriazol-2-yl<sup>205</sup> or benzimidazolyl<sup>206</sup>) indicate that the  $\text{Fe}^+$  ion has the  $d^7$  configuration and the NO groups are electroneutral.

The reaction of the low-spin  $[\text{Fe}^{\text{II}}\text{Cl}(\text{cyclam-ac})]$  complex (cyclam-acH is 1,4,8,11-tetraazacyclotetradecan-1-ylacetic acid) with NO in MeCN produced the octahedral  $[\text{Fe}(\text{NO})(\text{cyclam-ac})]^+(\text{PF}_6^-)$  complex ( $\{\text{Fe}(\text{NO})\}^{\text{ini}}; S = 1/2$ ), which can be subjected to chemical one-electron oxidation to the  $[\text{Fe}(\text{NO})(\text{cyclam-ac})]^{2+}(\text{PF}_6^-)_2$  ( $\{\text{Fe}(\text{NO})\}^{\text{ox}}; S = 0$ ) or  $[\text{Fe}(\text{NO})(\text{cyclam-ac})]^{2+}(\text{Cl}^-)(\text{ClO}_4^-)$  complex and also subjected to chemical or electrochemical one-electron reduction to the neutral  $[\text{Fe}(\text{NO})\cdot(\text{cyclam-ac})]^0$  molecule ( $\{\text{Fe}(\text{NO})\}^{\text{red}}; S = 0$ ).<sup>207</sup>



The oxidation states of iron and the NO ligand can be *a priori* represented as follows (the numbers below the formulae indicate the spin states of the iron ion and NO).

| $\{\text{Fe}(\text{NO})\}^{\text{ox}}$               | $\{\text{Fe}(\text{NO})\}^{\text{ini}}$           | $\{\text{Fe}(\text{NO})\}^{\text{red}}$           |
|------------------------------------------------------|---------------------------------------------------|---------------------------------------------------|
| $\text{Fe}^{\text{II}}\text{NO}^+$<br>0 0            | $\text{Fe}^{\text{II}}\text{NO}^\bullet$<br>0 1/2 | $\text{Fe}^{\text{II}}\text{NO}^-$<br>0 0         |
| $\text{Fe}^{\text{III}}\text{NO}^\bullet$<br>1/2 1/2 | $\text{Fe}^{\text{III}}\text{NO}^-$<br>1/2 0      | $\text{Fe}^{\text{III}}\text{NO}^{--}$<br>1/2 1/2 |
| $\text{Fe}^{\text{IV}}\text{NO}^-$<br>1 1            | $\text{Fe}^{\text{III}}\text{NO}^-$<br>1/2 1      |                                                   |

The electronic structures of these three complexes were established by ESR, UV-Vis, Mössbauer and IR spectroscopy. The crystal and molecular structures were determined by X-ray diffraction. Calculations by the DFT method provided information on the bonding in these haeme-free iron complexes. It was concluded that the oxidised complex (ox) contains the N-coordinated  $\text{NO}^+$  cation, the starting complex (ini) contains the neutral  $\text{NO}^\bullet$  radical, and the reduced complex (red) contains the  $\text{NO}^-$  anion. Therefore, only the NO ligand is involved in redox processes.

## VIII. Conclusion

The aim of the present review is to attract attention to the results of investigations on the nature of bonding between metals and ligands in non-innocent metal complexes synthesised primarily in the last decade. There is a great diversity of structural types of non-innocent ligands, from small molecules (NO) to macrocycles. In most cases, these ligands contain conjugated  $\pi$  systems capable of either accepting or donating electrons. In many cases, ligands rather than the central metal atom are redox-active.

As mentioned above, non-innocence is a property not only of ligands but of complexes as a whole, because the central metal atom can have a strong effect on the electronic structure of the ligand, if there is a strong mixing of the ligand and metal orbitals. Examples are known, where a free ligand is irreversibly reduced (a radical anion is unstable), but reduction of the ligand in a complex becomes reversible (the radical-anionic ligand becomes stable). Due to charge transfer between the metal and the ligand, the valence of the metal in the complex can vary even with changes in the temperature of the sample.

Electrochemical and spectroelectrochemical methods, X-ray diffraction analysis, low-temperature ESR and ENDOR, UV-Vis and near-IR spectroscopy are most informative and are most widely used to study the nature of bonding in non-innocent complexes. After the synthesis of new complexes, for example, of neutral  $[\text{ML}]^0$ , they are usually studied by a combination of the above-mentioned methods and also by quantum-chemical calculations (primarily, the geometry and usually with the use of the DFT method). Electrochemical methods allow generation of the ions and radical ions,  $[\text{ML}]^{2+}$ ,  $[\text{ML}]^+$ ,  $[\text{ML}]^-$  and  $[\text{ML}]^{2-}$ . If these species are stable, their structures are studied by appropriate spectroscopic methods. For example, the paramagnetic singly-charged anion in the nickel bis(dithiolenes)  $[\text{Ni}(\text{S}_2\text{C}_2\text{R}_2)_2]^-$  ( $z = 2-, 1-, 0$ ;  $\text{R} = \text{H}, \text{Me}, \text{CF}_3, \text{CN}, \text{etc.}$ ), which are stable in three redox states,<sup>96, 208</sup> was studied by ESR. The delocalisation of the spin predominantly on the ligand is direct evidence for its non-innocent nature. Calculations and UV-Vis spectra provide information on the structures of diamagnetic complexes. These data demonstrated that doubly-charged anions in nickel complexes with dithiolenes can be considered as normal  $\text{Ni}^{\text{II}}$  complexes with two doubly-charged anionic 1,2-dithiolate ligands. Bonding in neutral complexes remains an open question. One description assumes the biradical structure of the ground state of complexes with unpaired electrons localised on the ligands (primarily on the  $\alpha$ -C atoms bound to the S atoms). An alternative description is based on a delocalised structure including the resonance enedithiolate and diketone forms of the ligand. X-ray diffraction analysis allows one to determine the structural characteristics of the ligand in complexes {for example, for  $[\text{Ni}(\text{S}_2\text{C}_2\text{Me}_2)_2]$  in the

redox states of  $2-, 1-$  and  $0$ }<sup>85</sup> and draw conclusions about their electronic structures. This gives a better insight into the electronic structures and the nature of metal–ligand bonding in non-innocent complexes.

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# Liquid-crystalline ionomers as a new class of mesomorphic polymeric systems

D A Pebalk, E B Barmatov, V P Shibaev

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**Abstract.** Data on the synthesis, structure and physicochemical properties of liquid-crystalline ionomers, a new class of mesomorphic polymeric compounds, are summarised. The main classes of the liquid-crystalline ionomers studied to date (including comb-like and linear) and liquid-crystalline chelato-telechelic polymers are considered. It is demonstrated that the ionomer phase state and structure are determined by the ability of ion pairs to form stable ionic aggregates. A new model of the structural organisation of liquid-crystalline ionomers is proposed. The bibliography includes 110 references.

## I. Introduction

Mesomorphic polymeric systems including compounds with liquid-crystalline (LC) type of ordering belong to the most interesting aspects of modern chemistry and physics of high-molecular-mass compounds.<sup>1–5</sup> Based on such systems, new generations of polymeric materials and composites for application in holography, data storage systems, optoelectronics, optical filters and polarisers have been designed (and the work is in progress!). The most promising fields of application of LC polymers include reinforced organic fibre technologies,<sup>6</sup> fabrication of nonlinear optical media, ferroelectrics,<sup>7,8</sup> photonic crystals,<sup>9</sup> materials for recording and storage of optical information,<sup>7,10–12</sup> biologically active compounds,<sup>13</sup> etc.

Introduction of small amounts of metal ions (a few molar per cent) into copolymers of unsaturated hydrocarbons with aliphatic unsaturated acids (first of all, based on ethylene and acrylic acid) leads to fundamental changes in the physicochemical properties of the polymers, namely, a decrease in solubility, an increase in the glass transition temperature and improvement of mechanical characteristics.<sup>14–16</sup> Detailed investigations of such compounds, which were named ionomers, showed that in the solid phase or in nonpolar solvents they form complex ionic aggregates involving charged groups, which to a first approximation can be considered

as noncovalent cross-link points of the polymer chains. It is ionic aggregates that are responsible for specific physicochemical and mechanical properties of ionomers and peculiar features of the supramolecular organisation and structure of such systems.<sup>15–17</sup>

In spite of considerable advances in research on mesomorphic polymers, the structure and properties of ion-containing LC polymers and LC ionomers have not been systematically analysed until recently. Taking into account the incessant interest of researchers in metal-containing polymeric systems,<sup>18</sup> this is more than strange. This review can help to some extent bridge the gap.

The increasing interest in studies of comb-shaped LC ionomers is due to their ability to combine the supramolecular organisation, which manifests itself in the formation of ionic aggregates, with the ordering of side mesogenic fragments, which governs the formation of thermotropic mesophases. Owing to the dual nature of the molecular organisation, the LC ionomers can ‘inherit’ valuable properties and characteristics of both these classes of high-molecular-mass compounds. Because of this, they are of interest for both basic research and applied science as model systems for the design of novel materials and composites based on them.

The variety of molecular architectures of LC ionomers and ion-containing LC polymers is due to the complex chemical structure of this class of high-molecular-mass compounds (Fig. 1). The most important characteristic of these compounds is the content of charged groups in the macromolecules. Note that an old classification, which is nevertheless used in most studies, treats LC ionomers as mesomorphic polymers containing at most 5 mol.%–10 mol.% of charged groups. Polymers containing more than 10 mol.%–20 mol.% of charged groups are called LC ion-containing polymers or LC polyelectrolytes.<sup>19–21</sup> In spite

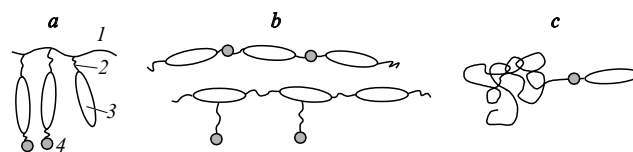


**Figure 1.** Structures of comb-shaped (a) and linear (b) LC ionomers and LC chelato-telechelic polymers (c). The main polymer chain (1), side chain (spacer) (2), mesogenic group (3) and charged (ionogenic) group (4).

D A Pebalk, E B Barmatov, V P Shibaev Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax/tel (7-095) 939 31 32, e-mail: dPebalk@mail.ru (D A Pebalk), barmatov@genebee.msu.ru (E B Barmatov), tel. (7-095) 939 11 89, e-mail: lcp@genebee.msu.ru (V P Shibaev)

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of the limited use of this classification (see below), we will also use it in this review because it is commonly accepted.

Specific features of mesophase formation in comb-shaped and linear LC polymers have been reported.<sup>4,22</sup> With allowance for this fact it is logical to classify LC ionomers based on such a macromolecular topology parameter as the position of mesogenic groups (in the backbone, in side chains, *etc.*). Below we will show an important role of the chemical nature of the monomer units bearing charged groups, in particular, the charge of counterions, and of the distance between the monomer unit and the polymer backbone (the length of the spacer).

The authors of this review have first analysed the state-of-the-art in the field of research on thermotropic LC ionomers using the published data and the results of their own studies. First, we outline the fundamentals of physical chemistry of random amorphous ionomers and then consider thermotropic LC ionomers with various molecular architectures. The emphasis is placed on the publications reported in the last 10–15 years, because the pioneering studies on the physical chemistry of thermotropic LC ion-containing polymers and LC ionomers date back to the late 1980s and early 1990s. Thus, the authors have tried to make the review accessible to a broader spectrum of readers and, at the same time, to present a comprehensive treatment of the subject and report recent advances in this interesting field of polymer science.

## II. Fundamentals of chemistry and physics of ionomers

### 1. Ionomers and polyelectrolytes

Traditionally, macromolecules containing charged groups are divided into two large classes, polyelectrolytes and ionomers.<sup>14,16</sup> Initially, ionomers included random copolymers comprised of monomers of the ethylene series and unsaturated acids (acrylic acid, methacrylic acid) in which a fraction of the protons of carboxyl groups (up to 10 mol.%) is replaced by alkali or alkali-earth metal ions. Such ion-containing copolymers are practically insoluble in conventional organic solvents.

Polyelectrolytes comprised<sup>14</sup> high-molecular-mass compounds containing a large amount of ionogenic groups, which can dissociate in polar solvents, *e.g.*, salts of polyvinylsulfonic acid, polyacrylic acid and salts of polybases, *e.g.*, quaternised (alkylated) polyvinylpyridine, *etc.* However, later this definition was recognised to be unsatisfactory, because essential differences in characteristics of the compounds belonging (from the standpoint of this definition) to the same class, were established.<sup>16</sup>

Basic to the modern classification of ion-containing macromolecules is the state of the charged groups they bear. To illustrate the fruitfulness of this approach, we will consider the simplest model of an ion pair as a constituent of a macromolecule (Fig. 2). According to the Coulomb law, the interaction energy of the point charges  $q_1$  and  $q_2$  of the ionogenic group and the counterion, respectively, separated by the distance  $r$  in the medium with the dielectric constant  $\epsilon$  is given by<sup>23</sup>

$$U_q = \frac{1}{4\pi\epsilon_0} \frac{q_1 q_2}{\epsilon r}. \quad (1)$$

The ratio of the attraction energy between the counterion and the oppositely charged ionogenic group of the polymer (electrostatic attraction factor) to the average thermal energy of the counterion (thermal factor) has the form

$$\frac{2}{3} \frac{U_q}{kT} = \frac{1}{6\pi\epsilon_0 k} \frac{q_1 q_2}{\epsilon r T}. \quad (2)$$

Two most important particular cases where this ratio is (i) much more and (ii) much less than unity are illustrated in Fig. 3. The former case (the electrostatic factor much exceeds the thermal factor) is characteristic of contact ion pairs. The latter case is typical of a dissociated pair in which the Coulomb attraction between ions cannot hold them together and the external ion not

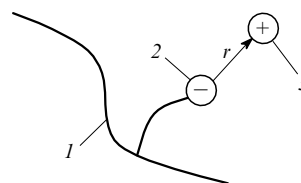


**Figure 2.** Model of an ion pair in a macromolecule. Backbone (1), charged ionogenic fragment (2) and counterion (3).

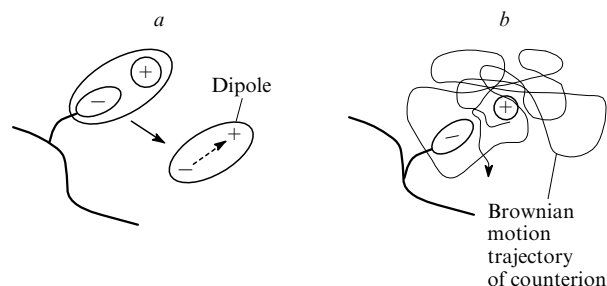


**Figure 3.** Ion pairs in the ionomer (a) and polyelectrolyte (b) regimes. Ratio (2):  $\gg 1$  (a) and  $\ll 1$  (b).

involved in covalent bonding with the polymer chain can experience Brownian motion.

From expression (2) it follows that contact ion pairs will mainly exist in condensed media with low dielectric constant ( $\epsilon \approx 1$ ) at moderate temperatures, which is characteristic of the vast majority of organic compounds with the hydrocarbon skeleton in the solid phase or in nonpolar solvents. In modern literature, this state (or mode) is called the ionomer state (mode) and the corresponding high-molecular-mass compounds are called ionomers.<sup>16</sup>

Individual ion pairs are electric dipoles because the positive and negative charges are separated by the distance  $r$  (see Fig. 2). The electrostatic interaction energy of coplanar electric dipoles (Fig. 4) is given by<sup>24</sup>

$$U_d = \frac{1}{4\pi\epsilon_0} \frac{\mu_A \mu_B}{\epsilon d^3} (2 \cos \theta_A \cos \theta_B - \sin \theta_A \sin \theta_B), \quad (3)$$

where  $\mu_A$ ,  $\mu_B$  are the dipole moments of the ion pairs A and B,  $d$  is the distance between the centres of the dipoles, and  $\theta_A$  and  $\theta_B$  are the angles between the axes of the dipoles and the line connecting their centres.

From Eqn (3) it follows that at the dipole–dipole separations  $d \approx 5-10$  Å at  $r \approx 1-2$  Å,  $\epsilon = 1$  the attractive energy of the ion pairs is comparable with the energy of hydrogen bonding,<sup>25,26</sup> which plays the key role in biochemistry, in the supramolecular structural organisation and in physical chemistry of liquid crystals.<sup>27-30</sup> It will be shown below that it is the dipole–dipole interaction of ion pairs that governs the specific features of the physicochemical properties and the supramolecular structure of ionomers.

High dielectric constants of media ( $\epsilon \gg 1$ , polar solvents) and an increase in temperature cause dissociation of ion pairs. This

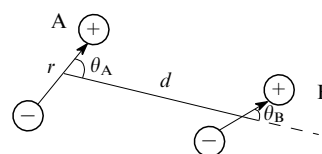


**Figure 4.** Electrostatic interaction between dipoles A and B.

mode is called polyelectrolyte mode and the corresponding compounds are called polyelectrolytes.<sup>16,24</sup> A macromolecule can contain thousands of ionogenic groups; therefore, it is clear that charges distributed over the polymer chain strongly affect the conformation and physicochemical properties of the polymer. For instance, it is repulsion between the similarly charged groups that is responsible for the well-known swelling of polyelectrolytes.<sup>31,32</sup>

Thus, depending on the particular conditions (primarily, on the dielectric constant of the medium and temperature), counterions near the charged groups of the same macromolecule can exist as free ions and as constituents of stable ion pairs. Correspondingly, such systems can possess the properties of both ionomers and polyelectrolytes. It seems likely that different conditions (modes) for the existence of ionogenic polymers rather than different classes of these compounds should be discriminated.<sup>16</sup> Since the ordering of macromolecules of thermotropic LC polymers occurs in the solid phase due to the interaction of anisometric mesogenic groups rather than in a particular range of concentrations, as for lyotropic liquid crystals, in the text below we will consider only the ionomer state of polymers and relevant features of their morphology and physicochemical properties.

## 2. Main models for the structure of ionomers

Pioneering experimental studies on the synthesis and properties of ionomers showed that introduction of charged groups into random alkene–unsaturated carboxylic acid copolymers leads to a decrease in their solubility and to an increase in the glass transition temperature.<sup>15</sup> One of the most significant factors indicating a complex supramolecular structure of ionomers is the detection of a characteristic maximum at small scattering angles in their X-ray diffraction patterns. The presence of this maximum, which is called the ‘ionic peak’, is indicative of the formation of ordered ionic aggregates within the nonpolar polymer matrix. Besides, analysis of the temperature dependences of the mechanical loss factor  $\tan \delta$  for these thin samples revealed two clearly seen maxima, which allowed the microphase separation in the samples to be suggested.<sup>15</sup> The model of formation of ionic aggregates in the polymer matrix has played an important role in the development of the concepts of structural organisation of ionomers.

One of the first and most significant theoretical studies in the field of physical chemistry of ionomers is the study by Eisenberg.<sup>24</sup> The model is based on the concepts of aggregation of ion pairs driven by the electrostatic dipole–dipole interaction (see above). Small aggregates comprising a few charged functional groups and corresponding counterions connected by strong Coulomb interactions were named ‘multiplets’. In the original model, Eisenberg assumed that an increase in the content of ion pairs in the polymer matrix will favour further electrostatic aggregation of multiplets, resulting in clustering. Clusters containing tens of multiplets can be treated as domains of a new phase dispersed in the initial polymer.

To explain the influence of multiplets on the polymer matrix, in the study cited it was assumed that the conformational mobility of the polymer chain in the vicinity of a multiplet is significantly restricted compared to the conformational mobilities of distant fragments of the macromolecule. Therefore, steric interaction between the polymer chains coordinated to the multiplet through their own ion pairs and noncoordinated chains in the environment affects the polymer matrix oppositely to the effect of plasticiser because any multiplet becomes surrounded by a ‘shell’ comprised of chain fragments with restricted mobility (Fig. 5).

The thickness of the region of restricted mobility in the vicinity of the multiplet is primarily determined by the flexibility of the polymer chains, namely, the higher the flexibility the thinner the multiplet shell. The range of action of a multiplet (distance at which the polymer chains ‘feel’ the effect of the multiplet) can hardly be determined quantitatively, but it must correspond to the persistence length of the polymer in the solid phase or the length of

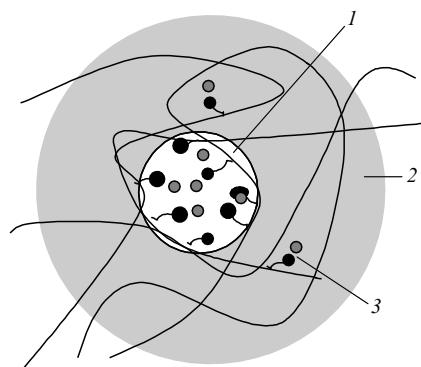


**Figure 5.** Structure of multiplets according to Eisenberg.<sup>17,24</sup>

Multiplet core (1), multiplet shell (region of restricted mobility of the polymer chains) (2) and isolated ion pair (3).

the Kuhn segment.<sup>†</sup> The formation of the core of a multiplet is accompanied by attraction of all neighbouring charged groups; therefore, the shell of the multiplet must be considerably depleted of ions.

From the aforesaid it follows that the effect of a multiplet comprised of a few ion pairs on the polymer matrix is weaker than the effect of a larger ionic aggregate. The smallest aggregate comprising two ion pairs, a quadruplet, plays the role of a conventional intermolecular cross-link, thus causing relevant changes in the physicochemical characteristics of the polymer sample. Generally, the region of restricted mobility of the polymer chains surrounding the multiplet is small and cannot be characterised by its own glass transition temperature; however, the presence of such regions favours an increase in the glass transition temperature of the whole polymer sample in accord with the mechanism considered above.<sup>24</sup>

The Eisenberg model provides no unambiguous interpretation of X-ray scattering data, but permits a qualitative explanation for the ‘microscopic’ two-phase morphology of ionomers. The model gave an impetus to further development of the theory of ionomers in the studies by Forsman,<sup>33</sup> Dreyfus,<sup>34</sup> Datye and Taylor,<sup>35</sup> Earnest *et al.*,<sup>36</sup> Squires *et al.*,<sup>37</sup> Marx *et al.*,<sup>38</sup> Yarusso and Cooper,<sup>39</sup> Ding *et al.*,<sup>40</sup> MacKnight *et al.*,<sup>41</sup> Roche *et al.*,<sup>42</sup> *etc.*

In 1989, Eisenberg’s group proposed an improved model of ionomers,<sup>17</sup> which is used at present. The model considers a number of factors responsible for the formation of multiplets, *e.g.*, the force of electrostatic interaction between charged groups, the concentration of ions (ion pairs) in the polymer, the chemical nature of the polymer matrix and steric factors.

The most important factor is the force of electrostatic interaction between ion pairs, which is determined by the size of ion and by the contribution of the covalent component to the ion–ion interaction. It is assumed that ions of small radii interact more efficiently and form stronger aggregates than do large charged groups. If the Coulomb forces between the ion dipoles are too weak to overcome the ‘elastic’ resistance of the polymer chains to which they are connected, no aggregation occurs.

Low dielectric constant and low glass transition temperature of the initial (non-ionised) polymer favour the formation of multiplets. An important role of the parameter  $\epsilon$  was mentioned above and the glass transition temperature correlates with the ease of deformation of the polymer chains, *viz.*, the higher the  $T_g$  the more difficult is to force the polymer chains to change their

<sup>†</sup> The persistence length is a measure of chain curvature of rigid-chain macromolecules. It is defined as half the length of the Kuhn segment, *i.e.*, the polymer chain segment in which the memory of the chain direction is retained.

positions at normal temperatures. Clearly, plasticisers present in a polymer composite can strongly influence the formation of ionic aggregates.

For the polymer chains of ionomers with bulky substituents one should expect the formation of very small multiplets. At the same time for the ionomers in which the charged groups are connected to the backbone through long and flexible side bridges (spacers), steric hindrances are weaker and large multiplets can form.<sup>43,44</sup> This is quite important for considering the molecular architecture of LC ionomers and for the interpretation of experimental data.

The average distance between multiplets must decrease on an increase in the concentration of ion pairs in the polymer matrix, which causes the shells of the neighbouring multiplets to overlap (Fig. 6). An increase in the number of overlapped fragments leads to the formation of extended regions in which the mobility of the polymer chains is restricted. Rather large regions with own glass transition temperatures are treated as clusters, *i.e.*, microdomains of a certain phase.<sup>17</sup>

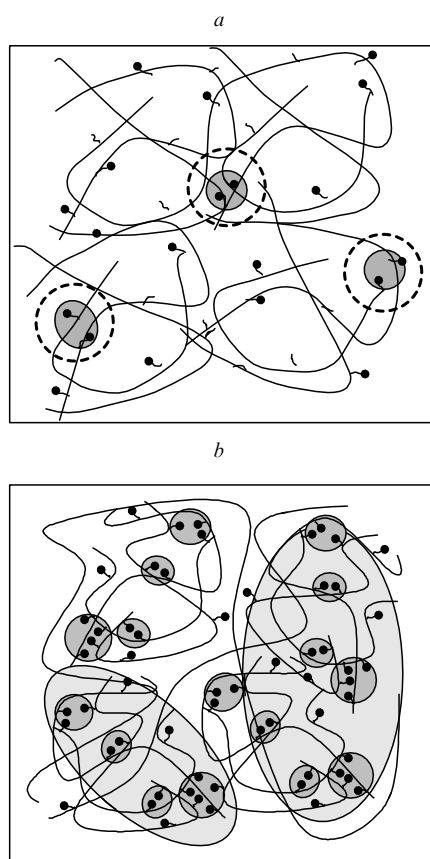


**Figure 6.** Transition from isolated multiplets (a) to clusters (b) caused by an increase in the content of ion pairs in polymer. Dashed lines denote individual multiplet shells; clusters are shaded light grey.

A salient feature of the Eisenberg model is the absence of constraints imposed on the geometry (shape) of multiplets and clusters (ionic aggregates of various shape can be formed).<sup>17</sup> In the modern version of this model, in contrast to the first formulation<sup>24</sup> and a number of more recent studies,<sup>33–37</sup> electrostatic interactions between multiplets are not treated as *causa proxima* for clustering. It is assumed that multiplets in the cluster do not form a single aggregate and only contact one another owing to the overlap of their shells (*i.e.*, regions of restricted mobility of the polymer chains, see Fig. 6).<sup>17</sup>

Thus, the main elements of supramolecular organisation of ionomers are ionic aggregates comprising charged groups (multiplets and clusters). They strongly influence the surrounding polymer matrix, being responsible for the changes in its physicochemical properties (increase in the glass transition temperature, two-phase micromorphology, *etc.*).

Traditionally, LC polymers containing a low proportion of charged groups are treated as LC ionomers (see above). With allowance for the aforesaid, one can use this definition in a broader sense and consider LC ionomers as a specific class of high-molecular-mass compounds characterised by coexistence of the regions of LC ordering and ionic aggregates (multiplets or clusters of various shape). Below we will consider three main groups of LC ionomers, namely, comb-shaped ionomers (see Fig. 1 a), ionomers with mesogenic groups in the backbone (see Fig. 1 b) and telechelic polymers (see Fig. 1 c).

### III. Thermotropic comb-shaped liquid-crystalline ionomers

The macromolecules of comb-shaped LC ionomers (see Fig. 1 a) contain two main types of side substituents, *viz.*, anisometric hard fragments (mesogenic groups) connected to the backbone through flexible spacers and charged ionogenic functional groups. They are responsible for the formation of LC order and the supramolecular structure characteristic of ionomers, respectively. Such a molecular architecture opens the possibility of using these compounds as promising models for studying the role of electrostatic interactions during the formation of mesophases in polymeric systems. Indeed, the concentration of charged groups can be varied with ease in the synthesis of LC ionomers; the upper limit of this concentration is governed by the proportion of functional fragments in the polymer matrix. This feature of the systems under study permits not only investigations of their phase states and structures upon a gradual change in the polymer composition but also, *e.g.*, efficiently influences the magnetic properties of ionomers containing transition-metal ions (see below). Besides, metal atoms can be introduced into virtually any part of a macromolecule (into the backbone, spacers, *etc.*); a vast variety of types of their bonding with the polymer substrate should also be pointed out. In other words, in comb-shaped LC ionomers it is possible to independently vary the nature and concentration of metal ions without changing the structure of the mesogenic fragment. This permits separate studies of the contributions of (i) mesogenic groups of the polymer matrix and (ii) metal atoms into the final characteristics of a compound.

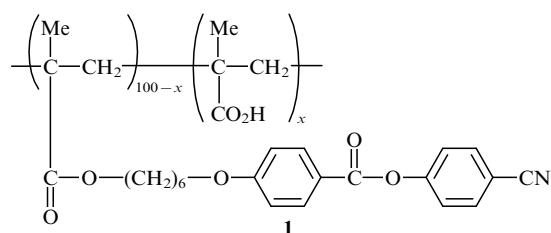
#### 1. Metal-containing comb-shaped liquid-crystalline ionomers

There are only a few publications on the synthesis and investigations of comb-shaped LC ionomers available at the moment. Systematic studies in this field have been carried out by some research groups headed by Zhao (Canada),<sup>45–49</sup> by Zentel (Germany)<sup>50–55</sup> and by the authors of this review.<sup>56–64</sup> These studies concerned the synthesis and investigations of the general physicochemical characteristics<sup>61,62,65,66</sup> of LC ionomers containing alkali,<sup>45–49,56,58</sup> alkaline-earth,<sup>60</sup> transition-metal<sup>50–55,61–63</sup> and rare-earth metal ions.<sup>64</sup> The most important results of these investigations and the corresponding model for structural organisation of comb-shaped LC ionomers will be discussed below. This model, which is based on the concepts of formation of ionic aggregates and microphase separation of charged groups, relates the physical characteristics of a polymer to the concentration, chemical nature and charge of the metal ions and to the distance between the charged groups and the polymer backbone.

##### a. Liquid-crystalline ionomers containing alkali metals

Pioneering studies concerned with analysis of the phase characteristics and structure of comb-shaped LC ionomers containing metal ions were reported in the early 1990s. Zhao and Lei<sup>45,46</sup>

synthesised such compounds using radical copolymerisation of a mesogenic monomer with methacrylic acid.



$x = 12$ .

Subsequent partial neutralisation of carboxyl groups of polymer **1** thus obtained with potassium carbonate in a benzene–methanol (95 vol.% : 5 vol.%)<sup>45</sup> mixture gave comb-shaped thermotropic LC ionomers **1-K(x)** containing at most 10 mol.% of potassium ions.<sup>‡</sup> An increase in the degree of neutralisation of carboxyl groups led to an increase in the glass transition temperature,  $T_g$ , and in a decrease in the clearing point,  $T_c$  (*i.e.*, narrowing of the temperature range in which the mesophase exists (Fig. 7).

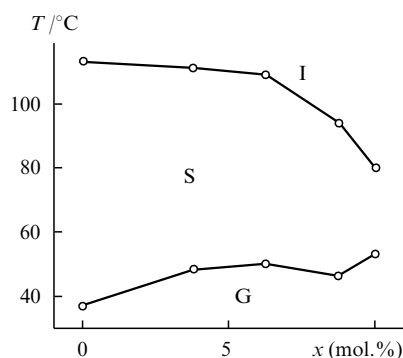
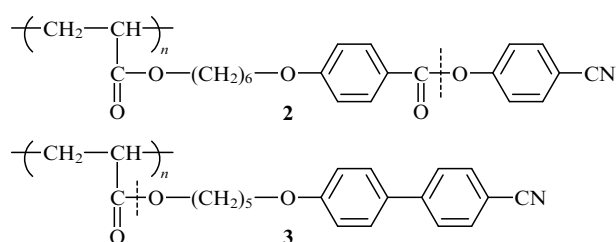


**Figure 7.** Phase diagram of LC ionomers **1-K(x)** containing potassium ions.<sup>45</sup>

Hereafter the following notations are used: I is isotropic melt, S is smectic phase and G is glassy state.

Another approach to the synthesis of ionomers involved partial alkaline hydrolysis of the side fragments of comb-shaped LC polymers **2** and **3**, which also leads to generation of charged groups.<sup>46</sup> The degree of hydrolysis was monitored using <sup>1</sup>H NMR spectroscopy, which revealed selective cleavage of the side groups of the LC polymers **2** and **3** (position of preferred hydrolytic cleavage of mesogenic groups under the action of alkali is shown by a dashed line). In the case of polymer **3**, charged groups appeared in close proximity to the backbone, whereas for polymer **2**, charged groups were distant from the backbone.



In contrast to LC ionomers **1-K** considered above, an increase in the content of sodium ions in the hydrolysis products of

polymers **2** and **3** was accompanied by not only a decrease in the thermal stability of the liquid-crystalline phase but also a marked decrease in the glass transition temperature. Probably, hydrolysis of bulky side substituents favoured an increase in the kinetic flexibility of the backbone,<sup>46</sup> which leads to a decrease in  $T_g$ . Besides, the glass transition temperature could be strongly influenced by water molecules retained in the course of hydrolysis (they play the role of a plasticiser for ionic aggregates and, correspondingly, enhance the mobility of polymer chains).<sup>17</sup>

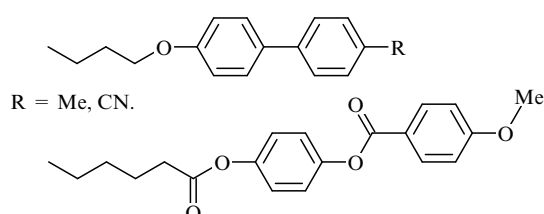
Based on the results obtained, Zhao and Lei concluded that the character of the influence of ionic aggregates on the formation of mesophase in comb-shaped LC ionomers is as follows. In accordance with the Eisenberg model (see above) they assumed that the mobility of mesogenic groups in comb-shaped macromolecules strongly depends on the conformational capabilities of the backbone in spite of the presence of flexible spacers. Mobility restrictions of the chains involved in the formation of multiplets cause defects in the packing of side mesogenic groups. As a consequence, the LC phase of ionomers becomes less stable with an increase in the content of the metal ion and its transition to isotropic melt is observed at lower temperatures as compared with the neutral polymer.<sup>46</sup> And although this explanation for the effect of ionic aggregates on the phase state of LC ionomers is questionable, it is based on commonly accepted concepts from physical chemistry of random ionomers<sup>17</sup> and is undoubtedly characterised by predictive power. This permits the use of the Zhao model for the interpretation of new experimental data.

A drawback of these methods for the synthesis of LC ionomers is the possibility of the hydrolytic cleavage of bonds in different positions of side groups with formation of products in which the charged groups are at different distances from the backbone. Investigations of such compounds revealed no influence of the position of the ionogenic groups on the physicochemical properties of the polymer phase. Besides, the polymer matrix must be purified of low-molecular-mass by-products and hydrolysis cannot be used for introduction of the transition metal and rare-earth metal ions, which significantly reduces the number of compounds to be studied. An exchange reaction involving an alkali<sup>46</sup> also seems to be somewhat inappropriate, because a strong base favours the occurrence of side reactions and the water molecules released play the role of a polar plasticiser and can therefore change the physicochemical properties of synthesised LC ionomers.

Recently, structurally similar polymeric systems have been investigated by researchers working at the Polymer Science Division (Department of Chemistry, M V Lomonosov Moscow State University), Institute of Macromolecular Compounds of the Russian Academy of Sciences and the Institute of Physics (Saint-Petersburg State University). Russian researchers first carried out a complex study of the dependence of the phase characteristics and structure of LC ionomers on the structure of initially functionalised LC copolymers (*i.e.*, on the chemical nature of mesogenic groups, length of aliphatic spacers, concentration of functional carboxyl groups), and on the concentration and charge (valency) of the metal ions.

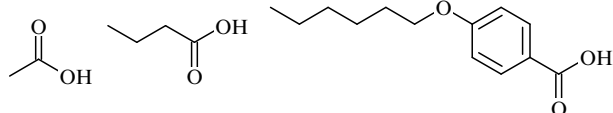
It should be noted that the ionomers studied always contained not only loose and/or contact ion pairs but also a proportion of non-ionised carboxyl groups.

#### Mesogenic groups

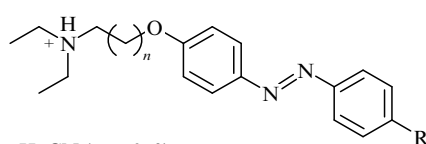


<sup>‡</sup> Hereafter, hyphens in the notations of ionomers are followed by the type of counterion and its content (in mol.%) given in parentheses.

## Ionogenic groups



## Organic ions



R = H, CN ( $n = 3, 9$ ),

$\text{H}_3\text{N}^+(\text{CH}_2)_n\text{Me}$  ( $n = 9, 17$ );

counterions are  $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{Rb}^+$ ,  $\text{Ca}^+$ ,  $\text{Cu}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$ .

Comb-shaped LC ionomers were synthesised using an original two-step procedure.<sup>56, 58, 67</sup> The first stage involved a radical

**Table 1.** Random LC copolymers studied in Refs 56–65.

| Chemical formula of copolymer | Compound  | $x$ (mol.%)    | Degree of polymerisation | Phase transitions <sup>a</sup>     |
|-------------------------------|-----------|----------------|--------------------------|------------------------------------|
|                               | <b>4a</b> | 27             | 100                      | G 41 N 112 I                       |
|                               | <b>4b</b> | 28             | 59                       | G 39 N 101 I                       |
|                               | <b>4c</b> | 30             | 45                       | G 38 N 92 I                        |
|                               | <b>4d</b> | 31             | 25                       | G 32 N 76 I                        |
|                               | <b>4e</b> | 9              | 31                       | G 42 N 103 I                       |
|                               | <b>4f</b> | 18             | 41                       | G 43 N 105 I                       |
|                               | <b>5</b>  | 30             | 45                       | G 40 SmA 109 I                     |
|                               | <b>6</b>  | 21             | 24                       | G 34 N 64 I                        |
|                               | <b>7</b>  | 28             | 14                       | G 18 N 95 I                        |
|                               | <b>8</b>  | 40             | 51                       | G 39 SmA 135 I                     |
|                               | <b>9</b>  | 10–39<br>45–60 |                          | N <sup>b</sup><br>SmB <sup>b</sup> |
|                               | <b>10</b> | 44             | 55                       | S 144 I                            |

<sup>a</sup> N is nematic; SmA, SmB are smectic types; figures denote transition temperature in °C. <sup>b</sup> Transition temperatures were not determined.



copolymerisation of two monomers (of, *e.g.*, acrylic or methacrylic series), one containing a mesogenic substituent (anisometric hard fragment) and the other bearing a functional substituent containing one or several ionogenic groups. In the second step the functionalised LC copolymers **4**–**10** thus obtained (see Table 1) were introduced into exchange reactions of functional carboxyl groups with metal acetates or metal acetylacetonates or with organic amine derivatives. For instance, metal-containing LC ionomers were obtained<sup>56,58</sup> by adding a dilute solution of an acetate,  $M(OAc)_n$ , or acetylacetonate,  $M(acac)_n$ , in EtOH or THF to a dilute solution of the functionalised LC copolymer in dehydrated THF and subsequent stirring of the mixture for some hours and removal of low-molecular-mass reaction products *in vacuo*. This procedure offers a number of advantages over the alkaline hydrolysis of ester bonds considered above, because only functional carboxyl groups, whose proportion is specified in the stage of synthesis of LC copolymers, can react with salts of weak acids, and this method permits introduction of various metal ions  $M^{n+}$ . Acetic acid or acetylacetone released in the course of the reaction do not lead to hydrolytic cleavage of the side mesogenic groups, which is confirmed by the absence of hydrolysis products in the reaction mixture. The exchange reaction is characterised by high conversion. This is indicated by the absence of the unreacted salt in the polymer matrix after annealing of the polymer, confirmed by the data of polarisation optical microscopy and X-ray scattering.

Thus, the synthetic technique proposed allows a controlled amount of metal ions to be introduced into the macromolecules of comb-shaped LC copolymers with retention of the side mesogenic groups. By monitoring the formation of charged groups in macromolecules (as a rule, by IR spectroscopy<sup>56,67</sup>) it is possible to establish the type of coordination between carboxylate ions and metal ions from the stretching vibration frequencies  $\nu_{COO^-}$ . As applied to carboxylate complexes of the metal salts of low-molecular-mass monocarboxylic fatty acids,<sup>68</sup> the monodentate coordination corresponds to the stretching vibration frequencies lying in the ranges  $\nu_a = 1600$ – $1630$  and  $\nu_s = 1350$ – $1380$   $cm^{-1}$ ; the frequency difference  $\Delta = \nu_a - \nu_s$  in this case is  $230$ – $300$   $cm^{-1}$ . In the case of bidentate chelate coordination of the  $M^{n+}$  ion the band frequencies  $\nu_a$  and  $\nu_s$  approach each other (to  $1500$ – $1530$  and  $1440$ – $1470$   $cm^{-1}$ , respectively).

In particular, the exchange reaction between ionogenic LC copolymer **4a** and sodium acetate is accompanied by the appearance of an absorption band of the carboxylate ion at  $1578$   $cm^{-1}$ , the band intensity increasing with an increase in the metal content (Fig. 8*a*). The formation of carboxylate ions was also indicated by a decrease in the intensity of the low-frequency and high-frequency wings of the complex band  $\nu_{C=O}$  ( $1770$ – $1690$   $cm^{-1}$ ) corresponding to free ( $1740$   $cm^{-1}$ ) and hydrogen bonded ( $1703$   $cm^{-1}$ ) carboxyl groups of the initial LC polymer **4a**.<sup>56,67</sup> Low frequency difference between the LC ionomers **5-Rb** and **5-Na** containing fragments of alkoxybenzoic acid ( $\Delta = \nu_a - \nu_s = 46$ – $53$   $cm^{-1}$ ) is an indication of bidentate chelate coordination. For **5-Rb**, the antisymmetrical and symmetrical stretching bands of carboxylate ions are shifted by  $34$   $cm^{-1}$  to the high-frequency region compared to the frequencies of ionomers containing lithium ions (Fig. 8*b*).

The authors of this review have synthesised metal-containing comb-shaped LC ionomers following the procedure mentioned above and studied their phase behaviour, structural and physicochemical characteristics. Differential scanning calorimetry (DSC) curves of a liquid-crystalline copolymer **4c** and ionomers **4c-Na** with various content of sodium ions are shown in Fig. 9. The DSC curves exhibit clearly seen characteristic transitions corresponding to the glass transition temperatures and endothermic peaks corresponding to the clearing point, *i.e.*, transition of the LC phase into isotropic melt. The introduction of alkali metal ions into the polymer matrix leads to marked broadening of the temperature interval of existence of the mesophase. For instance, the heat of transition to the isotropic phase ( $\Delta H = 1$ – $1.5$   $J g^{-1}$ )

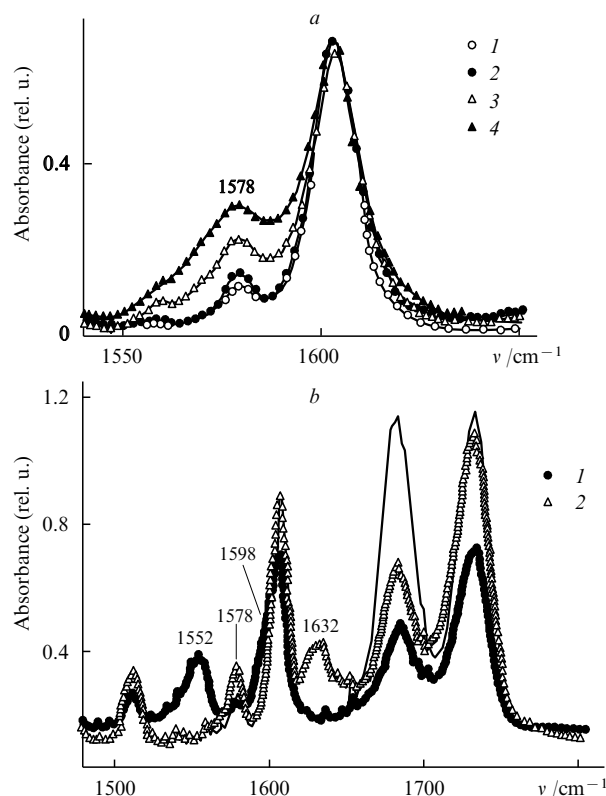


**Figure 8.** IR spectra of LC copolymers **4a** and LC ionomers **4a-Na** (a) and copolymer **5** (b) and ionomers **5-Li** and **5-Rb** (b).<sup>67</sup> (a): **4a** (1), **4a-Na**(4%) (2), **4a-Na**(10%) (3) and **4a-Na**(20%) (4); (b): **5** (solid line), **5-Li** (1) and **5-Rb** (2).

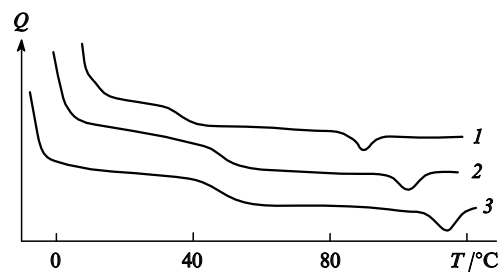


**Figure 9.** DSC curves of liquid-crystalline copolymer **4c** (1) and ionomers **4c-Na**(5%) (2) and **4c-Na**(10%) (3).<sup>57</sup>

obtained for the initial LC copolymer is characteristic of the nematic mesophase, being consistent with the polarisation microscopy data (Fig. 10*a*). At the same time, ionomers are characterised by higher  $\Delta H$  values ( $\Delta H = 1.5$ – $2.5$   $J g^{-1}$ ), which points to changes in their structure with an increase in the content of metal ions.

The liquid-crystalline phase of ionomers **4-Na** has a fan texture (Fig. 10*b*); its SAXS diffraction patterns exhibit an intense maximum corresponding to the period  $d_1 = 34.6 \pm 0.1$  Å (Fig. 11). Comparison of these data with the calculated length of mesogenic groups ( $\sim 18$  Å) suggests a layered packing of the polymer chains with partial overlap of side groups for **4-Na**.<sup>56,58</sup> The 2D X-ray diffraction pattern of an oriented sample clearly demonstrates that diffuse large-angle and small-angle reflections are split in mutually perpendicular directions. Such a character of the X-ray diffraction pattern indicates that mesogenic groups of the polymer are oriented along the magnetic field direction and permits unambiguous identification of the LC phase as smectic A (SmA).

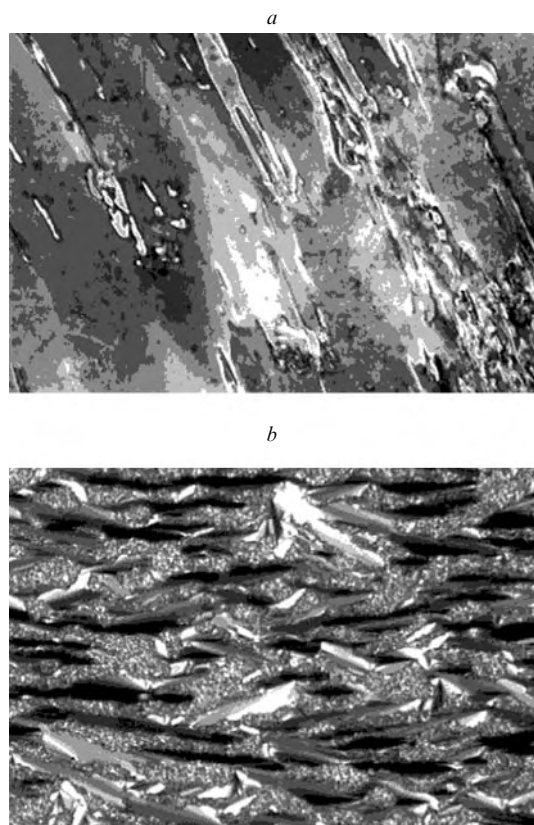


**Figure 10.** Characteristic optical textures of LC ionomers based on copolymer **4**.<sup>57</sup> Texture: marble (a) and fan (b); magnification 200.

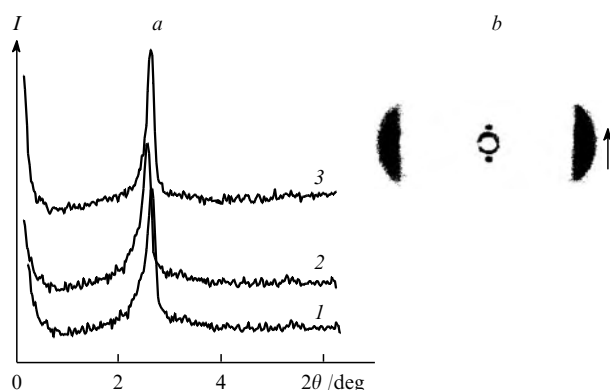


**Figure 11.** SAXS diffraction patterns (Cu  $K\alpha$ -radiation) of LC ionomers **4**-Na containing 1.2 (1), 5.0 (2) and 10.1 (3) mol.% of sodium ions (a) and 2D X-ray diffraction pattern of LC ionomer **4**-Na (2.3%) oriented in a magnetic field (b).<sup>57</sup> The arrow denotes the magnetic field direction.

The phase diagrams of ionomers **4**-Na differing in degree of polymerisation  $P_w$  and content of carboxyl groups in the initial copolymer are shown in Fig. 12. Construction of typical phase diagrams of the ionomers based on the fractions of LC copolymers **4a–d** with a similar content of carboxyl groups and different molecular masses (MM) (Fig. 12a) revealed the following.<sup>56</sup> First, replacement of protons in the functional carboxyl groups by  $\text{Na}^+$  ions led to an increase in the temperature interval of existence of the mesophase<sup>§</sup>

<sup>§</sup> The clearing point  $T_c$  and the glass transition temperature  $T_g$  respectively determine the upper and lower bounds of the existence region of mesophase in LC polymers.

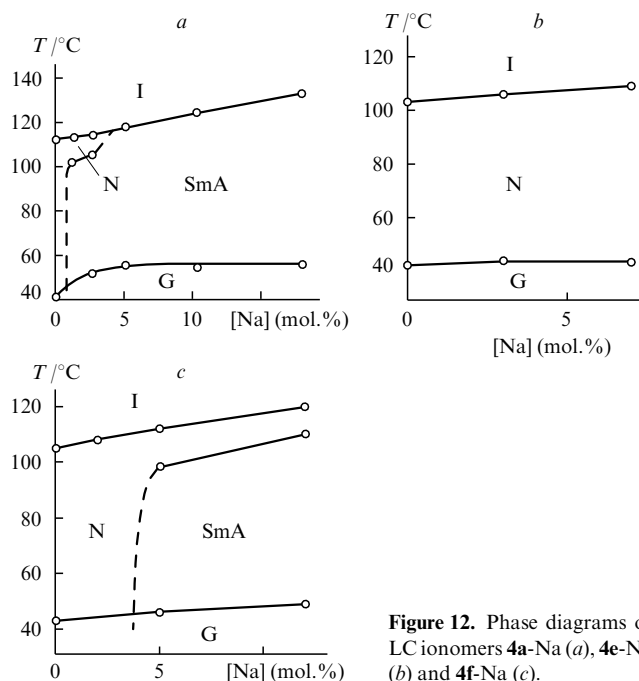


**Figure 12.** Phase diagrams of LC ionomers **4a**-Na (a), **4e**-Na (b) and **4f**-Na (c).

$$\Delta T = T_c - T_g.$$

Second, an increase in the content of sodium ions led to a nearly linear increase in the clearing point, whereas the glass transition temperature increased to some extent at  $\text{Na}^+$  content of 2 mol.%–5 mol.% and then remained unchanged. Third, introduction of metal ions into the polymer matrix led to a change in the phase state of the polymer, namely, not only the nematic phase but also the SmA phase was formed starting from a  $\text{Na}^+$  content of 1.2 mol.%. The general pattern of the phase behaviour of LC ionomers **4**-Na was almost independent of the MM, whereas the clearing points of different fractions varied over a wide range upon variation of  $P_w$  (Fig. 13).

An extremely low concentration of charged groups inducing the appearance of a smectic phase should be pointed out. LC ionomers **4a–d**-Na are characterised by a similar content of sodium ions at which transition from the nematic to smectic mesophase occurs ( $< 1.2$  mol.%). Nevertheless, even copolymers of identical composition contain different amounts of charged groups per macromolecule owing to a low degree of polymerisation and low concentration of metal ions. For instance, ionomers **4a**-Na(2%) with  $P_w = 100$  contain on average two sodium ions per polymer chain, whereas the ionomers **4c**-Na(2%) ( $P_w = 45$ ) and **4d**-Na(2%) ( $P_w = 25$ ) contain the same number of sodium ions per two and four polymer chains,

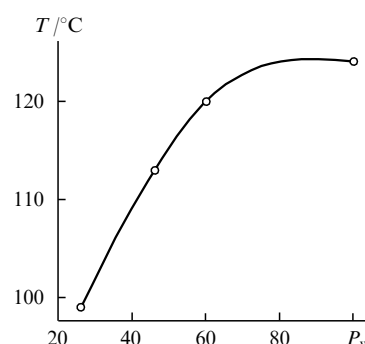


**Figure 13.** 'Liquid crystal–isotropic melt' transition temperature plotted vs. degree of polymerisation of LC ionomers **4**-Na(10%).<sup>56, 57</sup>

respectively. Thus, in the last-mentioned ionomer there are two polymer chains per  $\text{Na}^+$  ion, *i.e.*, 50% of the total amount of polymer chains contain no charged groups at all. Meanwhile, even such a small amount of charged groups is sufficient to change the phase behaviour of ionomers and to form a layered packing of the side mesogenic fragments. This observation has played a significant role in the development of model concepts of the structural organisation of LC ionomers (see below).

As shown above (see Section II), the modern theory of melts of random linear ionomers postulates the formation of ionic aggregates (multiplets, clusters) from charged groups in a nonpolar polymer matrix.<sup>16,17</sup> To a first approximation these aggregates can be treated as non-covalent cross-link points of the backbones. The authors assumed that it is the charged multiplets that have the structure-forming effect on the macromolecular system, resulting in broadening of the temperature interval of existence of the LC phases and in the appearance of the smectic phase.<sup>56</sup>

Often, the formation of smectic mesophases in comb-shaped LC polymers is attributed to microphase separation of the polymer chains and side mesogenic fragments.<sup>3,5</sup> The formation mechanism<sup>57</sup> of a smectic (lamellar) packing of side mesogenic groups involves the formation of a small amount of the simplest multiplets (quadruplets) comprising two ion pairs. Fixation of two polymer chains due to the formation of a quadruplet leads to a decrease in the entropy of macromolecules and facilitates the interaction of next ion pairs, resulting in the formation of a new ionic cross-link. Owing to a low degree of polymerisation (at most 100) the macromolecules of LC ionomers include only a few Kuhn segments.<sup>69</sup> Therefore, the presence of even a small amount of ionic cross-links must cause a substantial reduction of the number of possible conformations and rectification of the backbones of LC ionomers (because the number of segments between ionic cross-link points is insufficient for the formation of a bent chain fragment or a loop). It was theoretically substantiated<sup>70</sup> and experimentally proved<sup>71</sup> that the polymer chains of linear ionomers in the vicinity of multiplets are strongly rectified and their root-mean-square radii of gyration in the melt are larger than that of non-ionised copolymer. Rectification of polymer chains also reduces the translational mobility of side mesogenic groups, which apparently favours a transition from the nematic to smectic mesophase.

The molecular organisation of LC ionomers in the smectic mesophase is schematically shown in Fig. 14. Here, we deal with a 'shortcake'-type packing of macromolecules, which comprises layers formed by nonpolar (hydrophobic) mesogenic groups and layers formed by the main chains bearing ion pairs and functional carboxyl groups. It is logical to assume that an increase in polarity of the main polymer chains as a result of the presence of carboxyl groups and the appearance of charged groups will stabilise the layered structure, *i.e.*, favour broadening of the temperature interval in which the smectic mesophase exists.

The formation of multiplets was indirectly confirmed by a decrease in the solubility of ionomers in organic solvents and by an increase in the glass transition temperatures (see Fig. 12), which indicates that the polymer chains become more rigid. From the phase diagrams it is seen that changes in the glass transition temperature are most pronounced in a rather narrow range of compositions, being a maximum at 5 mol.% of  $\text{Na}^+$  and then reaching a plateau. Probably, this means that at high content of charged groups in the polymer matrix the average distance between ionic cross-links of the polymer chains becomes shorter than the length of the Kuhn segment.

The size and structure of the multiplets responsible for the phase state of LC ionomers must depend on the chemical nature of metal atoms. Fig. 15*a* presents the phase diagram of LC ionomers **4c-Rb** containing  $\text{Rb}^+$  ions whose ionic radius exceeds that of  $\text{Na}^+$  ion and Figure 15*b* demonstrates the dependences of the clearing point on the concentration of alkali metal cation for related ionomers **4c-Rb** and **4c-Na**.

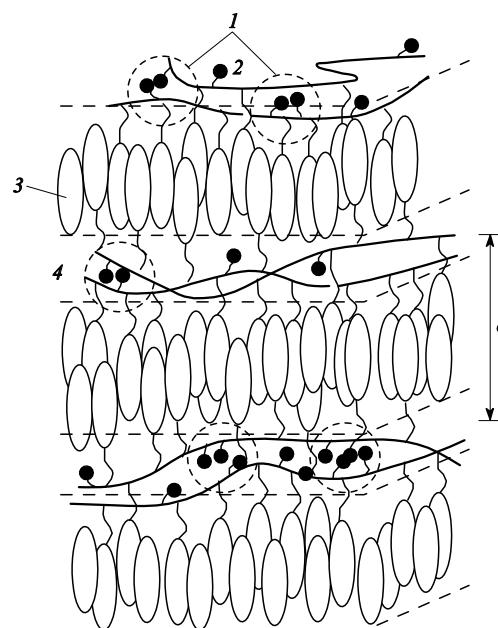


Figure 14. Model of the structure of smectic ionomer.

Multiplets (1), individual ion-containing groups (2), aggregation region of mesogenic groups in smectic layer (3) and aggregation region of the polymer chains and ion-containing groups in the interlayer space (4);  $d$  is the thickness of the smectic layer.

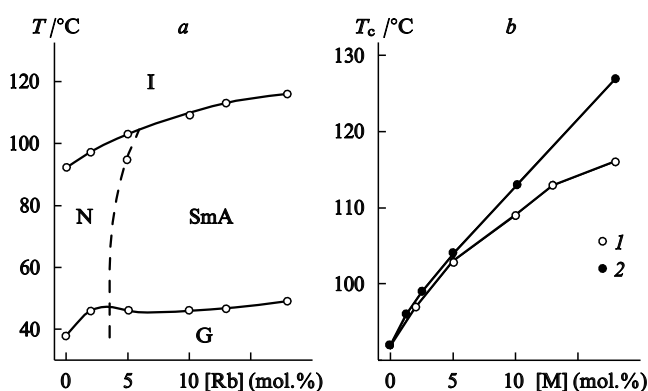


Figure 15. Phase diagram of LC ionomers **4c-Rb** (a) and clearing points ( $T_c$ ) of ionomers **4c-Na** and **4c-Rb** plotted vs. metal content (b).<sup>58</sup> Metal (M): Rb (1) and Na (2).

Comparison of the phase diagrams in Figs 12*a* and 15*a* shows that the phase behaviour of both types of LC ionomers obeys the same pattern. At the same time it is clearly seen that the clearing points of the ionomers containing  $\text{Na}^+$  ions are somewhat higher than those of their  $\text{Rb}^+$ -containing analogues (Fig. 15*b*). A higher rubidium concentration required for induction of the smectic phase should also be pointed out. We believe that this experimental result can serve as an additional substantiation of the formation of ionic aggregates in LC ionomers.<sup>58</sup>

**Role of polymer composition.** The results and model concepts considered above provide an incomplete explanation for the extremely low content of metal ions, which favours induction of the smectic mesophase in the LC ionomers **4-Na**. In this connection it is interesting to compare the character of the phase behaviour of ionomers with different side groups or differing in ratio of functional (ionogenic) and mesogenic fragments taking into account the published data for related comb-shaped LC ionomers.<sup>45,46</sup>

The effect of the composition and molecular architecture of the initial LC copolymers on the phase behaviour of corresponding ionomers was considered taking copolymers **4e–f** with smaller, compared to **4a–d**, initial content of carboxyl groups (see Fig. 12*b,c*) as examples.<sup>56</sup> As can be seen in these phase diagrams, the increase in the clearing point with an increase in the content of metal ions becomes less pronounced (especially, for **4e-Na**), whereas induction of the smectic mesophase for **4f-Na** requires a higher concentration of  $\text{Na}^+$ ; ionomers **4e-Na** retain the initial nematic phase over the whole range of investigated concentrations. Thus, a decrease in the total number of functional carboxyl groups in the initial LC copolymers **4a–f** makes the effect of metal ions much weaker, which is consistent with the concepts of microsegregation in comb-shaped polymeric systems (see Fig. 14).

The dependence of the phase state of LC copolymers **4** on the content of acrylic acid units (Fig. 16) shows that copolymers containing 30 mol.% carboxyl groups are near the induction region of the smectic mesophase. This means that a slight increase in polarity of polymer chains owing to introduction of additional carboxyl or ion-containing groups is sufficient for the formation of layered order. It is this effect that is achieved by replacing a small proportion of carboxyl protons by alkali metal ions. At the same time, polymer chains of the LC copolymers with a low content of acid groups are less prone to microphase separation and the induction of the smectic phase requires introduction of a much higher amount of charged groups into their macromolecules.

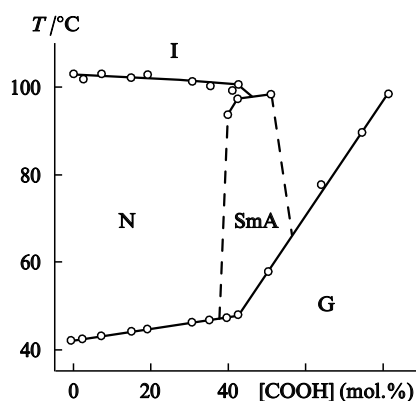


**Figure 16.** Phase diagram of copolymers **4** with different content of acrylic acid monomer units.<sup>59</sup>

It should be noted that consideration of the phase behaviour of LC ionomers in the framework of the modern theory of ionomers is consistent with its interpretation based on the concepts of microphase separation. Undoubtedly, the concept of microphase separation is more general in character because it can be applied to a broad range of polymeric systems containing structural units of different chemical nature. At the same time, model concepts in the field of physical chemistry of ionomers show how general regularities of the microphase separation work as applied to ion-containing macromolecules.

The model considered permits a clear interpretation of the increase in the clearing point of LC ionomers with an increase in the content of metal ions. Indeed, thermally induced disordering of the LC phase due to localisation of the mesogenic groups and main polymer chains in individual layers requires that not only the lateral interactions between mesogenic groups be overcome but also the layer comprising the main polymer chains and multiplets be broken down. The observed dependence can be explained by increasing the role of this additional structure-forming factor with an increase in the concentration of metal ions.

**Role of the side chain length.** From the modern theory of ionomers<sup>17</sup> and results of experimental studies<sup>43,44</sup> it follows that an increase in the distance between charged groups and the polymer backbone can lead to more efficient formation of ionic aggregates due to lower steric hindrance. The influence of this effect on the phase behaviour of LC ionomers was studied taking copolymers<sup>67</sup> with functional groups linked to the backbone through flexible methylene spacers  $(\text{CH}_2)_n$  as examples.

The phase diagram of LC ionomers **6-Na** containing charged carboxyl groups separated from the backbone by two methylene links is shown in Fig. 17*a*. An increase in the proportion of charged groups in the polymer matrix causes a slight increase in the clearing point. At the same time these ionomers form only the nematic phase in the whole investigated range of  $\text{Na}^+$  concentrations, which is confirmed by the polarisation microscopy and SAXS data.

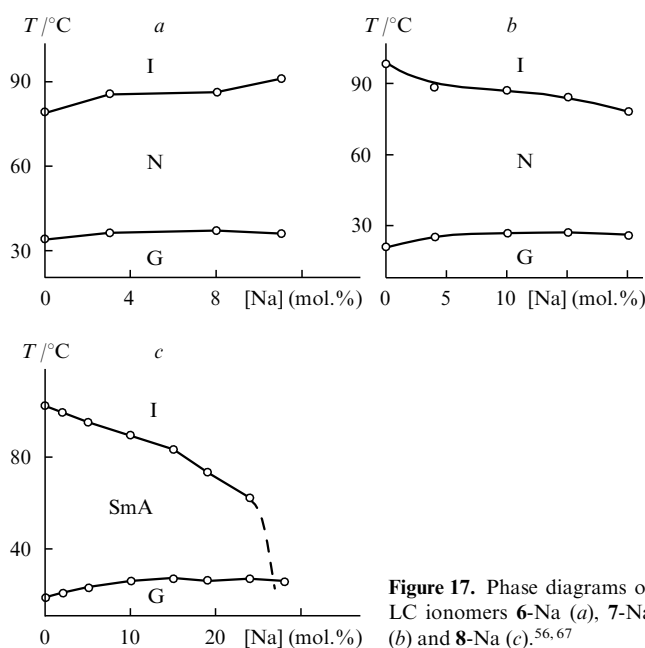


**Figure 17.** Phase diagrams of LC ionomers **6-Na** (*a*), **7-Na** (*b*) and **8-Na** (*c*).<sup>56,67</sup>

Thus, in contrast to the ionomers **4-Na** and **4-Rb** containing functional carboxyl groups directly connected to the backbone, ionomers **6-Na** with distant ionogenic groups exhibit no induction of the smectic mesophase with an increase in the concentration of charged groups in the polymer matrix. The different character of the influence of metal ions on the phase behaviour of LC ionomers is schematically shown in Fig. 18 as the ‘range of action’ of multiplets on the polymer matrix. As can be seen, in the case of ionomers **4-Na** and **4-Rb** multiplets are formed in the vicinity of the backbone and can therefore decrease its entropy to the greatest extent by reducing the number of accessible conformations. At the same time in the ionomers with distant charged fragments (**6-Na**) this effect is weakened due to the presence of flexible spacers between multiplets and the backbone.

These effects must be even more pronounced with an increase in the distance between charged carboxyl fragments and the backbone. For instance, an increase in the concentration of sodium ions in LC ionomers **7-Na** with a long spacer  $(\text{CH}_2)_6$  leads to reduction of the clearing point and only the initial nematic phase is retained over the whole range of compositions studied (Fig. 17*b*). Thus, ionic aggregates formed in the ionomers under consideration play a destabilising role and cause disordering of the mesophase. A conclusion about the destabilising effect of the charged groups distant from the backbone on the ordering of side mesogenic groups in comb-shaped LC ionomers was also drawn earlier.<sup>46</sup>

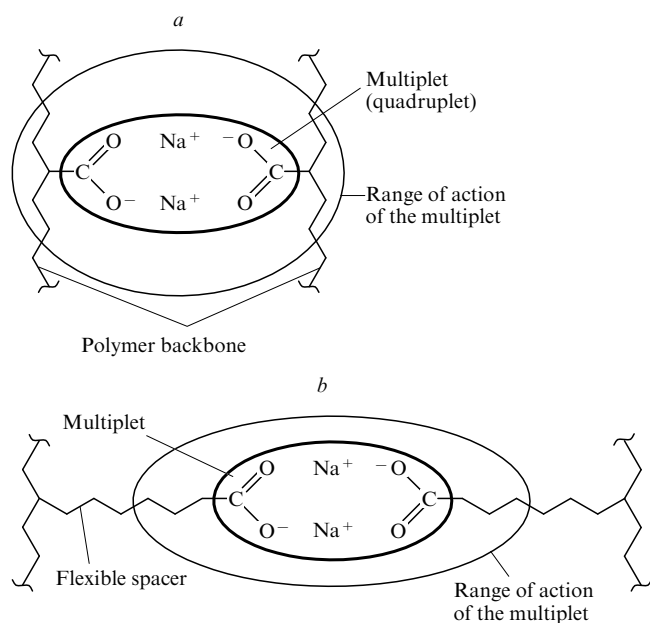


**Figure 18.** Schematic representation of the effect of ionic multiplets on the polymer matrix.<sup>67</sup> Functional groups are bonded to the backbone (a), charged groups are distant from the backbone (b).

It was interesting to check for this effect in copolymers with a smectic rather than nematic ordering type of the side mesogenic groups. Figure 17c shows retention of the smectic mesophase in LC ionomers **8-Na** in the Na<sup>+</sup> concentration range 0 mol.%–25 mol.%; however, an increase in the content of metal ions in the polymer matrix leads to a decrease in the clearing point and breakdown of the liquid-crystalline state.<sup>56</sup>

Thus, by placing charged groups at longer distances from the backbone it is possible to efficiently influence the temperature range of existence of the mesophase in LC ionomers. As the length of a flexible spacer between charged carboxylate ions and the backbone increases, the trend towards formation of smectic phases becomes less pronounced; the clearing point decreases as the content of charged groups in the polymer matrix increases. Hence, the key parameters responsible for the formation of ionic aggregates and their influence on the phase state of ionomers include not only the composition of the polymer matrix, the chemical nature of the metal and the concentration of metal ions but also the distance between functional ionogenic groups and the backbone. In the text below we will show that most of these regularities governing the structure and properties of LC ionomers containing alkali metal ions also hold for more complex systems containing multiply charged ions.

#### b. Liquid-crystalline ionomers containing calcium ions

An increase in the content of Ca<sup>2+</sup> ions in LC ionomers **4b-Ca** to 3 mol.% causes an increase in the melting point of the LC phase<sup>60</sup> (Fig. 19a). According to solid-state <sup>1</sup>H NMR spectroscopy data, the incorporation of Ca<sup>2+</sup> into the macromolecules **4b** not only presents no obstacles to the orientation of their side mesogenic groups in the magnetic field but is also accompanied by an increase in the orientation order parameter of the LC ionomers **4b-Ca**(3%). These results confirm the structure-forming effect of Ca<sup>2+</sup> ions on the polymer matrix by the mechanism of ion association and microphase separation, which was considered above taking LC ionomers containing alkali metal ions as examples. But in contrast to Na<sup>+</sup>-containing ionomers a further increase in the concentration of Ca<sup>2+</sup> ions (> 3 mol.%) does not lead to an increase in the clearing point; this parameter reaches a constant value and then remains unchanged.

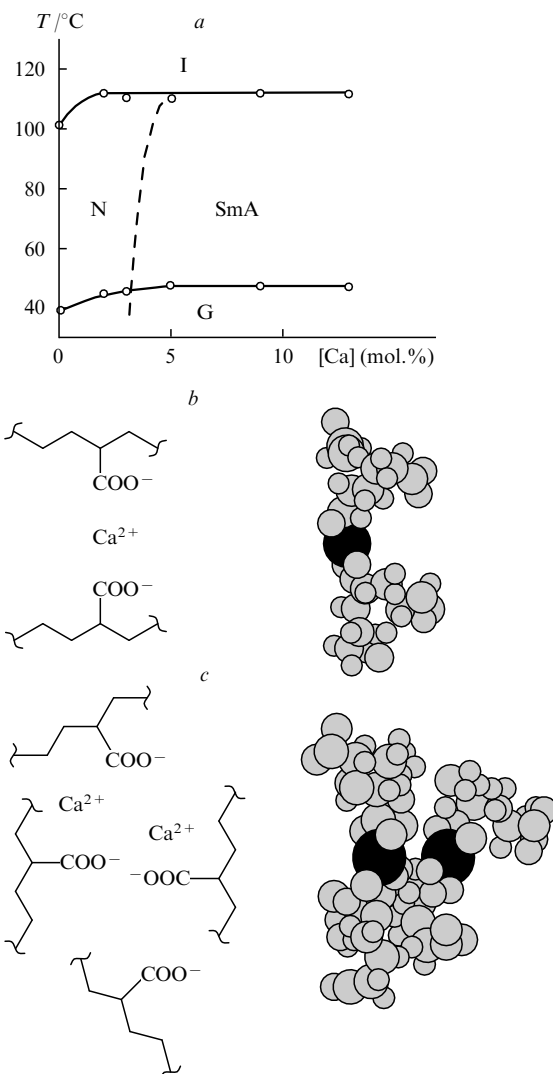


**Figure 19.** Phase diagram of LC ionomers **4b-Ca** (a), model of ionic cross-link (b) and the simplest multiplet (c) in LC ionomers containing calcium ions.<sup>60</sup>

This feature of the phase behaviour of Ca<sup>2+</sup>-containing ionomers can be explained by a higher coordination ability of the doubly charged ions compared to alkali metal cations.<sup>60</sup> According to dynamic light scattering data, exchange of the polymer protons by singly charged ions (Na<sup>+</sup>, Rb<sup>+</sup>) in a dilute solution causes no aggregation of macromolecules that exist as isolated coils and the multiplets are formed only after removal of the solvent as a result of bringing ion pairs closer to one another. If we deal with multiply charged ions characterised by stronger coordination ability, polymer chains can approach one another in the course of the synthesis of ionomers with the formation of salt ionic cross-links (Fig. 19b) or more complex aggregates (Fig. 19c). Indeed, an increase in the molecular mass of such ionomers in solution was detected by gel-permeation chromatography and by light scattering. During removal of the solvent the aggregates formed in the stage of ion exchange can lead to a sterically unfavourable arrangement of macromolecules and induce the appearance of defects in the packing of the side mesogenic fragments, thus leading to destabilisation of the mesophase formed. Mutual compensation of the stabilising contribution of ionic aggregates (due to the microphase separation and chain stiffening mechanism) on the one hand and an increase in the number of defects on the other hand corresponds to reaching a plateau in the clearing point plot of ionomers containing Ca<sup>2+</sup> cations (see Fig. 19a).

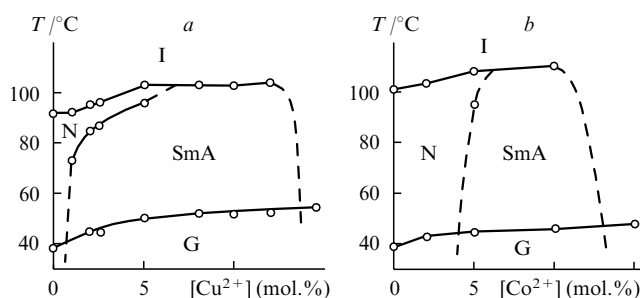


**Figure 20.** Phase diagrams of LC ionomers containing transition metal ions: **4c-Cu** (a) and **4b-Co** (b).<sup>61–63</sup>

### c. Liquid-crystalline ionomers containing transition metal ions

The temperature dependences obtained for the liquid-crystalline ionomers containing doubly charged transition metal ions (Fig. 20) are in general similar to those found for  $\text{Ca}^{2+}$ -containing ionomers.<sup>60</sup> At the same time, optical polarisation microscopy and microcalorimetry data revealed breakdown of the liquid-crystalline phase at a concentration of  $\text{M}^{2+}$  ( $\text{M} = \text{Co}$ ,  $\text{Ni}$  or  $\text{Cu}$ ) ions of nearly 12 mol.%. This is probably due to the formation of coordination bonds between the  $\text{M}$  atom and oxygen atoms and terminal CN groups in the mesogenic fragments of the copolymer. A trend towards an increase in the coordination numbers of  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$  and  $\text{Cu}^{2+}$  ions to 4–6 was confirmed by the UV spectra of films and solutions of the corresponding ionomers.

Strong coordination bonds between transition metal atoms and the polymer matrix can cause a considerable increase in the concentration of defects in the matrix and produce steric strain. If the formation of an ionic cross-link involving a  $\text{Ca}^{2+}$  ion leads to fixation of two  $\text{COO}^-$  groups (and corresponding polymer chains), a transition metal atom can form additional bonds with a number of neighbouring mesogenic groups. At a sufficiently high concentration of transition metal ions (from 10 mol.%–15 mol.% in the compounds we have studied), enhanced defect formation in the mesophase leads to complete disordering.<sup>61–64</sup>

Important experimental information on the supramolecular organisation of comb-shaped LC ionomers, the state of charged groups in them and the influence of such groups on the polymer matrix can be obtained by studying the magnetic properties of corresponding derivatives containing  $\text{Cu}^{2+}$  ions.

The energy of exchange interaction between metal atoms in ferromagnets and antiferromagnets is known to be comparable with the thermal energy, which gives rise to co-operative magnetic phenomena.<sup>72, 73</sup> (In ferromagnets, the atomic magnetic moments are directed parallel to one another, while in antiferromagnets they are directed antiparallel and compensate one another.) A measure of the degree of correlation of the atomic magnetic moments is the exchange parameter  $J$ . Note that isolated transition metal atoms (e.g., in a dilute solution) are not involved in the exchange interactions and, hence, can not induce co-operative magnetic phenomena.

Undoubtedly, investigations of the magnetic properties of LC ionomers are of considerable interest, because this makes it possible to establish the spin state of their metal atoms. The magnetic properties of compounds are described using a number of models of interacting metal atoms.<sup>73</sup> The simplest dimer model allows for the magnetic exchange between two metal atoms, while a more complex one-dimensional (1D) model considers infinite chains of interacting particles.

The temperature dependences of the magnetic susceptibility of LC ionomers **4c-Cu** in the temperature range 4.2–300 K (Fig. 21) revealed the absence of a maximum value and a low room-temperature magnetic moment characteristic of antiferromagnets. The experimental values of the magnetic susceptibility were approximated using the dimer model and the 1D Heisenberg model.

**Table 2.** Results of approximation of the data on the magnetic susceptibility of LC ionomers **4-Cu** using the 1D Heisenberg model and the dimer model.<sup>62</sup>

| Ionomer           | Model | $\sigma^2$ | $-J/\text{cm}^{-1}$ | $C_m(\%)$ | $C_j(\%)$ | $-\theta/\text{K}$ |
|-------------------|-------|------------|---------------------|-----------|-----------|--------------------|
| <b>4-Cu(9.9%)</b> | 1D    | 0.8        | 178                 | 3.6       | 96.4      | 2.9                |
|                   | dimer | 28.0       | 349                 | 15.3      | 84.7      | 26.0               |
| <b>4-Cu(5.0%)</b> | 1D    | 0.9        | 148                 | 5.3       | 94.7      | 5.0                |
|                   | dimer | 20.5       | 265                 | 12.7      | 87.3      | 16.3               |
| <b>4-Cu(2.5%)</b> | 1D    | 1.5        | 116                 | 4.7       | 95.3      | 4.1                |
|                   | dimer | 1.8        | 264                 | 22.2      | 77.8      | –28.0              |

**Note.** Notations are as follows:  $\sigma^2$  is the root-mean-square deviation of experimental data from the dimer model and 1D Heisenberg model;  $J$  is the magnetic exchange parameter;  $C_m$  and  $C_j$  are the concentrations of isolated and magnetically coupled copper ions; and  $\theta$  is the Curie–Weiss constant.

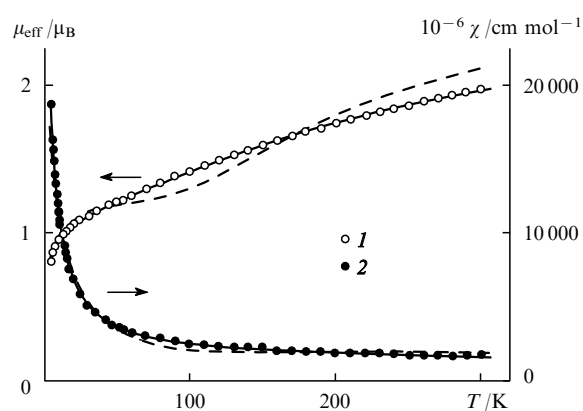


**Figure 21.** Magnetic moment (1) and magnetic susceptibility (2) of LC ionomer **4c-Cu**(9.9%) plotted vs. temperature.<sup>61</sup>

Full and open circles denote experimental data. Solid and dashed lines denote fits of experimental data by the 1D Heisenberg model and the dimer model, respectively.

Analysis of the approximation parameters (Table 2) showed that LC ionomers **4c-Cu** containing 2.5 mol.%–9.9 mol.% of copper atoms are antiferromagnets with high exchange parameters. At  $\text{Cu}^{2+}$  content from 5.0 mol.% to 9.9 mol.%, the temperature dependence of the magnetic susceptibility of ionomers is correctly described by the 1D Heisenberg model, whereas the use of the dimer model leads to marked deviations from the experimental curve. This unambiguously indicates that copper ions exist in LC ionomers in the form of complex aggregates.<sup>62</sup>

Low concentration (< 15%) of the  $\text{Cu}^{2+}$  ions not involved in the magnetic exchange should be pointed out. In the model of structural organisation of LC ionomers shown in Fig. 22 these ions correspond to isolated ionic cross-links. This fact is very important because it shows that steric hindrance in comb-shaped polymers with bulky side fragments (including the systems under study) does not preclude a trend towards formation of multiplets by the charged groups. At the same time it was impossible to propose an accurate structural model for magnetically interacting centres because of a limited number of compounds. Probably, copper atoms in the polymer matrix can be involved in both direct (if brought to close proximity) and indirect exchange through oxygen bridges of the ester groups.<sup>74</sup>

The magnetic properties of the LC ionomer **4-Cu**(2.2%) with low metal content are somewhat different from those considered above. This ionomer is also an antiferromagnet, but the root-mean-square deviations of the experimental data from both the Heisenberg model and the dimer model in this case are the same.

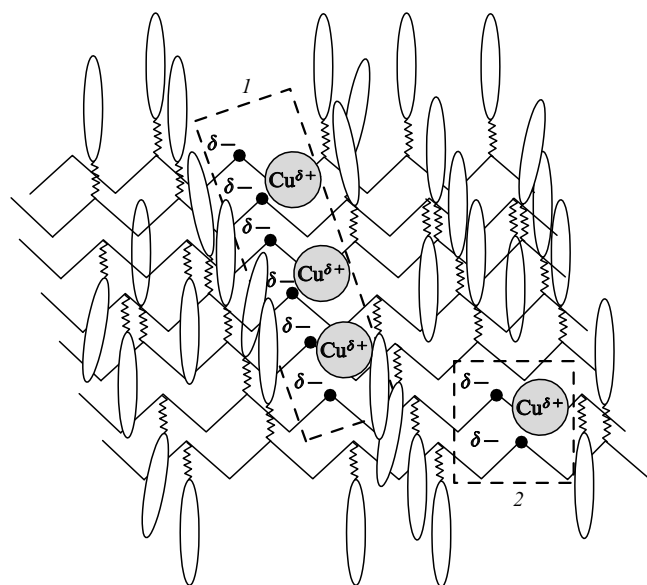


**Figure 22.** Model of LC ionomers containing  $\text{Cu}^{3+}$  ions (see Ref. 61). Multiplet (1) and isolated cross-link (2).

Thus, none of the models provides a correct description of the magnetism of compound **4-Cu**(2.2%). But it should be noted that manifestation of the antiferromagnetic properties at so low a copper content confirms the ability of charged groups to form aggregates (multiplets), because isolated copper atoms are not involved in co-operative magnetic interactions (see above).

Yet another approach to the synthesis of LC ionomers containing ferrocene in the side groups (**11a–c**) was reported in studies by Zentel *et al.*<sup>50–55</sup> (Scheme 1). The oxidation of ferrocene fragments to give cationic ferrocenium groups leads to some broadening of the interval of existence of the SmA phase and to a slight increase in the clearing points (Table 3). This can be explained by ordering of the mesogenic groups in the backbone (for details, see Section IV). The introduction of bulky isometric ferrocene fragments into the LC copolymer must lead to defect formation in the packing of the anisometric mesogenic groups. At the same time the oxidation of ferrocene groups produces ion pairs which tend to form aggregates that in turn form corresponding microphases. Thus, bulky ferrocene fragments can be treated as excluded from the mesophase and thus can affect its liquid-crystalline characteristics to a much lower extent.<sup>55</sup>

The formation of ionic aggregates in the ferrocene-containing LC ionomers investigated by the Zentel group was confirmed by

**Table 3.** Compositions and transition temperatures of comb-shaped ferrocene-containing LC polymers according to  $^1\text{H}$  NMR data (see Ref. 54).

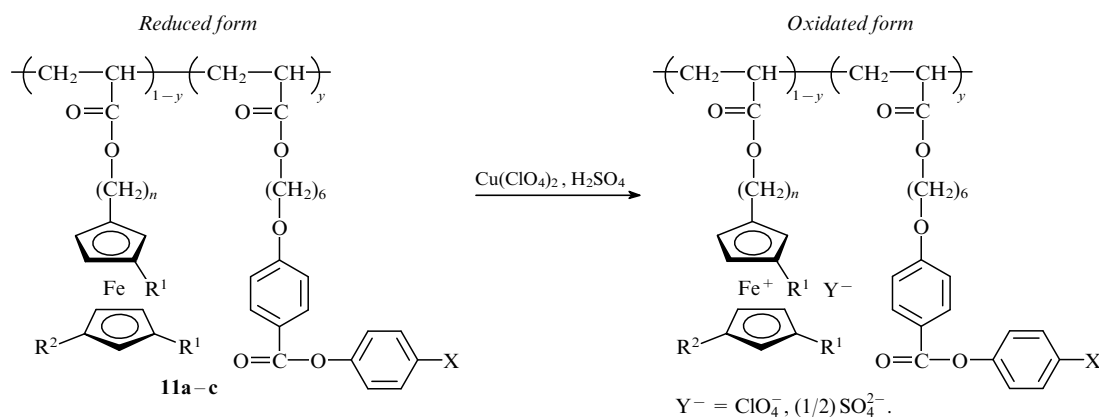
| Polymer    | $y$ (mol. %) | Phase transitions   |                                                               |
|------------|--------------|---------------------|---------------------------------------------------------------|
|            |              | reduced form        | oxidated form <sup>a</sup>                                    |
| <b>11a</b> | 4.3          | G 28 SmA 82 N 108 I | G 32 SmA 84 N <sup>b</sup> (ClO <sub>4</sub> <sup>−</sup> )   |
| <b>11a</b> | 9.5          | G 26 SmA 66 N 96 I  | G 36 SmA 97 N 1 <sup>b</sup> (ClO <sub>4</sub> <sup>−</sup> ) |
| <b>11a</b> | 13.2         | G 32 SmA 67 N 100 I | G 35 SmA 74 N 106 I (SO <sub>4</sub> <sup>2−</sup> )          |
| <b>11b</b> | 2.7          | G 28 SmA 85 N 110 I | G 32 SmA 87 N 105 I (SO <sub>4</sub> <sup>2−</sup> )          |
| <b>11b</b> | 4.4          | G 35 SmA 75 N 98 I  | G 29 SmA 81 N 100 I (SO <sub>4</sub> <sup>2−</sup> )          |
| <b>11c</b> | 2.3          | G 30 N 115 I        | G 32 N 118 I (SO <sub>4</sub> <sup>2−</sup> )                 |
| <b>11c</b> | 7.5          | G 26 N 106 I        | G 33 N 106 I <sup>b</sup> (ClO <sub>4</sub> <sup>−</sup> )    |
| <b>11c</b> | 8.3          | G 30 N 94 I         | G 37 N 95 I <sup>b</sup> (ClO <sub>4</sub> <sup>−</sup> )     |

<sup>a</sup> The counterion is given in parentheses. <sup>b</sup> With decomposition.

the results of dynamic mechanical measurements, small-angle X-ray scattering and by the orientation features of nematic samples in electric field.<sup>54</sup> The temperature dependences of the mechanical loss factor  $\tan \delta$  and the elastic modulus showed that the LC ionomers studied obey the regularities known for weakly cross-linked polymeric systems. At the same time studies on the orientation of samples in electric field revealed an interesting feature that is atypical of conventional LC polymers, *viz.*, the Frederix transition threshold<sup>¶</sup> was almost independent of the presence of charged groups.<sup>54</sup> These experimental results were explained by the possibility of breakdown of ionic aggregates and formation of new aggregates in other domains of the polymer matrix upon the motion of the polymer chains under the action of external field. At the same time the influence of the multiplet structure manifests itself as a considerable (by an order of magnitude) increase in the reorientation time of the LC ionomers.

Dielectric spectroscopy studies and thermodepolarising current measurements were carried out to obtain information on the molecular mobility of copper-containing LC ionomers and to establish how ionic aggregates influence the local and segmental motions of the polymer chains and side mesogenic groups.<sup>65</sup> The incorporation of copper ions into the LC copolymer **4** led to a slight decrease (by 3–4 °C) in the temperatures of co-operative  $\alpha$ - and  $\delta$ -processes (Fig. 23), which respectively reflect the segmental mobility of the backbone and the reorientation of the side

<sup>¶</sup> The critical strength of external field at which the orientation of mesogenic fragments (direction of director) in liquid crystal sample changes.



**11a:**  $\text{R}^1 = \text{R}^2 = \text{H}$ ,  $n = 2$ ;  $\text{X} = \text{OMe}$ ;

**11b:**  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = (\text{CH}_2)_2\text{CH}=\text{CH}_2$ ,  $n = 4$ ,  $\text{X} = \text{OMe}$ ;

**11c:**  $\text{R}^1 = \text{R}^2 = \text{H}$ ,  $n = 2$ ,  $\text{X} = \text{CN}$ .

Scheme 1

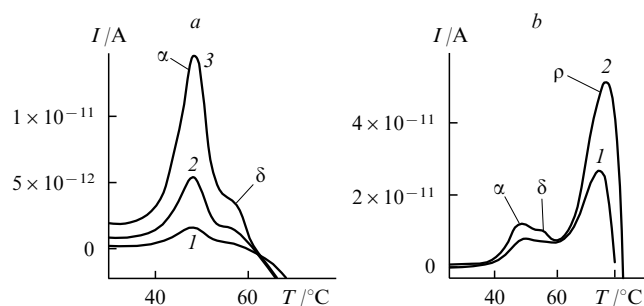


**Figure 23.** Depolarisation current plotted vs. temperature for copolymer **4** (a) and ionomer **4-Cu**(2.5%) (b).<sup>65</sup> Polarisation temperature is 60 °C and the electric field strength is 50 (1), 100 (2) and 300 V mm<sup>-1</sup> (3).

mesogenic groups of the copolymer, which proceeds at higher temperatures. At the same time studies of LC ionomer **4-Cu**(2.5%) at 74 °C revealed yet another intense co-operative  $\rho$ -process (also dipole in nature), which was characterised by significantly restricted molecular mobility compared to the  $\alpha$ - and  $\delta$ -processes.

The results obtained are consistent with the Eisenberg model of amorphous ionomers (see above), according to which the polymer chains in the multiplet shell are characterised by restricted mobility (see Fig. 5). The high-temperature process detected in the thermodepolarising current curves seems to correspond to the dynamics of the polymer chains in the regions of restricted segmental mobility in the multiplet shell. The temperatures of the local processes associated with the rotational mobility of the side mesogenic groups along the long axis and with the mobility of the methylene spacers are almost independent of the content of copper ions in the **4-Cu** ionomers.

All the LC ionomers discussed above belong to the acrylic and methacrylic series with nearly the same type of molecular architecture. Information on the systems with polysiloxane backbone<sup>75</sup> and comb-shaped LC ionomers with the charged groups localised within the backbone<sup>76</sup> is scarce. It is interesting that in last case the glass transition temperature and the clearing point of the liquid-crystalline phase depend only slightly on the structure of the side mesogenic fragments. This may be due to strong microsegregation of charged mesogenic fragments and poly(ethylene oxide) blocks incorporated into the backbone.

The results obtained in studies of comb-shaped metal-containing LC ionomers were analysed by the Zhao<sup>45–48</sup> and Zentel<sup>50–55</sup> groups and by the authors of this review. It was unambiguously shown that correct prediction of the physicochemical properties and structure of these compounds requires taking into account not only the concentration of charged groups but also some additional factors, *e.g.*, the chemical structure of macromolecules, the structure of functional (ionogenic) fragments, methods of synthesis, *etc.* The phase state and the structure of this class of comb-shaped polymers are primarily determined by competition between such processes as the formation of mesophase due to the dispersion interactions of mesogenic fragments, the ionic aggregation of charged groups and the microphase separation of the backbone and the side fragments.

We believe, and this was confirmed by the results of investigations of LC ionomers of different chemical nature (see Table 1), that prediction of the structural features and phase behaviour of these compounds first of all requires taking into account positions of the charged groups relative to the backbone and the ability of the starting polymer to form a smectic order (so named smectogeneity). For instance, the formation of smectic packing is characteristic of comb-shaped ionomers with high content of acrylic acid units (>30 mol.%) and cyanobiphenyl mesogenic fragments because of (i) the microphase separation between the polar chains and nonpolar side groups and (ii) ionic

aggregation. At the same time a decrease in polarity of the backbone makes this tendency much less pronounced.

A fundamentally different situation occurs for those LC ionomers in which functional groups are distant from the backbone. Irrespective of the phase character of the initial copolymer these compounds exhibit a decrease in the clearing point with an increase in the content of the charged groups owing to the disordering effect of ionic aggregates on the surrounding mesogenic fragments.

The phase behaviour and structure of the systems with multiply charged metal ions depend on the structure of the polymer matrix in a more complex fashion. This is associated with the possibility of formation of ionic cross-links or coordination bonds. It seems to be that the most important feature of such compounds is breakdown of the mesophase (amorphisation) at high concentrations of transition (or rare-earth) metals. This imposes limitations on the design of functional materials or composites based on LC ionomers containing multiply charged metal ions.

## 2. Comb-shaped liquid-crystalline ionomers containing organic counterions

A conventional method of preparation of thermotropic comb-shaped LC polymers involves the chemical addition of mesogenic groups to the side aliphatic branchings of comb-shaped polymers (Fig. 24a).<sup>3–5,7</sup> At the same time an approach to the design of comb-shaped LC copolymers by electrostatically binding diphilic molecules to the polymer chain with the formation of polycomplexes (Fig. 24b) has been intensively elaborated in the last decade. Research groups headed by Paleos,<sup>77,78</sup> Ujiie,<sup>79,80</sup> Bazuin<sup>81–83</sup> and Talrose<sup>84–88</sup> contribute largely to the development of this avenue. Physicochemical studies of various aspects of the structure formation and lyotropic mesomorphism in solutions of such polycomplexes can in fact be treated as a specific, important field of polymer science. It is necessary to emphasise that the subject of investigations carried out by all the research groups mentioned above is thermotropic mesomorphism, *i.e.*, the ability of polymeric systems to form LC phases in a particular temperature range under solvent-free conditions.

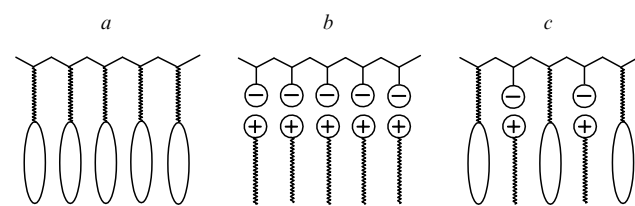


**Figure 24.** Schematic representation of the molecular structure of comb-shaped LC polymers with covalent (a), electrostatic (b) and mixed (c) type of addition of side groups.

Considerable advances in the design and synthesis of a novel class of thermotropic liquid-crystalline ion-containing polymers have been made by Russian scientists.<sup>84–88</sup> Polycomplexes obtained *via* molecular self-organisation of a polymer matrix and a low-molecular-mass amine form a smectic-type LC phase. It should be noted that the individual components of the complexes form no thermotropic mesophases. Conventionally used polymer matrixes include amorphous polyacids (polyacrylic acid, polymethacrylic or polymalonic acid) and polyvinylsulfonates. Amines can be chosen from a broader range of compounds, namely, from primary to quaternary amines with various structures of the lyophobic molecular fragment. The reaction between the polyacid and amine usually results in proton-transfer complexes.

It should be noted that basic to the mesomorphism revealed is the marked diphilicity of the polycomplex and the corresponding



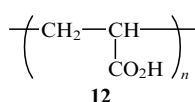
microsegregation processes rather than the rigidity or geometric anisotropy of the side groups. Such ionic complexes represent microheterogeneous systems in which the layered structures formed due to packing of the side chains are 'reinforced' with a network of electrostatic interactions and hydrogen bonds.<sup>85</sup> If one uses linear long-chain aliphatic amines, crystallisation of the complex involving the formation of crystalline or rotationally-crystalline phases is highly possible. At the same time it is assumed that incorporation of one or two aromatic or cyclohexane rings into the amine molecule must cause appreciable changes in the symmetry of the alkyl fragment, thus making crystallisation of the polycomplex less probable.<sup>84</sup>

Ion-containing polymeric LC systems obtained by non-covalent binding of the polymer chains to low-molecular-mass compounds are of considerable interest. Investigations of the properties of comb-shaped LC polymers of mixed structure (one type of the side groups of a macromolecule are covalently bonded while the other type of the side groups are attached through electrostatic interactions; Fig. 24 c)<sup>89–92</sup> are also of great importance. Polymeric systems containing relatively low concentrations of charged groups can be considered as a specific class of LC ionomers with organic counterions.

Mesomorphous ion-containing polycomplexes and comb-shaped LC ionomers with organic counterions exhibit a number of salient features distinguishing them from the metal-containing ionomer systems considered above. If the phase states and the structure of metal-containing ionomers depend on the chemical nature and concentration of metal ions and on the structure and mesomorphous characteristics of the polymer matrix, in the case of ionomers with organic counterions one should also allow for the concentration and structure of low-molecular-mass complexant. As will be shown below, long aliphatic or aromatic fragments of counterions can be involved in the formation of mesophase and also act as bulky packing defects of the side mesogenic groups.

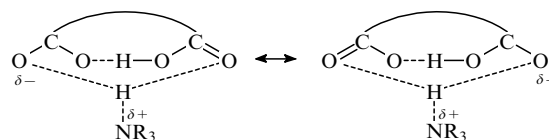
#### a. Synthesis of liquid-crystalline ionomers containing organic ions

Ion-containing complexes of polyacids with low-molecular-mass amines are obtained by mixing the initial components in the same solvent (ethanol, chloroform, pyridine) followed by concentration of the mixture or by the deposition of the polymer complex in an appropriate solvent (ethyl acetate, diethyl ether).<sup>83</sup> For instance, the reaction between amines and polyacrylic acid



was detected<sup>84–88</sup> from opalescence and precipitation on mixing transparent solutions of the initial components in ethanol. Even at a large excess of amine in the initial solutions the characteristic composition of the solid complex corresponds to a 2 : 1 polyacid : amine ratio (two carboxyl groups per amino group).<sup>84</sup> At the same time for mixtures of polymethacryloyl- $\alpha$ -aminocarboxylic acids with cetylamine  $\text{CH}_3(\text{CH}_2)_{15}\text{NH}_2$  (see Ref. 88), complexes of all polyacids studied contain 60 mol.%–70 mol.% of amine. Thus, the degree of substitution of carboxyl groups in these compounds depends only slightly on such characteristics of the polymer matrix as the distance between the COOH groups and the polymer chain.

Based on the results obtained in studies of model compounds (malonic and glutaric acids), it was proposed that non-stoichiometric complexes of polyacids are essentially stabilised by the intermolecular hydrogen bonds.<sup>84</sup> Seemingly, the case in point is the formation of a Y-shaped bond, because the proton involved in the strong hydrogen bond can form an additional H-bond with strong acceptors.



The reactions between polyacids and low-molecular-mass amines in a medium with low dielectric constant (THF) were also studied.<sup>89–94</sup> Good solubility of the polymer complex formed allowed complexes of controllable (stoichiometric) composition to be synthesised. The character of the polyacid–amine bond was studied in detail taking complexes of polymers **4d** and **10** with low-molecular-mass primary and tertiary amines as examples.

Analysis of the IR spectra of the products of the reaction between a nematic copolymer **4d** (based on acrylic acid and units containing mesogenic cyanobiphenyl groups) and octadecylamine  $\text{CH}_3(\text{CH}_2)_{17}\text{NH}_2$  (**13**) revealed<sup>89</sup> the absence of the antisymmetrical and symmetrical vibrational bands of  $\text{NH}_2$  groups (at 3340 and 3260  $\text{cm}^{-1}$ , respectively) characteristic of the spectrum of the low-molecular-mass amine (Fig. 25). The spectrum of ionomer **4d**·**13** exhibited reduced intensities of the  $\nu_{\text{C=O}}$  stretching bands of carboxyl groups. These data unambiguously point to the formation of an ionic complex *via* protonation of the amine  $\text{NH}_2$  groups by the carboxyl groups of copolymer **4d**. A polymer chain fragment of ionomer **4d**·**13** is schematically shown below for the case of incomplete substitution of carboxyl groups of the copolymer **4d**.

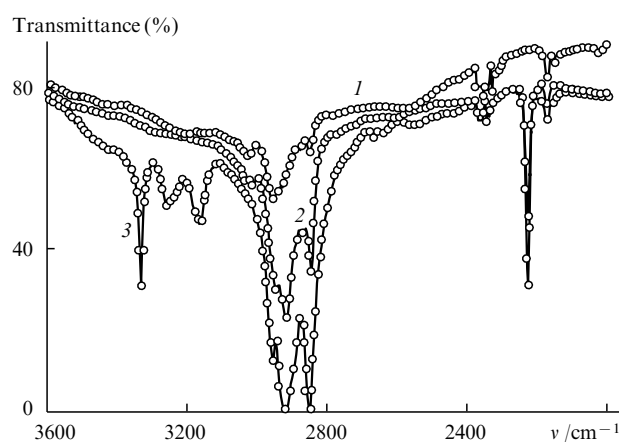
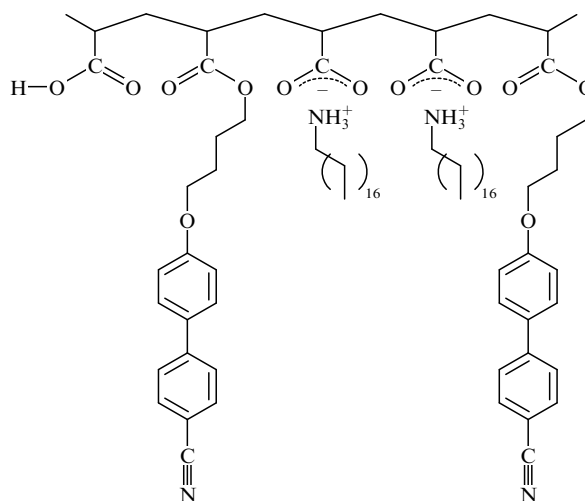
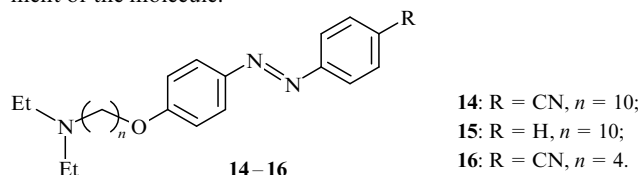


**Figure 25.** IR spectra of LC copolymer **4d** (1), ionomer **4d**·**13** (9%) (2) and low-molecular-mass amine **13** (3).<sup>89</sup>

In order to compare the ratios of the carboxyl groups involved and not involved in the formation of hydrogen bonds, differential IR spectra of mixtures containing different amine concentrations were studied.<sup>89</sup> A greater decrease in the band intensity of H-bonded carboxyl groups (at 1704 cm<sup>-1</sup>) means that they are more accessible to complexation. An analogous conclusion was drawn<sup>84</sup> for the complexes of compound **12** with salts of tertiary amines (**14–16**) differing in the structure of the lyophobic fragment of the molecule.



The reaction between polyacid **12** and photochromic tertiary amine **15** was confirmed by IR spectroscopic data (Fig. 26).<sup>92</sup> An increase in the concentration of tertiary amine **15** in the mixture of compounds **12** and **15** leads to a decrease in the intensities of the  $\nu_{O-H}$  and  $\nu_{C=O}$  stretching bands in the regions 3100–3700 and 1650–1750 cm<sup>-1</sup>, respectively. These changes are due to the decrease in the amount of carboxyl groups of polyacid **12** with an increase in the concentration of tertiary amine. The spectra of the complex obtained exhibit no intense  $\nu_{C-H}$  band of the methylene group at the nitrogen atom of the initial amine (at 2788 cm<sup>-1</sup>). The formation of a proton-transfer complex is also indicated by the appearance of the N–H stretching bands at 2505 and 2610 cm<sup>-1</sup>. A similar character of products of the reaction between acid **12** and a tertiary amine was revealed in studies.<sup>85–87</sup>

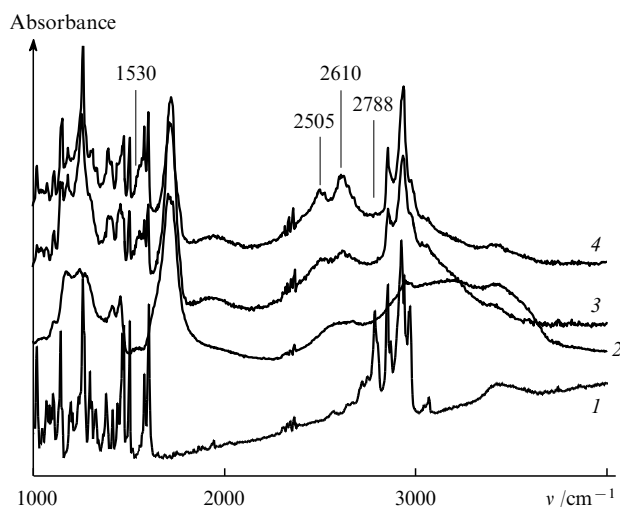


**Figure 26.** Fragments of IR spectra of polymer **12**, photochromic tertiary amine **15** and their mixtures with different content of amine **15**.<sup>92</sup> Content of amine **15** (mol.%): 100 (**1**), 0 (**2**), 29 (**3**) and 44 (**4**).

#### b. Structural organisation of liquid-crystalline ionomers containing organic ions

We will consider salient features of the phase behaviour of LC ionomers containing organic ions taking ionic complexes of nematic copolymer **4** with primary amine **13**<sup>59, 89, 90</sup> as examples. Mixtures with octadecylamine concentrations from 6 mol.% to 29 mol.% were obtained in THF solutions for this system. Investigations of samples with different concentrations of amine **13** allowed us to establish how sequential ‘build-up’ of a comb-shaped polymer by non-mesogenic low-molecular-mass amine molecules (see Fig. 24c) affects the state and thermal stability of the mesophase. This approach provides an effective method of

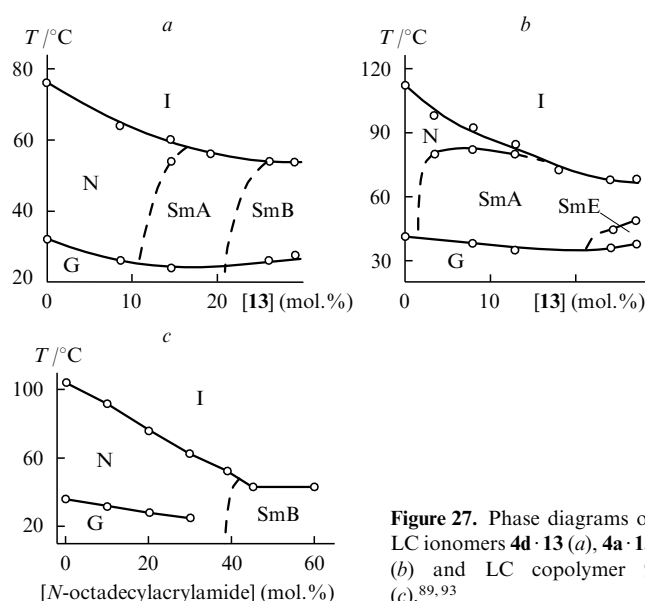


**Figure 27.** Phase diagrams of LC ionomers **4d·13** (**a**), **4a·13** (**b**) and LC copolymer **9** (**c**).<sup>89, 93</sup>

structure modification of comb-shaped LC copolymers and opens prospects for additional functionalisation of these compounds.

The phase diagrams of the LC ionomers **4·13** obtained using fractions of copolymer **4** with different molecular masses are shown in Fig. 27.<sup>89, 90</sup> Noteworthy is the disappearance of the nematic phase characteristic of the initial ionogenic copolymer and the formation of the SmA phase at concentrations of amine **13** of 5 mol.%–14 mol.%. Thus, the phase states of LC ionomers containing organic ions and metal cations obey similar patterns, namely, an increase in the content of charged groups is accompanied by an increase in the ordering of the side mesogenic fragments.

With allowance for the (i) phase transformations and structures of metal-containing LC ionomers (see above) and (ii) model concepts proposed for their interpretation, the formation of the smectic mesophase in the systems based on copolymers with organic counterions seems to be quite reasonable. Indeed, the formation of supramolecular aggregates and microphase separation, which plays a key role in the formation of mesophase, are primarily governed by the presence of ion pairs rather than the nature of the functional groups and counterions they are comprised of. Hence, all considerations concerning the character of the effect of the concentration of charged groups, the composition of the polymer matrix and the distance between functional groups and the backbone must also hold for the complexes of polymers with organic amines. The correctness of this approach is apparently confirmed by the features of the phase diagrams in the systems **4·13** (see above). However, the nature of the counterion can also influence the phase state of the complexes obtained and impart them in some cases the properties characteristic of the organic amine added.

Thus, the formation of the SmA phase in the LC ionomers **4·13** is governed by ionic aggregates. The effect of the aliphatic groups of octadecylamine manifests itself at high concentrations of this compound, which is associated with manifestation of the effects of microphase separation in the side groups of the comb-shaped polymer. If the concentration of amine **13** exceeds 24 mol.%, more ordered smectic mesophases (SmB, SmE) are formed. Samples with the degree of polymerisation  $P_w = 25–59$  form the smectic B phase while those characterised by  $P_w = 100$  form the smectic E phase. Apparently, the formation of these ordered mesophases is due to the microsegregation of long methylene chains of amine **13**.

This assumption was tested taking copolymers **9** of a mesogenic monomer 4-[(4'-cyano-1,1'-biphenyl-4-yl)oxy]butyl acrylate with *N*-octadecylacrylamide as examples. In these copolymers, the

octadecylamide fragment is chemically bonded to the polymer chain (Fig. 27 *c*). Microcalorimetric and X-ray diffraction studies showed that copolymer **9** forms an ordered mesophase with hexagonal packing of the side groups. However, this occurs at a much higher content of non-mesogenic monomer units (>40 mol.%) compared to the series **4**–**13** (25 mol.% of amine **13**). An increase in the content of aliphatic units in LC copolymers **9** leads to a faster (compared to ionomers **4**–**13**) decrease in the clearing points. A broad range of the nematic phase (>40 mol.%) and the absence of induction of the SmA phase in copolymers **9** should also be pointed out.

In a continuation of these investigations, comb-shaped functionalised LC complexes containing tertiary amine molecules **14**–**16** with azobenzene fragments were obtained.<sup>91,94</sup> Photochromic organic counterions were chosen to attain two goals, *viz.*, the incorporation of ion-containing groups simulating the structure of low-molecular-mass liquid crystals and the use of the ability of *para*-substituted azobenzene derivatives to undergo *cis*–*trans*-isomerisation and photo-orientation on exposure to polarised laser light.<sup>95</sup> The LC ionomers obtained are light-sensitive materials and can be used for recording and storage of optical information. A study of the kinetic curves of growth and of the relaxation of photo-induced birefringence revealed the influence of the electrostatic binding of the photochromic molecules with the polymer matrix on the character of photo-optical processes.<sup>91,92</sup>

The phase diagrams of the mixtures based on nematic compound **4c** and smectic compound **10** with low-molecular-mass components **14** and **15** are shown in Fig. 28. Irrespective of the phase state of the initial copolymer an increase in the concentration of dye in the mixture causes a monotonic decrease in the clearing point and the glass transition temperature; at a content of the photochromic component in the 15 mol.%–34 mol.% it undergoes partial crystallisation. All the mixtures based on the ordered smectic phase retain an orthorhombic pattern of packing of the side mesogenic groups in the smectic layer. An increase in the content of amine **16** only leads to thickening of the smectic layer due to the 'build-up' of the copolymer by photochromic amine groups, which are longer than the biphenyl mesogenic groups of the initial LC copolymer **10**. It should be emphasised that the addition of amine **15** (5 mol.%) to nematic polymer **4c** is accompanied by a change in the phase state, *viz.*, the formation of smectic phase and complete disappearance of nematic phases.

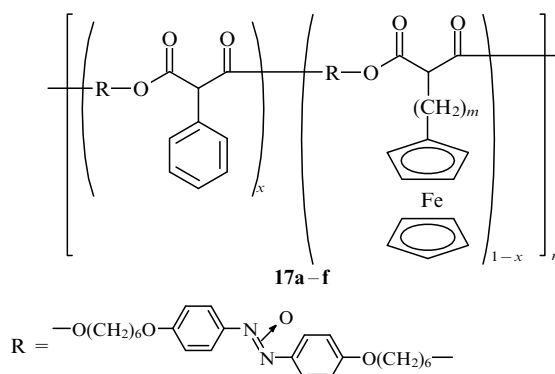
In these LC ionomers photochromic amines are not only involved in microphase separation and ionic aggregation but also induce the formation of defects during the ordering of side fragments, which governs the formation of mesophase. The role of defects can be played by bulky fragments of quaternary ammonium cations arranged near the polymer chain. Besides, long aliphatic bridges between the azobenzene fragment and the tertiary amino group hamper simultaneous packing of the photo-

chromic and mesogenic groups of LC copolymers, which manifests itself in a decrease in the clearing point and the enthalpy of melting of the LC phase with an increase in the content of amine. The use of amine **16**, containing a shorter spacer, is accompanied by a slight decrease in this negative influence. For example, an increase in the amine content in smectic ionomers **10**–**16** is accompanied by a much lower decrease in the clearing temperatures than in ionomers **10**–**14** (Fig. 28 *b*).

#### IV. Liquid-crystalline ionomers with mesogenic groups in the main chain

A significant role in the development of approaches to the synthesis of ferrocene-containing LC ionomers has been played by the studies of Zentel *et al.*<sup>55,96–99</sup> who showed that incorporation of ferrocene fragments into the polymer backbone followed by their oxidation produces no pronounced changes in the phase state of the systems under study.<sup>97,98</sup> This may be due to considerable steric hindrance to the formation of ionic aggregates in related polymeric systems. It is known that the macromolecules of LC polymers with mesogenic groups in the backbone adopt extended conformations. Due to the entropy and steric factors, this can be a possible reason for hindered interaction of charged groups, resulting in the formation of multiplets.

In order to reduce steric hindrance in the formation of ionic aggregates, a series of linear LC copolymers **17a–f** was obtained<sup>98</sup> by polycondensation. In these macromolecules, the ferrocene fragments were separated from the backbone through a flexible aliphatic bridge (CH<sub>2</sub>)<sub>*m*</sub>.



The ferrocene groups were oxidised by mixtures of *p*-benzoquinone with sulfuric or methylsulfonic acids or by a mixture of copper(II) perchlorate and perchloric acid.

The effect of the nature of the oxidant counterion Ox on the phase behaviour, structure and thermal stability of LC ionomers (**17a–f**)·Ox can be followed from the data listed in Table 4. In the case of the hydrosulfate and methylsulfonate counterions the compounds obtained are stable on heating above the clearing point, whereas systems with the perchlorate counterions slowly decompose under identical conditions. Irrespective of the nature of the counterion incorporation of charged groups into the macromolecule leads to some increase in the glass transition and clearing temperatures. If an increase in *T<sub>g</sub>* is typical of ionomers, an increase in *T<sub>c</sub>* is associated with microsegregation of the ferrocene fragments (see above), which facilitates packing of the mesogenic groups in the linear polymer (Fig. 29).

For the systems with charged groups smaller than ferrocene ions one can expect the formation of more stable ionic aggregates. Sulfite and phosphate groups were chosen<sup>99</sup> as candidates. The initial LC polymer **18**, to which charged groups were attached, forms a nematic rather than smectic mesophase unlike the derivatives **17a–f**. With allowance for this fact it was proposed that the formation of ionic aggregates in this polymer matrix will be associated with lower steric constraints and smaller entropy limitations.

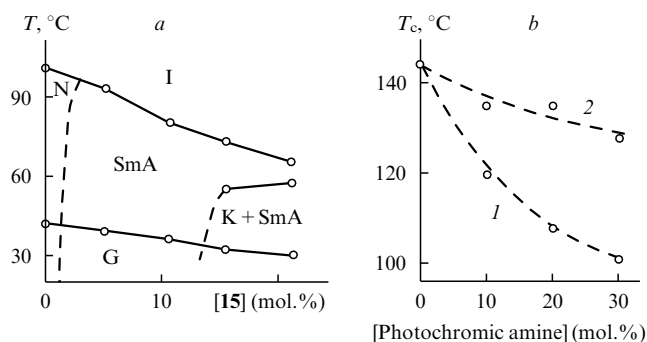
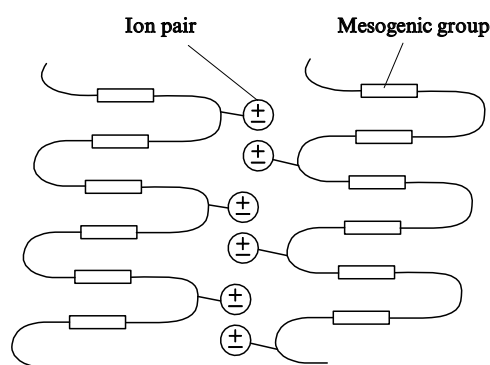
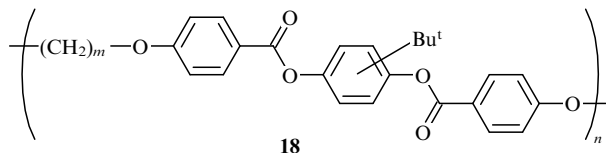


**Figure 28.** Phase diagram of LC ionomers **4c**–**15** (*a*) and dependence of clearing point on concentration of photochromic component for LC ionomers **10**–**14** (*1*) and **10**–**16** (*2*) (*b*).<sup>91,94</sup>

**Table 4.** Phase transition temperatures of ferrocene-containing LC polymers **17a–f** and LC ionomers (**17a–f**)·Ox with mesogenic groups in the backbone.<sup>55, 97</sup>

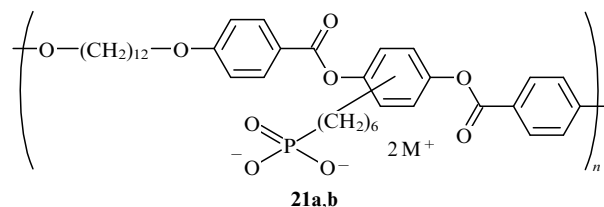
| Polymer    | <i>m</i> | Phase transitions in polymer | Phase transitions in oxidised LC ionomer <b>17</b> ·Ox |                                    |                                    |
|------------|----------|------------------------------|--------------------------------------------------------|------------------------------------|------------------------------------|
|            |          |                              | Ox = MeSO <sub>3</sub> <sup>−</sup>                    | Ox = HSO <sub>4</sub> <sup>−</sup> | Ox = ClO <sub>4</sub> <sup>−</sup> |
| <b>17a</b> | 2        | G 20 SmA 120 I               | G 20 SmA 121 I                                         | G 20 SmA 121 I                     | G 21 SmA 121 I                     |
| <b>17b</b> | 3        | G 17 SmA 111 I               | G 18 SmA 115 I                                         | G 17 SmA 115 I                     | G 24 SmA 119 I                     |
| <b>17c</b> | 4        | G 18 SmA 102 I               | G 22 SmA 107 I                                         | see <sup>a</sup>                   | G 27 SmA 112 I                     |
| <b>17d</b> | 5        | G 14 N 83 I                  | G 22 SmA 81 N 105 I                                    | see <sup>a</sup>                   | see <sup>a</sup>                   |
| <b>17e</b> | 7        | G 20 SmA 110 I               | G 23 SmA 115 I                                         | see <sup>a</sup>                   | see <sup>a</sup>                   |
| <b>17f</b> | 8        | G 15 SmA 105 I               | G 18 SmA 108 I                                         | see <sup>a</sup>                   | see <sup>a</sup>                   |

<sup>a</sup> Compound was not obtained.**Figure 29.** Schematic illustration of microsegregation of ionic multiplets and mesogenic groups in linear ferrocene-containing LC ionomers.<sup>97</sup>

Experiments showed that the LC ionomers **19** and **20** with sulfite ions exhibit a monotonic increase in the clearing point and a decrease in the glass transition temperature with an increase in the content of charged units. This was explained by the impossibility of efficient formation of ionic clusters in the absence of a spacer connecting the charged groups to the polymer backbone (reduction of  $T_g$ ) and by an increase in the anisometry of macromolecules upon incorporation of charged fragments (increase in  $T_c$ ), because these fragments are more anisometric than the mesogenic groups themselves.

The opposite was observed for LC ionomers **21a,b** with the phosphate charged groups separated from the backbone by flexible spacers. The glass transition temperatures of ionomers considerably increase compared to the  $T_g$  value of the uncharged polymer. This was associated with the formation of ionic clusters. At the same time the clearing point of compound **21a** somewhat

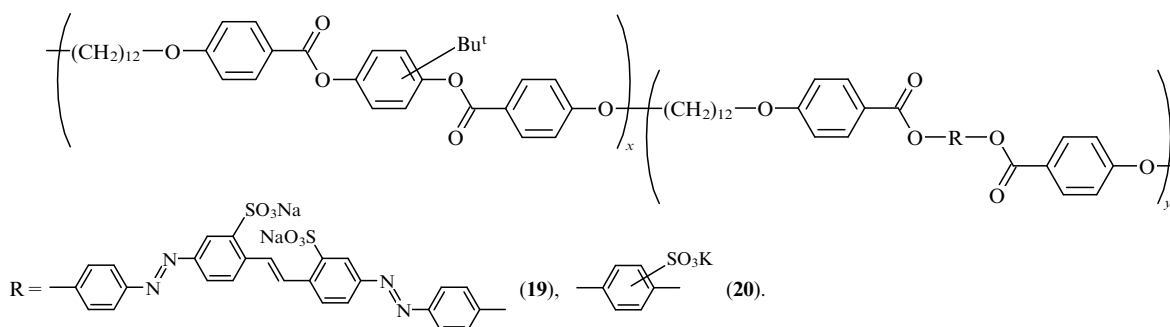
decreases while ionomer **21b** forms no LC phase at all, which can be explained by the undesired steric effect of the bulky counterion.<sup>99</sup> However, since these polymers contain charged groups in all monomer units, the interpretation of their properties based only on the model of random ionomers may be to some extent incorrect.

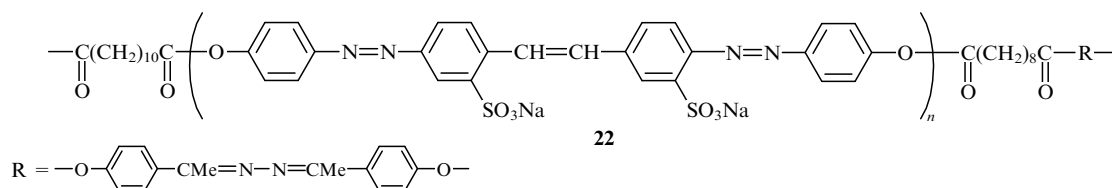


$M^+ = (1/2) Ba^{2+}$  (**21a**),  $NH_2(C_6H_{12})_2^+$  (**21b**).

The phase behaviour of structurally similar LC ionomers **22** was also studied.<sup>100</sup> It was established that an increase in the content of charged groups in these systems is accompanied by a decrease in the glass transition and clearing temperatures and the systems become more prone to thermal degradation. The decrease in  $T_g$  was associated with a decrease in the molecular mass of ionomers on an increase in the content of charged groups. At the same time, the overall narrowing of the temperature range of the existence of mesophase is due to undesired influence of ionic aggregates which play the role of packing defects in the mesogenic fragments. An additional confirmation of this conclusion is provided by the fact that the temperatures of transition to the isotropic phase for a number of ionomers with similar molecular masses decreased to a greater extent as the proportion of charged groups increased.<sup>100</sup> Thus, the model assuming the formation of microphases comprising ionic aggregates and corresponding improvement of packing of mesogenic groups (see above)<sup>55</sup> is inapplicable to these ionomers.

Important information on the ionic dissociation in LC ionomers **22** was obtained in solution studies of the behaviour of macromolecules. The solubility of samples of compounds **22** in chloroform decreased in a regular fashion with an increase in the content of charged groups and the concentration dependence of





the reduced viscosity was strongly different from the linear dependence characteristic of the initial polymer. Additional experiments showed that at low concentration of ionomer **22** in solution intramolecular ionic interactions favour a decrease in the size of the polymer coil, whereas at high concentrations of the ionomer the interaction of macromolecules is accompanied by a dramatic increase in the reduced viscosity. Thus, solutions of these LC ionomers excellently obey the regularities established in studies of amorphous random ionomers.<sup>16</sup>

Analysis of the data on the LC ionomers with mesogenic groups in the backbone provides an additional confirmation of the occurrence of ionic association in mesomorphous polymeric systems. However, a correct interpretation of the changes in the phase behaviour and structure, induced by the incorporation of charged groups in the polymer, requires taking into account a number of factors similarly to the case of comb-shaped ionomers.

## V. Thermotropic liquid-crystalline chelato-telechelic polymers

The so-called LC chelato-telechelic polymers (see Fig. 1c) represent a specific class of liquid-crystalline ionomers with unusual chemical structure and a vast variety of supramolecular structures. These are ionic complexes of anisometric low-molecular-mass compounds (mesogenic groups) with terminal functional groups of the polymer chains (Fig. 30). Intensive studies of these compounds have been carried out in a research group headed by Jerome.<sup>101–105</sup>

Liquid-crystalline chelato-telechelic ionomers are usually characterised by a low content of charged groups. The SAXS diffraction pattern of these compounds exhibit a characteristic 'ionic peak' (Fig. 31). Possible types of structural organisation<sup>105</sup> of these compounds are schematically shown in Fig. 32.

As mentioned above, the ionic peak is a direct indication of the formation of ionic aggregates (multiplets and clusters) responsible for specific features of the structure and physicochemical properties of ionomers. At the same time, microcalorimetric, polarisation microscopy and X-ray scattering data unambiguously confirm the possibility for mesophases to exist in such polymeric systems. The formation of smectic mesophases only was observed for all studied compounds as a result of combination of ionic interactions and microsegregation. It should be noted that the ionic and mesogenic (*i.e.*, corresponding to the packing of mesogenic groups) reflections can appear in the diffraction

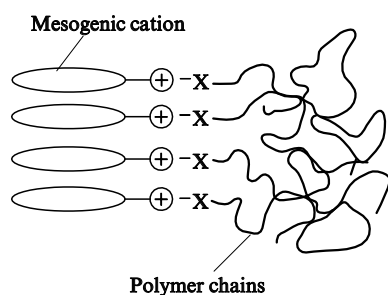


**Figure 30.** Chemical structure of linear LC chelato-telechelic polymers containing carboxyl groups ( $X^- = \text{COO}^-$ ) and sulfonic acid groups ( $X^- = \text{SO}_3^-$ ).<sup>105</sup>

patterns of LC chelato-telechelic polymers together or separately, which points to a complex character of supramolecular organisation of this type of compounds.<sup>105</sup>

According to Gohy and Jerome,<sup>105</sup> the key factors responsible for the supramolecular structure of LC chelato-telechelic polymers are the tendency of mesogenic fragments to form a liquid-crystalline order and the ionic aggregation of charged groups precluding this ordering (see Fig. 32). Some other factors, *e.g.*, the character of the bonds between functional groups of the polymer and mesogenic fragments, the glass transition temperature of the polymer (*i.e.*, the backbone flexibility), the molecular mass of the polymer and the mass fraction of mesogenic groups in the polymer matrix should also be taken into account. Let us consider them in more detail.

Let a terminal group of a polymer be connected to the mesogenic fragment owing to the formation of an ion pair with large dipole moment. In such polymeric systems, one should first of all expect the formation of ionic aggregates, which can suppress the structural organisation of mesogenic fragments, all things being equal.<sup>105</sup> This is characteristic of, *e.g.*, LC chelato-telechelic polymers with terminal sulfonic acid groups, whereas typical of

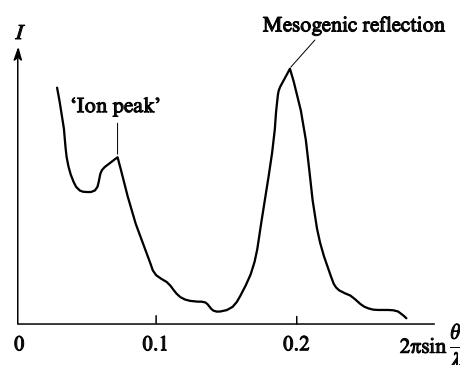


**Figure 31.** SAXS diffraction pattern of LC chelato-telechelic polymers.<sup>105</sup>

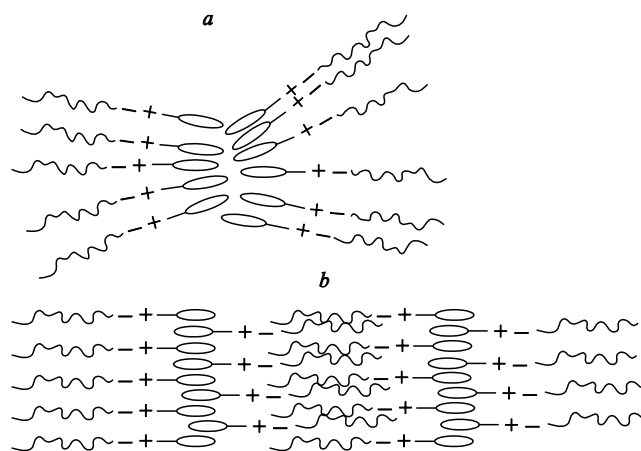


**Figure 32.** Supramolecular organisation of LC chelato-telechelic polymers according to SAXS data.<sup>105</sup> Multiplets (*a*) and layered organisation in the smectic mesophase (*b*). For notations, see Fig. 30.

carboxylate ions is full suppression of ionic association in favour of mesophase formation or coexistence of both these types of supramolecular organisation. In polymers with terminal carboxyl groups, the average distance between mesogenic groups is, for steric reasons, shorter than in the polymers containing sulfonic acid groups. This can facilitate effective side interactions resulting in liquid-crystalline ordering.<sup>103, 105</sup>

X-Ray diffraction patterns exhibiting ionic peaks are more typical of ionomers containing sulfonic acid groups bonded to polystyrene chains, whereas for more flexible polyisoprene macromolecules the formation of mesophase becomes possible. By decreasing the molecular mass of the polymer one can attain the appearance of an ionic peak, but this will lead to a regular decrease in the glass transition temperatures.

At very low concentration of mesogenic groups dispersed in the polymer matrix, they can no longer interact in a co-operative fashion and the formation of mesophase becomes impossible. In the case of LC chelato-telechelic polymers the content of mesogenic groups is unambiguously related to the molecular mass of the polymer chains and the amount of terminal functional groups per chain. In order to estimate the upper limit of the molecular mass at which the mesophase can still be formed, one should take into account the size of smectic layers formed by the mesogenic groups. Gohy and Jerome<sup>105</sup> believe that if the chain length is such that the polymer coil can not be effectively arranged within the layer of mesogenic groups, their coexistence is impossible. Clearly, the critical length depends on the chemical nature of the polymer used.

The dependence of the ionic peak position on the molecular mass of the polymer chains provides with information on the structure of ionic aggregates. In LC chelato-telechelic polymers the multiplets are cylindrical particles of radius  $\sim 3.5$  nm and a shell (region of restricted mobility of polymer chains<sup>17</sup>) size of  $\sim 5.5$  nm rather than spherical or lamellar entities.<sup>105</sup> Unfortunately, the length of such aggregates was not reported in the review cited.<sup>105</sup>

It is noteworthy that mesophase formation in the classical comb-shaped LC polymers is usually possible at a content of mesogenic groups of at least 50 mass%–80 mass% (this value decreases to 5 mass%–40 mass% for LC chelato-telechelic polymers<sup>101–105</sup>). Unusually low content of mesogens necessary for mesophase induction in such polymeric systems was explained<sup>101–105</sup> by strong microsegregation of charged mesogenic groups and the main polymer chains.

## VI. Conclusion

Analysis of the published data and the results obtained by the authors permits a step forward in the development of model concepts of the structure and physical chemistry of LC polymers and amorphous ionomers and their use for the description of specific features of the phase behaviour of comb-shaped LC ionomers. Using the methods of synthesis of LC ionomers considered in the review and the laws of mesophase formation, one can obtain novel metal-containing mesomorphous polymers and predict possible changes in the phase behaviour and structure of these compounds due to electrostatic interactions between charged groups. The review can be useful for those researchers who work in the field of design of new-generation LC polymers and materials based on them, *i.e.*, films, coatings, membranes, *etc.*

Investigations of LC ionomers containing transition metal ions make it possible to synthesise polymeric materials with controllable magnetic properties and to obtain mesomorphous nanocomposites which can find application as catalysts, nonlinear optical media, anisotropic conducting films and coatings. These fields are quite promising, as shown by studies on specific features of the state, structure and physicochemical properties of LC ionomers in the condensed phase.

Of considerable interest also are investigations of dilute solutions and gels of LC ionomers. In the text above we have

pointed to the dual nature of these macromolecules, which is due to the presence of hydrophobic mesogenic fragments responsible for the formation of the LC phase and hydrophilic functional groups, which are prone to form ionic multiplets. The diphilic nature of macromolecules predetermines an increased ability of a polymer to microsegregation, which leads to formation of a complex hierarchy of liquid-crystalline structures in the condensed phase. In solutions of LC ionomers the conformational state of macromolecules can be controlled by choosing particular solvent/precipitant ratios for selective solvation of functional groups. It is quite interesting to specify a conformation in solution by fine adjustment of hydrophobic–hydrophilic balance and then to try to ‘solidify’ it in the condensed state of the polymer by gradually removing or slowly displacing a certain solvent. This approach seems to be highly efficient for control of the character of packing and the size of liquid-crystalline nanostructures formed.

Unfortunately, such experiments have not been reported so far. However, similar, in some sense, investigations have long and successively been carried out by researchers from the Netherlands and Finland.<sup>106</sup> The focus of these studies has been design of self-organised supramolecular structures as a result of hydrogen bonding between block copolymer polyelectrolytes and low-molecular-mass non-mesogenic amphiphilic compounds. In such systems, phase separation due to variation of temperature causes the formation of optically anisotropic films comprising a number of types of lamellar nanostructures of different size (50 to 350 Å). These films closely resemble smectic mesophases of LC compounds and some block copolymers. Transitions between different structural types cause considerable (up to two orders of magnitude) changes in the electrical conductivity of the films. This offers interesting perspectives for the design of conducting polymer membranes in which the type of supramolecular organisation responsible for conductivity can be specified in solution.

Probably, an analogous approach can also be realised in the case of comb-shaped LC copolymers bearing functional groups by employing hydrogen bonding between these groups and corresponding dopants and introduction of charges into the polymer chain. Such ternary copolymers could also serve as models for some complex bioactive systems combining the ability of self-organisation and molecular recognition mechanisms.

In Japan, Prof. Osada and his collaborators do research in a related field. They design and study gel-like mesomorphous systems taking gels of comb-shaped LC polymers with mesogenic side fragments and functional carboxyl groups in the backbone (acrylic acid) or in side branchings as examples.<sup>107–109</sup> Strictly speaking, these compounds are not LC ionomers because the backbone contains no charged groups, but they belong to an interesting class of mesomorphous systems potentially capable of forming ionomers. Such copolymers readily form various types of mesophases and at low concentration of hydrophobic mesogenic groups some of them can dissolve in water giving anisotropic gels. Combination of the anisotropy of properties (in particular, birefringence) with a rather high molecular mobility allows LC gels to behave similarly to conventional low-molecular-mass liquid crystals and produce a fast response to the action of external (electric, magnetic, mechanic) fields accompanied by a change in the shape and size of the initial sample. Great prospects for the use of such systems in the design of novel ‘smart’ materials and possible fields of application have been outlined.<sup>110</sup>

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# Bimetallic cobalt catalysts for the synthesis of hydrocarbons from CO and H<sub>2</sub>

A L Lapidus, M V Tsapkina, A Yu Krylova, B P Tonkonogov

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**Abstract.** The mechanisms of promotion of cobalt catalysts used in the synthesis of hydrocarbons from CO and H<sub>2</sub> by Group VIII metals and rhenium are considered. The properties of the catalytic systems thus prepared are analysed. The bibliography includes 75 references.

## I. Introduction

Catalytic processes form the groundwork of petrochemistry and are widely employed in chemical technologies. Further perfection of the existing processes and enhancement of their efficiencies are impossible without application of novel catalysts with higher reactivities and selectivities to production. The solution of these practical tasks requires detailed analysis of structures and properties of catalytic systems, the methods for their preparation and activation, *etc.* Elucidation of relationships between the structures of active surfaces and properties of various catalysts and development of fundamentals of the selection of catalysts are central problems on the agenda of the present-day science of catalysis.

A search for reasonable alternative raw materials to crude oil, such as natural gas, coal, biomass, *etc.*, has received wide consideration in recent decades. Conversion of these basic raw materials into a carbon monoxide–hydrogen mixture (the so-called synthesis gas) and its use in preparation of hydrocarbon derivatives by the Fischer–Tropsch synthesis is one of their most promising applications. This trend competes favourably with conventional oil processing technologies used in liquid fuel production and organic synthesis. Today, the development of highly efficient and highly selective catalysts able to optimise the Fischer–Tropsch synthesis is a task of paramount importance.

At present, synthesis gas is employed for the preparation of aliphatic hydrocarbons on iron and cobalt catalysts. Co-containing systems are used as selective catalysts in the synthesis of linear

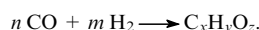
alkanes. However, many currently known Co-catalysts manifest low activities in the synthesis of n-paraffins.

Bimetallic cobalt catalysts have a number of advantages over monometallic systems, being wide-ranging with regard to activity and selectivity. One of the ways to increase the efficiency of Co-catalysts in the synthesis of hydrocarbons from CO and H<sub>2</sub> is doping by Group VIII transition metals. In turn, rationalisation of a search for highly reactive bimetallic catalysts puts forward the necessity to establish a correlation between the physicochemical and catalytic properties of catalytic systems, *i.e.*, their activities and selectivities in the processes under consideration.

This review covers the data published over the past 10–15 years devoted to cobalt-containing catalytic systems employed in the synthesis of liquid hydrocarbons from carbon monoxide and hydrogen. A separate chapter is devoted to the mechanisms of promotion of these catalysts by noble metals and rhenium.

## II. General information on the Fischer–Tropsch process

The conversion of synthesis gas can in general be described in terms of reductive oligomerisation of carbon monoxide on a heterogeneous catalyst:



Depending on the nature of the catalyst, reagent ratios and reaction conditions (temperature, pressure, *etc.*), the Fischer–Tropsch process yields hydrocarbons (alkanes, alkenes) and/or oxygen-containing products (alcohols, aldehydes, ketones, acids, esters, *etc.*).<sup>1</sup> As a rule, this synthesis does not afford individual products but, rather, a vast array of substances differing in the length of their alkyl chains typical of polymerisation reactions. The molecular mass distribution of these conversion products is well described by simple equations for polymerisation reactions which take into account the probability of chain growth and chain termination.

As regards the thermodynamics of the Fischer–Tropsch process, the hydrocarbons synthesised from CO and H<sub>2</sub> may possess any chain length, degree of saturation (with the exception of acetylene) and structures.<sup>1</sup> The Fischer–Tropsch synthesis normally yields alkenes as primary products; their subsequent hydrogenation affords alkanes.

Classical Fischer–Tropsch syntheses make use of metal catalysts (the latter are often referred to as ‘contacts’) based on iron, cobalt, nickel and ruthenium. The former two catalysts have found wide application in various industrial processes.

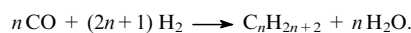
A L Lapidus, M V Tsapkina, A Yu Krylova N D Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prosp. 47, 119991 Moscow, Russian Federation. Fax (7-095) 135 53 28, tel. (7-095) 938 36 42, e-mail: albert@ioc.ac.ru (A L Lapidus), mvtsap@yandex.ru (M V Tsapkina), tel. (7-095) 730 61 01, e-mail: KrylovaAY@yukos.ru (A Yu Krylova)

B P Tonkonogov I M Gubkin Russian State Oil and Gas University, Leninsky prosp. 65, 119991 Moscow, Russian Federation. Fax (7-095) 135 88 56, tel. (7-095) 135 89 56 (B P Tonkonogov)

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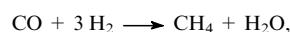
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The use of iron-based catalysts usually affords hydrocarbon mixtures with a high content of alkenes and branched paraffins as well as oxygen-containing products.<sup>1–3</sup> Cobalt-containing systems are considered to be the most efficient catalysts for the production of hydrocarbons from carbon monoxide and hydrogen, since they enable highly selective synthesis of saturated long-chain linear hydrocarbons:

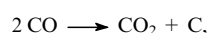


The Fischer–Tropsch synthesis involves some side reactions, *viz.*:

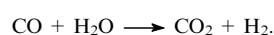
1) hydrogenation of carbon monoxide to methane:



2) the Bell–Boudouard reaction (disproportionation of CO):



3) water gas equilibrium:



Synthesis of paraffins from CO and H<sub>2</sub> may be accompanied by secondary reactions over the whole range of temperatures used and includes the formation and hydrogenation of lower alkenes, partial hydrocracking and dehydrogenation of alkanes formed, hydrogen-transfer rearrangements, *etc.*

The actual composition of the products prepared from CO and H<sub>2</sub> differs substantially from the theoretical equilibrium composition. This reaction is kinetically controlled and the final composition of its target products is determined by the nature of the catalyst and the reaction conditions. In turn, the properties of Co-catalysts used in the Fischer–Tropsch syntheses strongly depend on the nature of substrates, percentage of the active metal components and sample activation conditions.

### III. Bimetallic cobalt catalysts

#### 1. Promotion by iron-subgroup metals

Recently, the attention of investigators has become focused on bimetallic catalysts for the Fischer–Tropsch synthesis. First, by varying the metal ratios, one can change their catalytic properties.<sup>4–7</sup> Second, combination of several active components in a catalyst makes it more stable and resistant against poisoning and coking.<sup>8</sup>

The Fischer–Tropsch synthesis involves preliminary reduction (or activation) of heterogeneous catalysts. All the catalysts undergo chemical transformations (so-called phase changes) upon reduction and subsequent synthesis of hydrocarbons from CO and H<sub>2</sub>. For example, reduced Fe-samples interact with synthesis gas to yield carbides and oxides; the activity of a catalyst increases upon preliminary carbide formation on its surface. On the contrary, cobalt catalysts are much less prone to form carbides and carbide formation prior to the synthesis markedly decreases their activity. Nevertheless, simultaneous introduction of iron and cobalt into the catalyst allows conversion of synthesis gas into hydrocarbons.<sup>9, 10</sup>

The activity and selectivity of cobalt catalysts is enhanced upon promotion by Group VIII transition metals and rhenium. The Fischer–Tropsch synthesis (250 °C, 10 atm) in the presence of various catalysts was studied by Ishihara *et al.*<sup>11</sup> It was shown that 10% Co/SiO<sub>2</sub> and 10% Fe/SiO<sub>2</sub> manifested unusually lower activities in comparison with those reported by other authors (see Refs 12–16): the conversion of carbon monoxide on these catalysts was as low as 5.2% and 0.2%, respectively. Introduction of two metals (Fe and Co) into the catalyst increased its activity in comparison with the monometallic systems, being dependent on the metal ratio. A decrease in the mass ratio Fe:Co from 3.0 to 0.35 (at the total metal content in the catalyst of 10%) resulted in an increase in CO conversion from 7.7% to 21.5%, in the selectivity of formation of hydrocarbons containing no less than two carbon atoms (C<sub>2+</sub>) from 49.8% to 71.6% and a decrease in

the methane content in the reaction products from 50.2% to 28.4%. It is noteworthy that the increased yields of paraffins C<sub>2</sub>–C<sub>5</sub> and decreased yields of hydrocarbons C<sub>6+</sub> was concomitant with a decrease in the relative content of Fe in the bimetallic contact.

The same authors<sup>11</sup> investigated also the properties of 10% Co–Ni-containing systems manifesting higher activities in the Fischer–Tropsch synthesis than the monometallic catalysts Co/SiO<sub>2</sub> and Ni/SiO<sub>2</sub>. It was found that with an increase in the mass ratio Co:Ni from 0.35 to 3.0 at the total metal content of 10%, the extent of CO conversion increased showing a maximum (32.3%) at Co:Ni = 1. All the samples of this series manifested similar selectivities in the synthesis of hydrocarbons C<sub>2+</sub> (67%–71%). However, the compositions of the products prepared on Co–Ni-contacts differed from those synthesised on Fe–Co, *viz.*, the former contained less alkenes and more hydrocarbons C<sub>6+</sub>. Heavier (in comparison with the monometallic samples) hydrocarbons were synthesised in the presence of a Co–Ni-catalyst.

X-Ray phase analysis has shown<sup>11</sup> that the surfaces of reduced monometallic catalysts Co/SiO<sub>2</sub>, Ni/SiO<sub>2</sub> and Fe/SiO<sub>2</sub> contained oxide phases. In the case of bimetallic samples, reduction brought about alloying of cobalt with iron or nickel. This favoured the reduction of iron and cobalt oxides to metals so that no oxide phases remained on the surface of the cobalt catalysts. Alloying of Co with Ni also facilitated their reduction which resulted in the increase in the amount of the activated reagents (hydrogen and carbon monoxide) (data from thermoprogrammed desorption of CO and H<sub>2</sub>) in parallel with the increase in the catalyst activities. It has been found<sup>17, 18</sup> that alloy particles present on the surface of Fe–Co-contacts differ in size. Under the conditions used, no carbide phases are formed from these metals, and the metals manifested enhanced hydrogenating activities in comparison with surface sites containing the carbide phase.

Studies of Co–Ni-catalysts supported on ZrO<sub>2</sub> have shown<sup>19</sup> that the increase in the Co content due to the increase of the mass ratio Co:Ni from 0.3 to 2.4 resulted in a twofold decrease in the content of the light hydrocarbons C<sub>1</sub>–C<sub>4</sub> in the products, while that of paraffins C<sub>5+</sub> increased from 35% to 63%. The degree of CO conversion did not change under these conditions and constituted 4%–5% at 250 °C and ambient pressure. Using thermoprogrammed reduction (TPR, see below), it was found that Ni promotion of Co/ZrO<sub>2</sub> catalysts induced a marked shift of the TPR signals towards the low-temperature region. Based on these data, it was suggested that nickel favours the reduction of cobalt oxide due to hydrogen spillover effect. As nickel is reduced earlier than cobalt, it begins to adsorb and activate hydrogen as a result of which the latter migrates towards cobalt oxide.

These examples clearly demonstrate that introduction of a second metal into Co-based catalysts not only increases their activities, but also allows control over their selectivities in the formation of a vast array of hydrocarbons.

#### 2. Promotion by noble metals and rhenium

Introduction of a tenth and even a hundredth of percent of noble metals into cobalt catalysts changes significantly their physicochemical and catalytic properties. It was found<sup>20, 21</sup> that Co-catalysts promoted by Pt, Rh, Pd, Ru and Re manifest high activities and selectivities in the syntheses of aliphatic hydrocarbons with various structures (both liquid and solid), which allows these processes to be conducted at relatively low temperatures (190–200 °C).

##### a. Studies of bimetallic cobalt catalysts by physicochemical methods

Promotion of cobalt catalysts was studied using various physicochemical methods, in the first place, by thermoprogrammed reduction (TPR). This method is used in the analysis of reducing potentials of catalysts as well as for establishing the compositions of non-reduced catalysts.

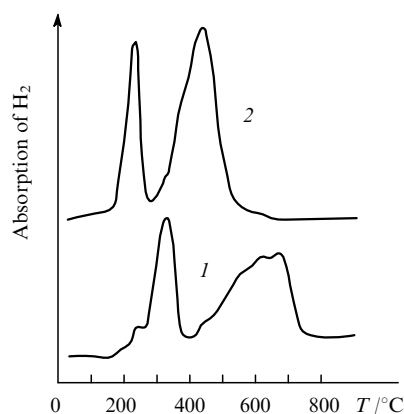


**Figure 1.** TPR spectra of the catalysts Co/Al<sub>2</sub>O<sub>3</sub> (1) and Co–Ru/Al<sub>2</sub>O<sub>3</sub> (2) recorded after calcination of the samples (300 °C, 14 h).<sup>22</sup>

The TPR spectrum of 20% Co/Al<sub>2</sub>O<sub>3</sub> prepared by impregnation of the support with cobalt nitrate is shown in Fig. 1 (curve 1).<sup>22</sup> The addition of 0.5% Ru (from the corresponding nitrosyl nitrate) to this catalyst favoured its easier reduction as can be evidenced from the nearly 100 °C shift of the TPR signal of the Co–Ru contact towards lower temperatures (see Fig. 1, curve 2). Cobalt oxide in the composition of the bimetallic sample was almost completely reduced to Co<sup>0</sup>, while the degree of reduction of a non-promoted catalyst was only 60%. It was supposed<sup>22</sup> that ruthenium formed upon reduction of its oxide prior to cobalt adsorbs and activates hydrogen. Hydrogen migrates towards Co<sub>3</sub>O<sub>4</sub> by a spillover mechanism and thus favours its easier reduction. Quite probably, ruthenium also either inhibits the formation of cobalt compounds that are difficult to reduce, e.g., by preventing the interaction of cobalt oxide with Al<sub>2</sub>O<sub>3</sub> to yield a Co–Al spinel, or favours their partial reduction. The absence of high-temperature peaks at >450 °C in the TPR spectrum of the Co–Ru-catalyst and the presence of a signal with  $T_{\text{max}} = 600$  °C in the TPR spectrum of the monometallic cobalt sample corroborates this hypothesis. According to hydrogen chemisorption data, the number of metallic cobalt atoms on the surface of a cobalt catalyst increases threefold upon promotion with ruthenium.

In the TPR spectra of palladium- or ruthenium (0.3%)-promoted Co samples, two signals were also shifted towards the low-temperature region in comparison with the monometallic catalyst (10% Co/Al<sub>2</sub>O<sub>3</sub>).<sup>23</sup> In the ruthenium-promoted catalyst, the first signal was shifted by 46 °C, while the shift of the second signal was 9 °C. The shifts were even more pronounced (195 and 72 °C, respectively) for the Co–Pd contact.

The effects of palladium additives to the catalyst Co/SiO<sub>2</sub> prepared by the sol–gel method (Fig. 2) have been studied by Guzzi *et al.*<sup>24</sup> The presence of a very broad peak in the TPR spectrum of a monometallic Co-contact (curve 1) points to a high degree of dispersion of cobalt particles. Introduction of Pd and subsequent reduction of the catalyst increases the content of metallic cobalt in the sample. At the mass ratio Co : Pd = 2 (see Fig. 2, curve 2), the peak corresponding to the reduction of cobalt oxide was shifted from 450 °C to 375 °C (Fig. 2, curve 1). It is noteworthy that the reduction of the monometallic catalyst 5% Pd/SiO<sub>2</sub> occurred at 150 °C (Fig. 2, curve 5). With a further increase in the Pd content, the shift of the characteristic peak was even more pronounced, *viz.*, up to 350 °C (Fig. 2, curves 3, 4). In the authors' opinion, a shoulder at 220 °C suggests the formation of bimetallic particles Co–Pd; this conclusion was confirmed by X-ray photoelectron spectroscopic (XPS) data.

The formation of bimetallic particles under TPR conditions was also observed in the analysis of rhodium-containing Co-catalysts.<sup>25–27</sup> The samples for this study were prepared on different oxide supports, e.g., SiO<sub>2</sub>, Al<sub>2</sub>O<sub>3</sub>, TiO<sub>2</sub>. (A more detailed

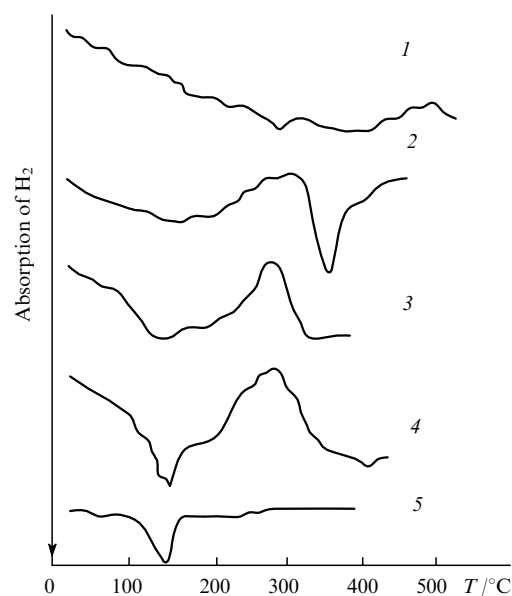


**Figure 2.** TPR spectra of the samples Co/SiO<sub>2</sub> (1); Co–Pd/SiO<sub>2</sub> (2–4); Pd/SiO<sub>2</sub> (5).<sup>24</sup> The Co : Pd atomic ratios are equal to 2 (2), 1 (3) and 0.5 (4).

description of characteristic features of these catalytic systems will be given below).

As a case in point, let us consider the results of a TPR analysis of Co/SiO<sub>2</sub> and Rh/SiO<sub>2</sub> samples and a bimetallic catalyst (Co–Rh/SiO<sub>2</sub>) prepared by impregnation with cobalt nitrate and rhodium chloride (total metal content was 4.9%, the atomic ratio Co : Rh was 1 : 1) (Fig. 3).<sup>25</sup> In this study, complete reduction of the catalyst Rh/SiO<sub>2</sub> occurred at 140 °C. The reduction of Co–Rh/SiO<sub>2</sub> occurred at a lower temperature (237 °C) than reduction of the monometallic cobalt sample (327 °C), which suggests that cobalt nitrate and cobalt oxide are reduced at higher rates in the presence of rhodium. It was found also<sup>25</sup> that the reduced catalyst Co–Rh/SiO<sub>2</sub> contains bimetallic particles, their inner part is enriched with metallic rhodium, while the outer layer is enriched with cobalt (see below, Section IV).

The addition of platinum to Co-containing systems also facilitates the reduction of cobalt oxides.<sup>28–30</sup> The results of a TPR study of the promoting effect of platinum on Co-catalysts are shown in Fig. 4.<sup>28</sup> A comparison of the TPR spectra of the monometallic sample (9% Co/Al<sub>2</sub>O<sub>3</sub>) (Fig. 4, curve 2) and the catalyst (9% Co–0.4% Pt/Al<sub>2</sub>O<sub>3</sub>) (Fig. 4, curve 3) shows that in

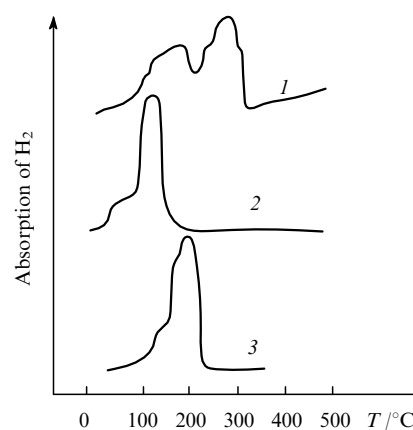


**Figure 3.** TPR spectra of the catalysts Co/SiO<sub>2</sub> (1), Rh/SiO<sub>2</sub> (2) and Co–Rh/SiO<sub>2</sub> (3).<sup>25</sup>

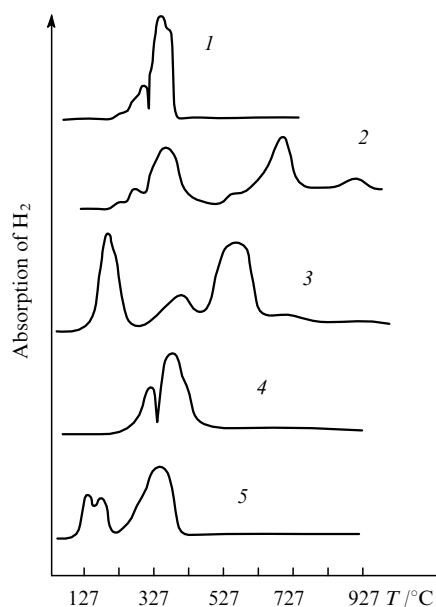


**Figure 4.** TPR spectra of the samples  $\text{Co}_3\text{O}_4$  (1), 9%  $\text{Co}/\text{Al}_2\text{O}_3$  (2), 9.2%  $\text{Co}-0.4\%$   $\text{Pt}/\text{Al}_2\text{O}_3$  (3), 8.9%  $\text{Co}/\text{SiO}_2$  (4), 8.7%  $\text{Co}-0.4\%$   $\text{Pt}/\text{SiO}_2$  (5).<sup>28</sup>

the latter case the peaks corresponding to the reduction of Co oxide phases are shifted towards the low-temperature region by more than 100 °C. The peak corresponding to the reduction of  $\text{Co}_3\text{O}_4$  is shifted from 377 to 207 °C, while the peak corresponding to the mixed cobalt–aluminium oxide is shifted from 717 to 587 °C. The TPR spectrum of the Co–Pt sample contained an additional signal (at 417 °C), which was assigned<sup>28</sup> to the reduction of  $\text{Co}_3\text{O}_4$  without involvement of platinum. Similar dependences were observed when  $\text{SiO}_2$  was used as a substrate, *viz.*, the peak corresponding to the platinum-promoted reduction of  $\text{Co}^{3+}$  to  $\text{Co}^{2+}$  was shifted from 327 to 147–177 °C (see Fig. 4, curves 4 and 5), while the shift of the peak assigned to the reduction of  $\text{Co}^{2+}$  to  $\text{Co}^0$  was less pronounced (from 397 to 357 °C).

As with platinum, promotion of the cobalt catalyst (20%  $\text{Co}-1\%$   $\text{Re}/\text{Al}_2\text{O}_3$ ) by rhenium shifted the signals in the TPR spectra towards the low-temperature region in comparison with the monometallic sample (Fig. 5).<sup>31</sup> However, in contrast to plati-

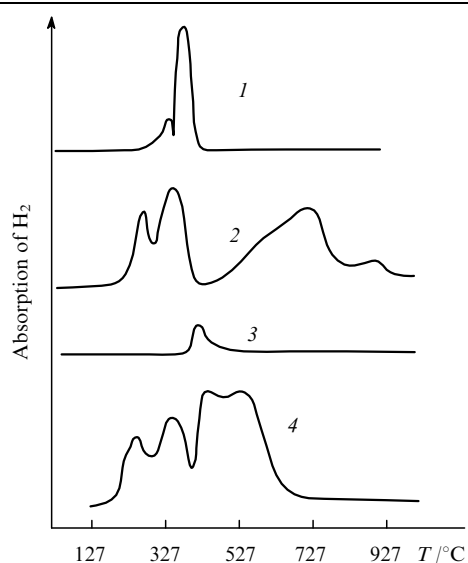


**Figure 5.** TPR spectra of the samples  $\text{Co}_3\text{O}_4$  (1),  $\text{Co}/\text{Al}_2\text{O}_3$  (2),  $\text{Re}/\text{Al}_2\text{O}_3$  (3) and  $\text{Co}-\text{Re}/\text{Al}_2\text{O}_3$  (4).<sup>31</sup>

num, which favours the reduction of the dominant cobalt oxide phases on the surface of a bimetallic contact at lower temperatures, rhenium brings about the reduction of both the highly dispersed surface phase of Co ( $T_{\text{max}} = 727$  °C for the monometallic sample, the TPR signal was shifted by 200 °C) and the spinel  $\text{CoAl}_2\text{O}_4$ . In the presence of rhenium, the latter was reduced practically completely as can be evidenced from the absence of signals at temperatures above 800 °C. It is noteworthy that the TPR spectrum of a monometallic Re sample displays a single signal at 425 °C.

Promotion of the catalyst 8.7%  $\text{Co}/\text{Al}_2\text{O}_3$  by platinum and rhenium increases the degree of reduction ( $R_{\text{Co}}$ ) and dispersity ( $D$ ) of metallic cobalt.<sup>32</sup> The former value reflects the number of metallic cobalt atoms with respect to the total content of cobalt atoms in the catalyst, while the latter indicates the number of surface metal atoms with respect to the total number of metallic cobalt atoms.

| Additive            | Without additive | 1% Pt | 1% Re |
|---------------------|------------------|-------|-------|
| $R_{\text{Co}}$ (%) | 52               | 79    | 78    |
| $D$ (%)             | 6.7              | 13.9  | 16.5  |

These data confirm the promoting effects of Pt and Re on the reduction of cobalt oxides.

However, some authors hold the opinion<sup>33</sup> that unlike noble metals, rhenium does not influence the reduction of cobalt catalysts. The extent of cobalt reduction was not changed upon addition of 0.6% Re to 5%  $\text{Co}/\text{Nb}_2\text{O}_5$  and constituted 48%. The TPR spectra of monometallic Co and a rhenium-promoted catalyst were also virtually identical. It should be noted however that the addition of rhenium to a Co-catalyst increased the dispersity of metallic cobalt from 8% to 12.5% in parallel with a decrease in the size of cobalt crystallites from 12 to 8 nm.

The TPR method was used to study the formation of bimetallic catalysts  $\text{Co}-\text{M}/\text{SiO}_2$  ( $\text{M} = \text{Pt}, \text{Ru}, \text{Rh}, \text{Pd}$ ).<sup>34</sup> The samples were prepared by repeated impregnation of the support with the salts  $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ ,  $\text{RhCl}_3 \cdot 4\text{H}_2\text{O}$ ,  $\text{RuCl}_3$ ,  $\text{PdCl}_2$  or the  $\text{Pt}(\text{acac})_2$  complex. After each (except for the last) impregnation, the samples were calcined at 450 °C. The results of these studies are presented in Figs 6 and 7 where the TPR spectra are superimposed for convenience. It was found that cobalt nitrate and cobalt oxide were present on the surface of the non-reduced catalyst  $\text{Co}/\text{SiO}_2$  (see Fig. 6, curve 1). The former underwent reductive decomposition ( $T_{\text{max}} = 235, 278$  °C), while the stepwise reduction of the latter to  $\text{Co}^0$  ( $\text{Co}_3\text{O}_4 \rightarrow \text{CoO} \rightarrow \text{Co}^0$ ) occurred at  $T_{\text{max}} = 330$  and 412 °C. Co–support compounds that are difficult to reduce ( $T_{\text{max}} = 479$  °C) were also found on the surface. The addition of platinum, palladium or rhodium (see Fig. 6, curves 2–4) to a monometallic catalyst resulted in an appreciable shift of the overall TPR spectrum towards the low-temperature region and the appearance of isolated signals at temperatures

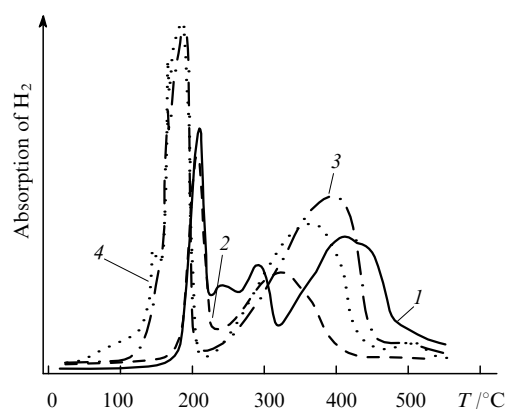


**Figure 6.** TPR spectra of the samples  $\text{Co}/\text{SiO}_2$  (1) and  $\text{Co}-\text{M}/\text{SiO}_2$ , where  $\text{M} = \text{Rh}$  (2),  $\text{Pd}$  (3) and  $\text{Pt}$  (4).<sup>34</sup>

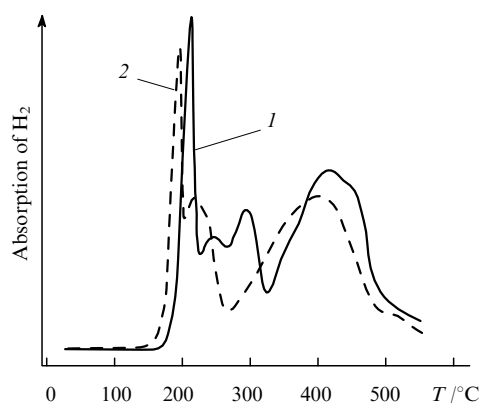


**Figure 7.** TPR spectra of the samples Co/SiO<sub>2</sub> (1) and Co-Ru/SiO<sub>2</sub> (2).<sup>34</sup>

below 200 °C in the former two cases (Pt and Pd). This peak corresponds to the reduction of platinum (palladium) oxide or mixed Co-Pt(Pd) oxides. The presence of a noble-metal phase on the surface of a substrate led the authors to postulate its role in the autocatalytic reduction of Co samples. Ruthenium formed no individual phase on the surface of a bimetallic contact and had virtually no effect on the reduction of the dominant cobalt phases as can be judged from the similarity of the TPR spectra of Ru-containing and Ru-free samples (see Fig. 7). Presumably, the properties of reduced bimetallic cobalt-containing catalysts depend on the nature of the promoter. Based on these data, the authors proposed a model of formation of active sites for a series of Co-M/SiO<sub>2</sub> catalysts (M = Pt, Ru, Rh, Pd) (see below).<sup>34</sup>

Thus, introduction of Pd, Rh, Ru, Pt and Re into cobalt catalysts results in considerable changes in their physicochemical properties. In the presence of noble metals, the reduction of cobalt oxides on the surface of a catalyst occurs more easily in the stage of activation due to hydrogen spillover. The number of active sites on the surface of cobalt catalysts increases with the increase in the degree of cobalt reduction rate and dispersity. This effect contributes significantly to the enhancement of activity of catalytic systems.

### b. Studies of bimetallic cobalt catalysts in the Fischer-Tropsch synthesis

Changes in the physicochemical properties of cobalt catalysts upon introduction of noble metals or rhenium result in changes in their catalytic properties. The use of such modified systems in hydrocarbon syntheses from CO and H<sub>2</sub> makes it possible to increase the activity of catalysts and the selectivity of formation of liquid hydrocarbons (C<sub>5+</sub>).

The effects of platinum and rhenium additives on the activities of Co-catalysts in the Fischer-Tropsch synthesis with 10% Co/Al<sub>2</sub>O<sub>3</sub> and 10% Co/SiO<sub>2</sub> as the original systems have been studied.<sup>28, 29, 32</sup> The catalysts were prepared by co-impregnation, drying and calcination in a flow of air (400 °C, 2 h) with subsequent reduction by hydrogen (14–16 h, *T* = 350 °C). The specific activities of Al<sub>2</sub>O<sub>3</sub>-based catalysts in the hydrocarbon synthesis from CO and H<sub>2</sub> (220 °C, 1 atm) at the molar ratio H<sub>2</sub>:CO = 7.3 were shown to increase substantially upon addition of 1% platinum or rhenium [from 18.4 for the monometallic sample to 36.8 and 38.3 μmol CO (g Co s)<sup>-1</sup>, respectively].<sup>32</sup> According to other authors,<sup>29</sup> the addition of 1% Pt to 10% Co/Al<sub>2</sub>O<sub>3</sub> increases the catalytic activity from 11 to 19 μmol CO (g Co s)<sup>-1</sup> (200 °C, 1 atm, H<sub>2</sub>:CO = 2). A 3–5-fold increase in the catalytic activity was also observed after addition of 0.4% Pt to 9% Co/Al<sub>2</sub>O<sub>3</sub> (SiO<sub>2</sub>) (210 °C, 1 atm, H<sub>2</sub>:CO = 7).<sup>28</sup>

The addition of small amounts of palladium or ruthenium (0.1%–0.7%) to 10% Co/Al<sub>2</sub>O<sub>3</sub>(SiO<sub>2</sub>) prepared by impregnation

with cobalt nitrate allows one to increase the extent of conversion of carbon monoxide and the yield of hydrocarbons C<sub>5+</sub> in the Fischer-Tropsch synthesis. Thus the extent of CO conversion on a Co-Pd-contact (200–210 °C, 1 atm, H<sub>2</sub>:CO = 2) was > 80%, and the yield of hydrocarbons C<sub>5+</sub> reached 95–97 g m<sup>-3</sup> (see<sup>†</sup>) (cf. 70% and 55 g m<sup>-3</sup>, respectively, for a non-promoted Co-catalyst). The selectivity of the synthesis of liquid hydrocarbons in the presence of Co-Ru-catalysts exceeded 80%.<sup>23, 35–38</sup> The effects of minor concentrations of Pt (0.1%–0.7%) on the activity of a cobalt catalyst (10% Co/SiO<sub>2</sub>) have been studied.<sup>39</sup> It was found that the contact 10%Co-0.7%Pt/SiO<sub>2</sub> manifested the highest activity in the hydrocarbon synthesis from CO and H<sub>2</sub> (200 °C, 1 atm, H<sub>2</sub>:CO = 2). With this catalyst, the yields of the liquid hydrocarbons increased to 92 g m<sup>-3</sup> at the degree of CO conversion rate of 87%, while the selectivity of their formation was 71%. The fractional compositions of the reaction products did not depend on the concentrations of Pd, Ru and Pt added to the Co-catalyst, viz., the content of hydrocarbons C<sub>5</sub>–C<sub>10</sub> was 65%–70%, that of hydrocarbons C<sub>11</sub>–C<sub>18</sub> was 27%–32%, while that of the C<sub>19+</sub> fraction was insignificant (1%–4%).<sup>36–39</sup>

The activities of Co/SiO<sub>2</sub> catalysts promoted by the platinum-group metals in the Fischer-Tropsch synthesis have been compared.<sup>34</sup> In all cases, the introduction of a second metal (Pt, Rh, Pd, Ru) resulted in a significant increase of the activities and selectivities of the bimetallic catalytic systems. Catalysts of this series manifested the following properties in the hydrocarbon synthesis from CO and H<sub>2</sub> (190–200 °C, 1 atm, H<sub>2</sub>:CO = 2):

1) the yields of liquid hydrocarbons (g m<sup>-3</sup>) decreased in the following order:

Co-Pt (139) > Co-Ru (129) > Co-Rh (124) > Co (118) > Co-Pd (82);

2) the selectivities of the formation of liquid hydrocarbons (%) decreased in the following order:

Co-Pt (81) > Co-Ru (77) > Co (76) > Co-Rh (72) > Co-Pd (60).

The liquid products obtained in the presence of the bimetallic catalysts contained predominantly saturated hydrocarbons with normal structures (64%–74%).

There is a large body of evidence in the current literature concerning Co-Ru catalysts of the Fischer-Tropsch synthesis.<sup>22, 40–51</sup> The synergism of catalytic effects of cobalt and ruthenium reported by most investigators suggests that bimetallic contacts exceed their monometallic counterparts in both activity and selectivity.

The addition of ruthenium to the catalyst 11.6% Co/TiO<sub>2</sub> (SiO<sub>2</sub>) changed the atomic ratio Ru:Co from 0.001 to 0.014.<sup>43</sup> In all cases, the rate of hydrocarbon synthesis<sup>‡</sup> (200 °C, 20 atm, H<sub>2</sub>:CO = 2) showed a tendency to increase. Thus for Ru:Co = 0.0067, this increased twofold, i.e., from 3.9 × 10<sup>-4</sup> to 6.4 × 10<sup>-4</sup> s<sup>-1</sup>. Under these conditions, the degree of carbon monoxide conversion increased from 49% to 51%, while the selectivity of liquid hydrocarbon synthesis reached 85%–86%. Calcination of a bimetallic Co-Ru-catalyst prior to reduction (1 h, 300 °C) brought about a further twofold increase in the reaction rate: the degree of conversion of CO and the selectivity of the synthesis of the hydrocarbons C<sub>5+</sub> amounted to 61% and 91%, respectively. These parameters were compared<sup>43</sup> to those obtained under similar conditions with 1.1% Ru/TiO<sub>2</sub>.<sup>44</sup> The extent of CO conversion on Ru/TiO<sub>2</sub> was 35%, i.e., lower than on the bimetallic contact with nearly the same selectivity (93% and

<sup>†</sup> The activities of the catalysts of the Fischer-Tropsch synthesis are usually estimated by the yields of the hydrocarbons [g per 1 m<sup>3</sup> of synthesis gas (CO + 2 H<sub>2</sub>) corrected to normal conditions (n.c.)]. The theoretical yield of the hydrocarbons is 208.5 g m<sup>-3</sup> (n.c.).

<sup>‡</sup> In this case, the synthesis rate is expressed by a value termed as 'reaction turnover number', i.e., the number of reaction acts per unit time.

91%). It is of note that the dispersity of the cobalt catalyst was not changed upon promotion by ruthenium.

Based on the data from electron microscopy, X-ray absorption spectroscopy and thermogravimetric analysis, it was suggested<sup>43</sup> that more rapid reduction of cobalt oxide requires a contact between Co and Ru to yield a mixed oxide upon calcination of bimetallic samples prior to reduction. Such treatment triggers the migration of ruthenium and cobalt oxides over the catalyst surface resulting in the formation of mixed Co–Ru oxides ( $\text{Co}_{3-x}\text{Ru}_x\text{O}_4$ , where  $0 < x < 1$ ). The presence of ruthenium decelerates deactivation of the catalyst due to coking. As a consequence, the activity of the Co–Ru-contact and the selectivity of formation of liquid hydrocarbon increase.

The properties of mono- and bimetallic catalysts containing 6% Co and/or 2% Ru supported onto  $\text{SiO}_2$  or  $\text{Al}_2\text{O}_3$  were examined under differential, static and flowing regimes.<sup>45,46</sup> In all the three cases, the bimetallic catalysts manifested the highest selectivities in the Fischer–Tropsch synthesis, the highest selectivity (69%) of the synthesis of hydrocarbons  $\text{C}_{2+}$  in a flow reactor (240–280 °C, 1 atm,  $\text{H}_2:\text{CO} = 1$ ) being manifested by the bimetallic contact Ru–Co/ $\text{Al}_2\text{O}_3$ . In addition, in this case the highest yield of alkenes (19%) was achieved. The activities of the catalysts Ru/ $\text{Al}_2\text{O}_3$  and Ru–Co/ $\text{Al}_2\text{O}_3$  appeared to be similar as could be judged from the extent of conversion of carbon monoxide: the extent of CO conversion ( $K_{\text{CO}}$ ) was 14% and 16%, respectively, which markedly exceeded that for Co/ $\text{Al}_2\text{O}_3$  ( $K_{\text{CO}} = 8.2\%$ ). The degree of cobalt reduction in the bimetallic contact was higher in comparison with the corresponding monometallic catalyst, which can be attributed to the activation of  $\text{H}_2$  on the surface of ruthenium and its subsequent spillover to cobalt oxide as well as to the formation of Ru and Co alloys as can be evidenced from the appearance of signals corresponding to mixed clusters  $\text{RuCo}^+$  in the mass spectra of secondary ions.

Co–Ru-Catalysts prepared on mixed oxide supports ( $\text{ThO}_2\text{--Al}_2\text{O}_3$  and  $\text{La}_2\text{O}_3\text{--Al}_2\text{O}_3$ ) also exceeded monometallic Co-samples in activity; the selectivity of formation of liquid hydrocarbons reached 79%.<sup>47–49</sup> The activity and selectivity of a bimetallic Co–Ru-sample increased noticeably after calcination and subsequent reduction.

It is of note that the temperature of preliminary calcination of a cobalt-containing catalyst influences the extent of cobalt reduction and, as a consequence, its catalytic activity. The properties of a contact 20% Co–0.5% Ru/ $\text{Al}_2\text{O}_3$  employed in the synthesis of hydrocarbons from CO and  $\text{H}_2$  (220 °C, 1.8 atm,  $\text{H}_2:\text{CO} = 10$ ) have been investigated.<sup>50</sup> With an increase in the calcination temperature from 250 to 400 °C, the peaks in the TPR spectra were shifted towards higher temperatures (Fig. 8), while the extent of Co reduction decreased from 77% to 59%. This was accompanied by a decrease in the extent of carbon monoxide conversion (from 11% to 5%), reaction rate [from 50 to 23  $\mu\text{mol CO (g Co s)}^{-1}$ ] and selectivity of methane synthesis (from 84% to 73%).

Besides, catalytic properties of bimetallic contacts strongly depend on the method of preparation and the nature of the substrates and the starting metal salts. Thus the catalyst 20% Co–0.5% Ru/ $\text{Al}_2\text{O}_3$  was prepared from different ruthenium derivatives, viz.,  $\text{Ru(NO)(NO}_3)_3$  and  $\text{RuCl}_3$ , using combined or sequential impregnation.<sup>22</sup> The Fischer–Tropsch synthesis was carried out at 220 °C, 1 atm and the  $\text{H}_2:\text{CO}$  ratio = 2. The catalyst prepared by co-impregnation with  $\text{Co(NO}_3)_2 \cdot 6\text{H}_2\text{O}$  and  $\text{RuCl}_3$ , drying (5 h, 115 °C) and calcination (2 h, 300 °C) manifested the highest activity. The reaction rate on this catalyst was 0.342 g  $[-\text{CH}_2-]$  (g of catalyst h)<sup>–1</sup>.

Samples containing 5% Co on  $\text{SiO}_2$ ,  $\text{Al}_2\text{O}_3$  or aluminosilicate ( $\text{SiO}_2 \cdot \text{Al}_2\text{O}_3$ ) were prepared by impregnating the support with a solution of cobalt carbonyl in n-hexane. The addition of 0.5% Pd to such a catalyst increased its activity and the yield of liquid hydrocarbons.<sup>51</sup> The bimetallic contact with  $\text{SiO}_2 \cdot \text{Al}_2\text{O}_3$  as a support manifested the highest activity in the Fischer–Tropsch synthesis (210 °C, 1 atm,  $\text{H}_2:\text{CO} = 2$ ) which increased from

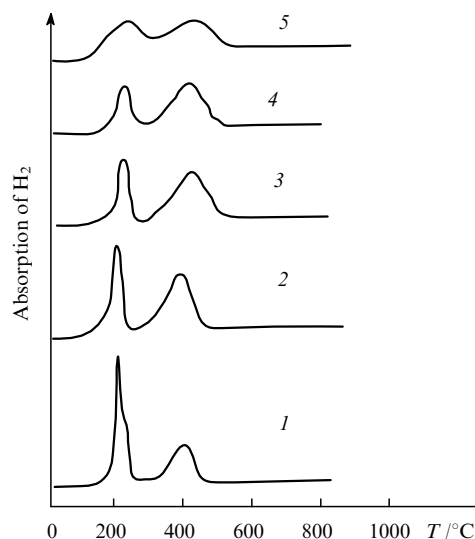


**Figure 8.** TPR spectra of the sample Co–Ru/ $\text{Al}_2\text{O}_3$  calcined at different temperatures: non-calcinated (1); 250 °C (2); 300 °C (3); 350 °C (4); 400 °C (5).<sup>50</sup>

$6.6 \times 10^{-3}$  to  $8.7 \times 10^{-3}$  mmol CO (g of Co s)<sup>–1</sup> in comparison with the monometallic Co-sample. The yield of liquid hydrocarbons increased from 57 to 72 g m<sup>–3</sup>, while the selectivity of their formation increased from 33% to 42%. The extent of cobalt reduction increased from 55% to 62%. Presumably,<sup>51</sup> Co–Pd-clusters are formed on the surface of this catalyst and autocatalytic reduction of Co occurs by spillover of hydrogen adsorbed on palladium.

It has been found<sup>24</sup> that the rate of hydrocarbon synthesis from CO and  $\text{H}_2$  (250 °C, 1 atm,  $\text{H}_2:\text{CO} = 2$ ) increased 35-fold upon addition of palladium to a catalyst Co/ $\text{SiO}_2$  (the atomic ratio Pd : Co = 1 : 2, total metal content = 5%). This was accompanied by a sharp (from 91% to 59%) decrease in the methane content, a marked (from 1% to 26%) increase in the n-paraffin ( $\text{C}_{2+}$ ) content in the reaction products and an increase in the hydrocarbon chain length (the probability coefficient for the chain growth,  $\alpha$ , increased from 0.29 to 0.78). Methane was the only product formed on a monometallic Pd-sample (yield 100%).

Ion exchange of solutions of  $\text{Co(NH}_3)_6\text{Cl}_3$  and  $\text{RuCl}_3$  in 8%  $\text{NH}_4\text{OH}$  was employed for the preparation of a series of catalysts (3% Co/ $\text{SiO}_2$ , 3% Co–3% Ru/ $\text{SiO}_2$  and 3% Ru/ $\text{SiO}_2$ ) for the Fischer–Tropsch synthesis (250 °C, 21 atm,  $\text{H}_2:\text{CO} = 2$ ).<sup>52</sup> The activity of the Co–Ru contact exceeded that of the non-promoted Co-sample 4.6-fold and was nearly twice as low as that of the monometallic Ru-sample ( $K_{\text{CO}}$  were 9.6%, 2.1% and 18.7%, respectively). Methane (71%) was formed predominantly on Co-catalysts; the reaction products contained 25% of hydrocarbons  $\text{C}_{2+}$  and 4% of alcohols. Upon addition of Ru, the amount of methane formed decreased twofold (36%), while that of hydrocarbons  $\text{C}_{2+}$  increased 1.7-fold. Other reaction products included alcohols (MeOH, EtOH,  $\text{Pr}^n\text{OH}$ ); their total content was 20%. The Ru/ $\text{SiO}_2$  sample manifested the highest selectivity in the synthesis of paraffins (63%), virtually no alcohols were formed.

Hydrocarbons  $\text{C}_{2+}$  were predominantly formed on catalysts prepared by spraying carbonyls  $\text{Co}_{4-n}\text{Ru}_n\text{H}_n(\text{CO})_{12}$  ( $n = 0\text{--}4$ ) or  $\text{Co}_2\text{Ru}_2(\text{CO})_{13}$  onto  $\text{SiO}_2$  under identical conditions (250 °C, 21 atm,  $\text{H}_2:\text{CO} = 2$ ) (see Ref. 53). These catalysts differed from those prepared by ion exchange<sup>52</sup> in lower methane yields (13%–25%) and higher selectivities with respect to hydrocarbons  $\text{C}_{2+}$  (64%–79%). The content of oxygen-containing reaction products and  $\text{CO}_2$  was insignificant (0.2%–5%).

Ion-exchange and impregnation were used for the preparation of Pt–Co-catalysts on zeolite NaY.<sup>54</sup> Synthesis of hydrocarbon from CO and  $\text{H}_2$  was carried out at 232 °C, 10 atm and

H<sub>2</sub>: CO = 2. In the former case, methanol was the major product (50%). Methane (51%) and hydrocarbons C<sub>2+</sub> (49%) were formed on a catalyst prepared by impregnation, oxygen-containing products were formed in trace amounts. The difference in the reaction of the target products are usually attributed to the difference in the sizes of the bimetallic Co–Pt-particles formed in the course of the preparation procedure. If ion-exchange is used, the size of the particles is less than 2.5 nm, which can be attributed to the small size of zeolite NaY pores. If the catalysts are prepared by impregnation, their particles have a larger size (~ 20 nm) and are localised on the zeolite surface.

It has been found<sup>55</sup> that a catalyst prepared by co-precipitation of cobalt and cerium oxides manifested high activity in the Fischer–Tropsch synthesis. The reaction products comprised lower alkenes and higher n-alkanes; the amount of CO<sub>2</sub> was negligible. The activities of such a catalyst increased threefold upon promotion by 0.3% Ru [from Ru<sub>3</sub>(CO)<sub>12</sub>] and remained virtually unchanged over 100 h, the degree of CO conversion being > 40%. However, the selectivity of the synthesis catalysed by a promoted sample did not change. TPR studies have shown<sup>55</sup> that the temperature of CeO<sub>2</sub> reduction decreased in the presence of Co<sub>3</sub>O<sub>4</sub> on the surface of a non-promoted catalyst, while the addition of Ru decreased the reduction temperatures of both Co<sub>3</sub>O<sub>4</sub> and CeO<sub>2</sub> due to hydrogen spillover. As a result, the surfaces of Ru-promoted contacts contained more Co<sup>0</sup> particles than non-promoted samples, which increased their catalytic activities.

It has been shown<sup>56</sup> that introduction of 0.2% ruthenium, platinum or palladium strongly affected the catalytic and physicochemical properties of 10% Co/SiO<sub>2</sub> prepared from a cobalt acetate–cobalt nitrate mixture. According to the extent of carbon monoxide conversion (%) in the methanation reaction (240 °C, 1 atm, H<sub>2</sub>: CO = 2), all the catalysts of this series can be arranged in the following order: Co–Ru (72) > Co–Pd (58) > Co–Pt (50) > Co (34) > Ru (3). It is noteworthy that the turnover number of the most reactive Co–Ru-sample ( $12.7 \times 10^{-2} \text{ s}^{-1}$ ) exceeded that of the monometallic Co-catalyst ( $9.3 \times 10^{-2} \text{ s}^{-1}$ ). For the Co–Pt- and Co–Pd-contacts, the turnover numbers are equal to  $4.2 \times 10^{-2}$  and  $5.9 \times 10^{-2} \text{ s}^{-1}$  respectively.

The higher activity of the Co–Ru-contact in comparison with a monometallic sample was attributed<sup>56</sup> to the increase in the extent of cobalt reduction (from 50% to 100%) upon promotion by Ru and the increase in the size of Co crystallites from 12 to 13 nm. In Pt- and Pd-promoted cobalt catalysts, the extent of cobalt reduction also increased to 56% and 53%, respectively, but the size of crystallites decreased to 4 and 6 nm. IR spectroscopic studies have shown that CO adsorption on Co–Ru-catalysts is of a bridging type (an intense band at 1950 cm<sup>-1</sup>). It was suggested<sup>56</sup> that the bridge form exceeds the linear form in reactivity. High catalytic activity of the Co–Ru-contact can be explained by the increase in the number of bridging-type CO-absorbing sites. In the bridge form, carbon monoxide readily dissociates into carbon and oxygen.

Nb<sub>2</sub>O<sub>5</sub> prepared by calcination of niobic acid in an air flow (550 °C, 2 h) was used as a support for cobalt-containing catalysts.<sup>33</sup> Samples containing 5% Co and 0.6% ruthenium or rhenium were prepared by co-impregnation of niobium oxide with aqueous solutions of cobalt nitrate and the corresponding metal chlorides. Hydrocarbons were synthesised at 220 °C, 1 atm and H<sub>2</sub>: CO = 2. Promotion of Co-catalysts by ruthenium or rhenium increased the selectivity of synthesis of liquid hydrocarbons C<sub>5+</sub> from 55% to 60% and 81%, respectively. The selectivity of methane formation on a Co–Ru-contact decreased from 10% to 3.5% in comparison with the monometallic sample. However, the introduction of Pd, Pt and Rh into the catalyst Co/Nb<sub>2</sub>O<sub>5</sub> increased its activity in the Fischer–Tropsch synthesis in parallel with the increase in the selectivity of formation of liquid hydrocarbons and lower alcohols (MeOH, EtOH).<sup>57</sup> TPR and XPS studies of this effect revealed that promotion by noble metals

favours the reduction of Co<sup>3+</sup> and Co<sup>2+</sup> phases on the catalyst surface.

It is important to note that cobalt catalysts promoted by noble metals can be regenerated directly in the reactor in the course of operation.<sup>58,59</sup> At 200 °C, 5.5 atm and the volume velocity of synthesis gas of 1200 h<sup>-1</sup> (volume velocity is the volume of a gas that has passed through a unit of catalyst volume per unit time), the extent of conversion of carbon monoxide on Co–Ru/TiO<sub>2</sub> was 26% for the atomic ratio Co:Ru of 10–400, while the selectivity with respect to liquid hydrocarbons was 85.7%. Regeneration of the deactivated catalyst with hydrogen was performed in the same reactor at 190–260 °C which provided a 90%–100% recovery of the catalytic activity. This is of considerable practical importance, since large capacities of modern reactors for conducting large-scale Fischer–Tropsch syntheses create inevitable problems connected with the loading/unloading of the catalysts in the course of their regeneration.

It may be concluded from these data that introduction of noble metals into Co-catalysts significantly increases their activities and selectivities in the Fischer–Tropsch synthesis. Physicochemical studies have shown that introduction of noble metals (or Re) into bimetallic cobalt catalysts facilitates reduction of surface oxide phases and increases the extent of reduction and/or dispersity of cobalt independently of the preparation procedure (impregnation or ion exchange),<sup>50–52</sup> cobalt source (carbonyl, nitrate, acetate, etc.),<sup>60,61</sup> the nature of supports and activation conditions.<sup>47, 62</sup>

The mechanism of this promoting effect is not clearly understood yet. Neither do the above-described data provide explicit evidence in favour of one of the two mechanisms underlying this effect, *viz.*, hydrogen spillover from a noble metal to cobalt (see Refs 19–24, 28, 31 and 32) or direct interaction between metals resulting in the formation of bimetallic particles.<sup>25–27</sup> Let us consider these mechanisms in more detail.

#### IV. Mechanisms of promotion of cobalt catalysts by noble metals and rhenium

The phenomenon of hydrogen spillover on Al<sub>2</sub>O<sub>3</sub> and SiO<sub>2</sub> coated with platinum, rhodium, rhenium and nickel is well established.<sup>63–66</sup> Spillover represents migration of hydrogen atoms from one adsorption site to another across the surface. Depending on conditions, the migrating hydrogen exists as H<sup>+</sup>, H<sup>-</sup> and H<sup>•</sup>. There is evidence that the spillover rate of activated hydrogen atoms depends on the state of the surface which is the hydrogen acceptor. In particular, this depends on the degree of hydroxylation of the support surface and increases markedly following preliminary adsorption of water. It is believed that the surface OH-groups form bridges through which the atomic hydrogen migrates to the adsorption sites of a support. Alternatively, it is water molecules that create the active sites enabling additional spillover.

The effect of rhenium on the reduction of a catalyst Co/Al<sub>2</sub>O<sub>3</sub> was studied using TPR.<sup>31</sup> Treatment of Co–Re/Al<sub>2</sub>O<sub>3</sub> with water and drying at 97 °C favours its reduction owing to hydrogen spillover from rhenium to cobalt oxide. In the authors' opinion, the magnitude of the promoting effect of Re depends on the efficiency of hydrogen transport from the reduced promoter to cobalt oxide. To test this hypothesis, Co/Al<sub>2</sub>O<sub>3</sub> and Re/Al<sub>2</sub>O<sub>3</sub> mixtures were prepared by two different methods, *viz.*, mechanical mixing of sample powders and fine grinding to a state where the particle size was smaller than the size of the original particles. TPR analysis showed that the extent of cobalt reduction increased upon direct interaction of metal particles which can be achieved if the second preparation procedure is used. The TPR spectrum of the bimetallic catalyst prepared by mechanical mixing was similar to that of the monometallic catalyst except that the former contained an additional peak at 447 °C corresponding to the reduction of rhenium oxides. Thus, rhenium has no effect on the extent of cobalt reduction.

The promoting effect of rhenium was observed for the catalysts prepared by fine grinding. The TPR spectra of mono- and bimetallic samples differed in that the peak at 727 °C of a Co/Al<sub>2</sub>O<sub>3</sub> sample corresponding to reduction of the cobalt–aluminate surface phase was shifted by 200 °C towards the low-temperature region upon addition of Re, while the 927 °C peak characteristic of CoAl<sub>2</sub>O<sub>4</sub> reduction was absent. This suggests that cobalt reduction on modified catalysts occurs more smoothly due to hydrogen spillover from metallic rhenium to cobalt oxide.<sup>31</sup>

However, other investigators (see Refs 25–27, 67–70) explain also the promoting effects of noble metals on Co-catalysts by the formation of reactive bimetallic particles on the catalyst surface. Let us consider the mechanism of formation of some bimetallic Co catalysts promoted by Group VIII metals.

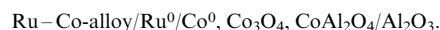
A series of Co–Rh-catalysts on various supports (Al<sub>2</sub>O<sub>3</sub>, SiO<sub>2</sub> and TiO<sub>2</sub>) were examined using TPR and thermoprogrammed oxidation (TPO).<sup>25–27</sup> Bimetallic catalysts prepared by co-impregnation of supports with the corresponding metal salts are reduced at lower temperatures in comparison with their monometallic counterparts independently of the nature of the support and of whether they underwent preliminary calcination or not. Thus, rhodium catalysed the reduction of both the salt and cobalt oxide, although the nature of the support is also important. Thus the catalyst Co/Al<sub>2</sub>O<sub>3</sub> forms spinel-like compounds of the CoAl<sub>2</sub>O<sub>4</sub> type that are difficult to reduce; in Co/SiO<sub>2</sub> catalysts, complete reduction of cobalt ions occurred; the formation of a mixed oxide CoRh<sub>2</sub>O<sub>4</sub> was recorded on TiO<sub>2</sub>. Notwithstanding, van't Blik *et al.*<sup>25–27</sup> have developed a general model of structural changes in these catalysts under different pretreatment regimes (Fig. 9). This model has got the name 'a cherry pit model'.

Within the framework of this model, after impregnation of a support (TiO<sub>2</sub>, SiO<sub>2</sub> or Al<sub>2</sub>O<sub>3</sub>) with salts [RhCl<sub>3</sub> or Co(NO<sub>3</sub>)<sub>2</sub>] cobalt and rhodium ions occupy adjacent positions. The outer layers of bimetallic Co–Rh-particles formed upon reduction are enriched with Co<sup>0</sup>, whereas the kernels ('cherry pits') consist predominantly of metallic rhodium. If Al<sub>2</sub>O<sub>3</sub> is used as a support, cobalt partly reacts with Al<sub>2</sub>O<sub>3</sub> before Co–Rh-particles are formed; the resulting spinel CoAl<sub>2</sub>O<sub>4</sub> is not reduced even at 500 °C.

Although the structures of bimetallic particles remain unchanged upon passivation of the reduced catalysts, Co<sup>0</sup> is oxidised to a significantly greater extent than rhodium as a result of which a rhodium-enriched 'cherry pit' appears to be covered with cobalt oxide. Thus, passivated Co–Rh-particles consist of a

rhodium core and a cobalt oxide shield (see Fig. 9). Complete oxidation of the catalyst brings about structural changes in bimetallic particles, resulting in the formation of adjacent metal oxides. Thus, Rh<sub>2</sub>O<sub>3</sub> localised on the catalyst surface becomes fully exposed.

Unlike rhodium, the ruthenium component of bimetallic catalysts may come into contact with cobalt to yield alloys. Studies by XPS and mass spectrometry of Co–Ru-catalysts and secondary ions revealed<sup>67</sup> that the state of metals, their surface concentrations and distribution across the layer depend on the nature of the support used (Al<sub>2</sub>O<sub>3</sub> or SiO<sub>2</sub>). This can be explained by different dispersities of the metal particles and different types of interactions, metal–support and metal–metal. For example, mass spectra of samples on an Al<sub>2</sub>O<sub>3</sub> support contain peaks with the mass numbers (*m/z*) 86, 102 and 129, which correspond to the clusters CoAl<sup>+</sup>, CoAlO<sup>+</sup> and CoAl<sub>2</sub>O<sup>+</sup>, thus suggesting the formation of surface aluminates. The reduced cobalt reacts with Ru<sup>0</sup> to form Ru–Co microcrystallites as can be judged from the appearance in their mass spectra of a peak with *m/z* 160 assigned to the cluster RuCo<sup>+</sup>. Based on these data, the authors have developed a layer-by-layer model for the Co–Ru-catalyst:<sup>67</sup>



An alternative model for the formation of bimetallic catalysts has been proposed.<sup>68–70</sup> The structures of the contacts Pt–Co/Al<sub>2</sub>O<sub>3</sub> and their catalytic activities in the Fischer–Tropsch synthesis were studied by TPR and XPS. The catalysts prepared by impregnation of alumina with Co(NO<sub>3</sub>)<sub>2</sub> and H<sub>2</sub>PtCl<sub>6</sub> possessed variable compositions Pt<sub>1–x</sub>Co<sub>x</sub>/Al<sub>2</sub>O<sub>3</sub> (total metal content was 10%) and were active as regards the synthesis of hydrocarbons and alcohols from CO and H<sub>2</sub>. Methanol was mainly formed on samples where the platinum content exceeded that of cobalt (Pt > Co); for Co > Pt, hydrocarbons and higher alcohols were the main reaction products.

Studies of monometallic Co-catalysts revealed that mild (297 °C, 1 h) calcination of cobalt nitrate results in its conversion into [Co(III) and Co(II)] oxides. Part of CoO formed a highly dispersed difficult-to-reduce phase on the surface of the support (Al<sub>2</sub>O<sub>3</sub>), predominantly as a monolayer. With an increase in the cobalt content in the catalyst, Co<sub>3</sub>O<sub>4</sub> crystallites are predominantly formed.

Hydrogenation of a monometallic Co-sample at 300 °C yields only CoO. Reduction of a platinum-promoted catalyst under similar conditions converts Co<sub>3</sub>O<sub>4</sub> into Co<sup>0</sup>. The cobalt surface phase (CSP), which is firmly bound to Al<sub>2</sub>O<sub>3</sub>, is not reduced even in the presence of Pt.

Two mechanisms of surface conversions at different molar ratios of Pt and Co (Pt > Co and Co > Pt) have been pro-

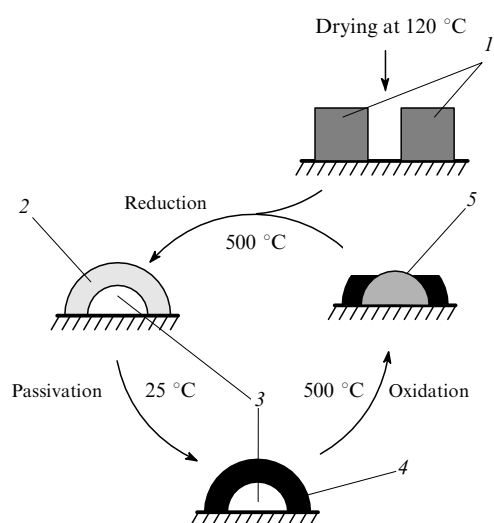


**Figure 9.** A model of formation of a Co–Rh-catalyst.<sup>25,27</sup>

(1) RhCl<sub>3</sub> + Co(NO<sub>3</sub>)<sub>2</sub>, (2) Co-enriched shell, (3) Rh-enriched core, (4) Co<sub>3</sub>O<sub>4</sub>, (5) Rh<sub>2</sub>O<sub>3</sub>.

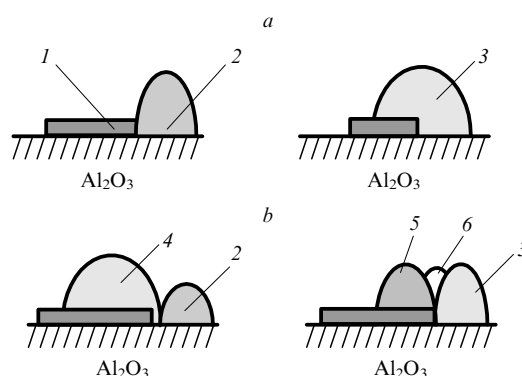


**Figure 10.** Conversion of Pt- and Co-phases on the surface of the contact Pt–Co/Al<sub>2</sub>O<sub>3</sub> upon its reduction at different ratios of the metals: Pt > Co (a) and Co > Pt (b).<sup>68,70</sup>

(1) CPS, (2) Pt ions, (3) Pt<sup>0</sup>, (4) cobalt oxide, (5) Co<sup>0</sup>, (6) bimetallic phase Co<sup>0</sup>–Pt<sup>0</sup>.



posed<sup>68–70</sup> (Fig. 10). In the first case, the surface Co monolayer is formed upon calcination (CSP), whereas platinum ions exist as particles of a fairly large size. CSP is not reduced upon treatment of the catalyst with hydrogen (300 °C, 1 h), but becomes partly covered by Pt<sup>0</sup> formed upon conversion of platinum ions.

In the second mechanism ( $\text{Co} > \text{Pt}$ ), calcination of the catalyst yields CSP, platinum ions and  $\text{Co}_3\text{O}_4$ . Under mild conditions ( $300^\circ\text{C}$ ), no reduction of CSP takes place, but Pt ions and cobalt oxide are reduced to  $\text{Pt}^0$  and  $\text{Co}^0$ , respectively, and the metal particles interact. It was supposed<sup>68-70</sup> that partial shielding of Pt by metallic cobalt and formation of a bimetallic phase ( $\text{Co}^0-\text{Pt}^0$ ) occurs.

The formation of Co–Pt particles was confirmed by EXAFS (Extended X-Ray Absorption Fine Structure) and X-ray diffraction analysis of Pt<sub>0.6</sub>Co<sub>0.4</sub> samples.<sup>71</sup> The size of Co–Pt-particles in this catalyst was 15 nm (*cf.* ~11 nm in the Pt<sub>0.5</sub>Co<sub>0.5</sub> contact). Additional evidence in favour of formation of Co–Pt-particles on the surface of the PtCo<sub>x</sub>/Al<sub>2</sub>O<sub>3</sub> catalysts ( $x = 0-0.67$ ) was obtained using XPS.<sup>72</sup>

As a matter of fact, the two models of formation of the Co–Rh catalysts, which imply appearance of different types of bimetallic particles, are essentially similar. Whereas the ‘cherry pit’ model<sup>25–27</sup> suggests the presence of a core consisting of metallic rhodium and an outer shell enriched with cobalt, in the second model metallic cobalt particles partly shield reduced platinum to form a Co<sup>0</sup>–Pt<sup>0</sup> interface (see Refs 69 and 70).

A model for active sites formation in the catalysts Co/SiO<sub>2</sub> promoted by noble metals (Pd, Pt, Rh, Ru) has been developed by Lapidus *et al.*<sup>34</sup> According to the previously postulated mechanism of hydrocarbon synthesis from CO and H<sub>2</sub> in the presence of Co-catalysts,<sup>16,73,74</sup> the synthesis of liquid hydrocarbons occurs on a bifunctional active site, *i.e.*, a polymerisation site. This site is localised at the interface between metallic cobalt and the oxide (the latter behaves as a Lewis acid). The electron density of cobalt ions in such a site is shifted towards the oxide, as a result of which the metal acquires a partial positive charge ( $\delta^+$ ).

Some characteristics of oxide phases on the surfaces of reduced catalysts were obtained by TPR of samples following preliminary reduction under isothermal conditions (TPRPR) (Table 1). As can be seen, the TPR spectrum of a Co/SiO<sub>2</sub> sample following reduction at 450 °C contains four signals with  $T_{\text{max}} = 127, 210, 388$  and  $561$  °C. The second and the third peaks correspond to the reduction of underreduced Co<sup>2+</sup> ions and Co<sub>3</sub>O<sub>4</sub>, respectively. It is known that the latter manifests the properties of a Lewis acid. The high-temperature peak corresponds to the reduction of mixed Co-support oxides, while the low-temperature signal with  $T_{\text{max}} = 127$  °C corresponds to the easily oxidisable species Co<sup>δ+</sup>, which represents a constituent of the polymerisation site. Its oxidation can occur under the action of, *e.g.*, water released in the course of reduction. Thus, the polymerisation site is predominantly localised at the Co<sup>δ+</sup>-Co<sub>3</sub>O<sub>4</sub> interface on the surface of a reduced catalyst Co/SiO<sub>2</sub>.<sup>34</sup>

The addition of platinum increases the concentrations of both  $\text{Co}^{\delta+}$  (manifested in the appearance of an additional peak in the low-temperature region I) and  $\text{Co}_3\text{O}_4$ , the acidic component of the

bifunctional centre (see Table 1), that is, increases the number of polymerisation sites. The yield of liquid hydrocarbons increases from 118 (in the case of a non-promoted sample) to 139 g m<sup>-3</sup>, while the selectivity of their formation in the Fischer–Tropsch synthesis increases from 76% to 81%.<sup>34,75</sup>

The content of  $\text{Co}_3\text{O}_4$  in Co–Pd-catalysts decreased (the peak at 406 °C was characterised by  $S = 28\%$ ). In this case, the oxide phases were largely represented by  $\text{Co}^{2+}$  and  $\text{CoO} \cdot x\text{H}_2\text{O}$  species, which did not manifest the properties of Lewis acids. This circumstance might account for the relatively low activity of these catalysts in the synthesis of liquid hydrocarbons  $\text{C}_{5+}$  (the yields of  $\text{C}_{5+}$  decreased to  $82 \text{ g m}^{-3}$  and the selectivity, to 60%).

The introduction of rhodium into the contacts  $\text{Co/SiO}_2$  had no effect on the content of  $\text{Co}^{8+}$  (the total area of the low-temperature peaks in their TPR spectra was 10%, see Table 1), whereas that of  $\text{Co}_3\text{O}_4$  increased from 33 (in the case of the non-promoted sample) to 40%. The ratios of metallic and oxide phases in the bifunctional centre changed thereby with a concomitant increase in the catalytic activity. However, the oxide phases of  $\text{Co-Rh}$  contain predominantly  $\text{Co(II)}$  and  $\text{CoO} \cdot x\text{H}_2\text{O}$  (the total area of the peaks in regions II and III is 49%). This may be the reason for the lower selectivity of this catalyst as regards synthesis of liquid hydrocarbons (72%) in comparison with the monometallic sample ( $\text{Co/SiO}_2$ ).

The concentration of  $\text{Co}^{\delta+}$  on the surface of Co–Ru-samples ( $S = 5\%$ ) is twice as low as that in monometallic Co-catalysts (12%). Nevertheless, it is quite probable that high content of  $\text{Co}_3\text{O}_4$  (53%) significantly increases the probability of formation of catalytic sites of the type  $\text{Co}^{\delta+} - \text{Co}_3\text{O}_4$ . As a consequence, the yields of liquid hydrocarbons on Co–Ru-catalysts were only somewhat higher ( $129 \text{ g m}^{-3}$ ), while the selectivity of their formation was virtually the same (77%) in comparison with monometallic samples.

It may thus be concluded that the introduction of noble metals into monometallic cobalt catalysts changes the mode of formation of their active surfaces.<sup>16, 34</sup> Hydrogenation of Co-M/SiO<sub>2</sub> (M = Pt, Pd, Rh, Ru) brings about the formation, on their surface, of bifunctional centres (Co<sup>δ+</sup> - Co<sub>3</sub>O<sub>4</sub>), which play the role of polymerisation sites in the Fischer-Tropsch syntheses.

\* \* \*

The data presented above provide an illustrative example of the interest of investigators in the study of bimetallic Co-containing catalysts for the synthesis of hydrocarbons from CO and H<sub>2</sub> and in the elucidation of mechanisms of their promotion by noble metals and rhenium.

In summary, the following conclusions can be made. The introduction of platinum-containing metals into Co-catalysts facilitates the reduction of cobalt derivatives and increases their catalytic activities. There is still no consensus, however, concerning the reasons for the promoting effect of rhenium for Co-catalysts. Some authors hold the opinion<sup>31,32</sup> that, similar to noble metals, rhenium facilitates reduction of the cobalt oxide phases on the surface of the catalysts by hydrogen spillover from rhenium to cobalt, while other authors suggest<sup>33</sup> that Re increases

**Table 1.** Temperatures of the peaks ( $T$ ) and their relative areas ( $S$ ) obtained by deconvolution of the TPR spectra of the reduced catalysts Co–M/SiO<sub>2</sub> (I–V are the temperature regions where hydrogen adsorption takes place).

| Promoter         | I                    |         |                      |         |                      |         | II                   |         | III                  |         | IV                   |         | V                    |         |
|------------------|----------------------|---------|----------------------|---------|----------------------|---------|----------------------|---------|----------------------|---------|----------------------|---------|----------------------|---------|
|                  | $T/^{\circ}\text{C}$ | $S(\%)$ | $T/^{\circ}\text{C}$ | $S(\%)$ | $T/^{\circ}\text{C}$ | $S(\%)$ | $T/^{\circ}\text{C}$ | $S(\%)$ | $T/^{\circ}\text{C}$ | $S(\%)$ | $T/^{\circ}\text{C}$ | $S(\%)$ | $T/^{\circ}\text{C}$ | $S(\%)$ |
| Without promoter | —                    | —       | 127                  | 12      | —                    | —       | 210                  | 27      | —                    | —       | 388                  | 33      | 561                  | 28      |
| Pt               | 47                   | 9       | 128                  | 7       | —                    | —       | 186                  | 11      | 274                  | 23      | 381                  | 49      | —                    | —       |
| Pd               | 78                   | 1       | 110                  | 2       | 147                  | 18      | 201                  | 15      | 248                  | 33      | 406                  | 28      | 499                  | 4       |
| Rh               | 70                   | 1       | 117                  | 2       | 144                  | 7       | 198                  | 16      | 257                  | 33      | 431                  | 40      | 516                  | 1       |
| Ru               | —                    | —       | 118                  | 5       | —                    | —       | 209                  | 39      | —                    | —       | 415                  | 53      | 553                  | 3       |

the dispersity of cobalt and diminishes the size of Co crystallites without any effect on reduction.

Thus, there are several viewpoints concerning the mechanisms of action of Group VIII metal-promoted cobalt catalysts in the synthesis of hydrocarbons from CO and H<sub>2</sub>. This problem may be solved in the near future through wide purpose-oriented application of modern physicochemical methods.

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# Nanotubes and related nanostructures of d-metal oxides: synthesis and computer design

G S Zakharova, V L Volkov, V V Ivanovskaya, A L Ivanovskii

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**Abstract.** State-of-the-art studies on the synthesis, properties and the computer design of nanotube forms of transition metal oxides are analysed. Main methods for the preparation of oxide nanotubes and related quasi-one-dimensional nanostructures (nanobundles, nanoribbons, *etc.*) are discussed. Data on the morphology and physicochemical properties of these materials and prospects for their technological applications are summarised. The results of the computer design of atomic structures and results of quantum-chemical calculations of electronic structures and chemical bond parameters of Ti, V and Mo oxide nanotubes and their fullerene-like molecules are considered. The bibliography includes 427 references.

## I. Introduction

The discovery (in 1991) of quasi-one-dimensional (1D) nanostructures, *viz.*, carbon nanotubes (NT),<sup>1</sup> and the design of nanomaterials with unique properties<sup>2–28</sup> have stimulated theoretical and experimental studies aimed at searching for and preparing analogues of such materials based on other simple substances and inorganic compounds. The advances made in this field by the early 20th century have been covered in reviews.<sup>29–39</sup>

Nanotubes of numerous inorganic compounds were synthesised. Nanotubes of  $\text{MoS}_2$ ,<sup>40</sup> other layered d-metal dichalcogenides  $\text{MX}_2$  ( $\text{M} = \text{Mo}, \text{W}$  or  $\text{Ta}$ ;  $\text{X} = \text{S}$  or  $\text{Se}$ )<sup>41–55</sup> and hexagonal boron nitride (BN), boron carbide ( $\text{BC}_x$ ) and boron carbonitride ( $\text{B}_x\text{C}_y\text{N}_z$ ) were among the first to be prepared.<sup>56–63</sup> Nanotube forms of numerous chalcogenides were synthesised:  $\text{InS}$ ,<sup>64</sup>  $\text{ZnS}$ ,<sup>65</sup>  $\text{Bi}_2\text{S}_3$ ,<sup>66</sup>  $\text{ReS}_2$ ,<sup>67</sup>  $\text{W}_x\text{Mo}_y\text{C}_z\text{S}_2$ ,<sup>68</sup>  $\text{ZrS}_2$ ,  $\text{HfS}_2$ ,<sup>69,70</sup>  $\text{NbSe}_2$ ,<sup>71–73</sup>  $\text{TiS}_2$ ,  $\text{TiSe}_2$ ,<sup>74–76</sup>  $\text{MoTe}_2$ ,<sup>77</sup>  $\text{WSe}_2$ ,<sup>78</sup>  $\text{MoS}_{2-x}\text{I}_y$ ,<sup>79</sup>  $\text{CdS}$ ,  $\text{CdSe}$ ,<sup>80,81</sup>  $\text{Ag}_2\text{S}$ <sup>82</sup> and  $\text{Li}_2\text{MoS}_2$ .<sup>83</sup> The synthesis of  $\text{NiCl}_2$  nanotubes was also documented.<sup>84–86</sup> Tubular forms of semiconducting materials, such as  $\text{SiGe}$ ,  $\text{InAs/GaAs}$ ,  $\text{InGaAs/GaAs}$ ,  $\text{SiGe/Si}$  and  $\text{InGeAs/GaAs}$ ,<sup>87–89</sup> are also known.

Cobalt,<sup>90</sup> antimony,<sup>91</sup> tellurium<sup>92–94</sup> and bismuth<sup>95–97</sup> nanotubes were synthesised. The atomic structures, electronic

properties, stability factors and possible procedures for the preparation of nanotubes of metals ( $\text{Na}$ ,  $\text{Cu}$ ,<sup>98</sup>  $\text{Ni}$ ,<sup>99</sup>  $\text{Ag}$ ,  $\text{Au}$ <sup>100,101</sup> and  $\text{Bi}$ <sup>102,103</sup>), boron,<sup>104</sup> silicon,<sup>105</sup> metal diborides  $\text{MB}_2$  ( $\text{M} = \text{Mg}, \text{Al}, \text{Sc}, \text{Ti}$  and  $\text{Zr}$ ),<sup>106–110</sup>  $\text{CaSi}_2$ ,<sup>111</sup> ternary silicides with  $\text{AlB}_2$ :  $\text{Sr}(\text{Ga}_x\text{Si}_{1-x})_2$  and  $\text{Ca}(\text{Al}_x\text{Si}_{1-x})_2$  structures,<sup>112</sup> layered metal halide nitrides  $\beta\text{-MNX}$  ( $\text{M} = \text{Zr}$  or  $\text{Hf}$ ;  $\text{X} = \text{Cl}$  or  $\text{Br}$ )<sup>113</sup> and high-temperature superconducting complex ceramics<sup>114</sup> were theoretically predicted.

In recent years, p-, d- and f-metal ( $\text{Al}$ ,  $\text{Ge}$ ,  $\text{Ti}$ ,  $\text{Nb}$ ,  $\text{Ta}$ ,  $\text{Zr}$ ,  $\text{V}$ ,  $\text{Mo}$ ,  $\text{Dy}$ ,  $\text{Tb}$ , *etc.*) oxides, along with the above-mentioned substances and compounds, have found wide application in the design of nanostructured functional materials as films, nanorods, mesoporous systems, nanoclusters and nanocrystallites and their various associates. Some of these nanosized materials can be prepared with the use of carbon nanotubes. For example, these compounds can be prepared as nanofibres and nanotubular ceramics by filling inner (and intertubular) cavities in carbon tubes (or their bundles) with oxides  $\text{V}_2\text{O}_5$ ,  $\text{MoO}_3$ ,  $\text{PbO}$  or  $\text{Bi}_2\text{O}_3$  followed by the removal of the carbon shell by chemical methods. The design of various nanocomposites based on or involving metal oxides has attracted considerable attention.

One of the main lines of investigation of nanostructured metal oxides is the preparation of their nanotube forms. Phases, which have (like graphite) layered (quasi-two-dimensional, 2D) structures and are characterised by pronounced anisotropy of interatomic interactions, are generally considered as substances or compounds promising for the preparation of such tubular forms.<sup>6–9, 18, 29–39</sup> The anisotropy of interatomic interactions is determined by a combination of strong covalent (or covalent-ionic) bonds and weak van der Waals interactions between the layers. These structural features and characteristics of chemical bonding are less typical of metal oxides than, for example, of d-element dichalcogenides. Hence, methods for the preparation of metal oxide nanotubes have essential distinguishing features and often produce hollow nanotubes along with a broad range of other quasi-one-dimensional nanostructures (nanorods, nanoribbons, *etc.*)

It should be noted that data on the synthesis, structures, properties and fields of application of carbon NT are summarised in monographs<sup>3–7</sup> and numerous reviews,<sup>8–32</sup> whereas publications, in which the results of studies of non-carbon nanotubes were generalised, are scarce<sup>29–39</sup> and were devoted primarily to the most well-studied groups of such materials, *viz.*, nanotubes (and fullerene-like clusters) of graphite-like boron nitrides, carbides and carbonitrides and d-metal dichalcogenides. Selected results of the synthesis and investigations of oxide NT were included in the reviews.<sup>37,38</sup> The review<sup>39</sup> dealt with practical procedures for the

G S Zakharova, V L Volkov, V V Ivanovskaya, A L Ivanovskii Institute of Solid State Chemistry, Urals Branch of the Russian Academy of Sciences, ul. Pervomaiskaya 91, 620219 Ekaterinburg, Russian Federation. Fax (7-343) 374 44 95, tel. (7-343) 349 30 09, e-mail: volkov@ihim.uran (G S Zakharova, V L Volkov), tel. (7-343) 349 33 87, e-mail: viktoria@ihim.uran.ru (V V Ivanovskaya), tel. (7-343) 374 53 31, e-mail: ivanovskii@ihim.uran.ru (A L Ivanovskii)

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preparation and modelling of titanium and vanadium oxide nanotubes.

In the present review, we consider the state-of-the art studies of all known nanotube forms of transition metal oxides. Main methods for the preparation of oxide nanotubes and related quasi-one-dimensional nanostructures (nanofibres, nanorods, nanoribbons, *etc.*) are summarised. Data on the morphology and physicochemical properties of such materials are discussed. The possible fields of technological applications are considered. The results of computer design of atomic structures and quantum-chemical calculations of electronic structures and chemical bond parameters of Ti, V and Mo oxides nanotubes and related fullerene-like molecular clusters are analysed.

It should be noted that the known nanotube forms of oxides are not limited to transition metal oxides considered below. Nanotubes and nanotube composites of p-element (aluminium, silicon and gallium) oxides have attracted considerable attention.<sup>115–125</sup> The studies aimed at synthesising nanotubes of f-element oxides (for example,  $\text{Tb}_2\text{O}_3$ <sup>126</sup> and  $\text{Dy}_2\text{O}_3$ <sup>127</sup>) are presently underway. However, data on the structures and properties of 1D forms of these oxides are scarce, and analysis of such materials is beyond the scope of the present review.

## II. Synthesis and properties of nanotubes and related nanostructures of metal oxides

The classification of nanosized materials used in the literature and their principal geometric parameters are given in Table 1. Nowadays, the main lines of investigation of nanostructured metal

**Table 1.** Structural types of nanosized materials and their geometric parameters.

| Structural type        | Description <sup>a</sup>                                                                                                                                  |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nanotubes              | tubular structures with an outer diameter of up to 100 nm, $L < 1 \mu\text{m}$                                                                            |
| Nanorods               | quasi-one-dimensional cylindrical structures, $D < 100 \text{ nm}$ , $L < 1 \mu\text{m}$                                                                  |
| Nanowire               | the same, $D < 100 \text{ nm}$ , $L > 1 \mu\text{m}$                                                                                                      |
| Nanofibres             | threads, $D \leq 50 \text{ nm}$ , $L > 1 \mu\text{m}$                                                                                                     |
| Nanoparticles          | compact particles, $D < 10 \text{ nm}$                                                                                                                    |
| Nanopowder             | the same, $D < 100 \text{ nm}$                                                                                                                            |
| Nanodots               | crystals with sizes up to 100 nm                                                                                                                          |
| Nanowhiskers           | needle-like structures with a length of several millimetres and a base thickness of $< 100 \text{ nm}$                                                    |
| Nanoribbons            | structures as planar ribbons with a thickness of up to 100 nm and a width larger than the thickness                                                       |
| Nanocolumns            | nanostructures with $D \leq 100 \text{ nm}$ , $L > D$                                                                                                     |
| Nanocable              | structures with a morphology of a coaxial cable, $D \leq 100 \text{ nm}$                                                                                  |
| Nanobridges            | structures with a morphology analogous to a bridge construction with a length of tens of micrometers containing 'details' with a diameter of up to 100 nm |
| Nanonails              | nail-like structures, $D \leq 100 \text{ nm}$                                                                                                             |
| 4(6)-Fold nanorotors   | nanostructures as four(six)-blade rotors; the constituent diameter is up to 100 nm                                                                        |
| Tetrapod nanostructure | nanostructures consisting of four nanorods ( $D \leq 100 \text{ nm}$ ) sharing a centre                                                                   |
| Nanocomposite          | material consisting of particles of different compounds with sizes up to 100 nm                                                                           |

<sup>a</sup>  $D$  is the diameter,  $L$  is the length.

oxides are as follows: the development of methods for their synthesis and study of the morphology and physicochemical characteristics of the products. Progress in the synthesis of oxide nanotube materials with reproducible properties determines to a large extent the prospects of their practical use.

Modern investigations of nanotubular oxides and related materials are aimed at developing and improving particular synthetic schemes and extending the range of oxides, whose nanotube forms can be prepared. In most original publications, procedures for the preparation of nanotubes of a particular oxide and their selected characteristics (generally, the elemental composition, the morphology and the structural parameters) were reported. Experimental data accumulated in this new field do not allow one to reveal general regularities of the formation of particular nanostructures and decide which methods for their synthesis are most efficient and universal. Hence, in the present review, we summarise methods for the preparation of nanotubular oxides and related quasi-one-dimensional forms. A comparison and critical analysis of these methods are beyond the scope of this review.

Modern methods for the preparation of nanosized forms of simple and complex oxides can be classified into two main groups, *viz.*, chemical and template methods. The chemical synthesis involves the spontaneous formation of nanostructures in reactions of the starting reagents existing in different states (aqueous or aqueous-organic media, solid or vapour phases, during thermolysis of salts, *etc.*). The template method is based on the formation of nanostructures on the surfaces of solid materials (organic and inorganic), which dictate the size and morphology of the reaction products. In particular, organic molecules can serve as templates. Such molecules are inserted into layered structures of oxides, thus making it possible to change the form of nanotubes in their synthesis. Among these methods, vapour condensation of oxides and their electrochemical deposition also hold promise.

Below we consider methods for the synthesis and properties of three main groups of 1D nanostructures formed by first-, second- and third-row transition metal oxides. Main data on their compositions and morphology are given in Table 2.

### 1. Nanostructures of 3d4s-metal oxides

#### a. Titanium oxides

Nanosized forms of titanium dioxide can be prepared by both chemical and template methods. Well-crystallised nanotube forms of  $\text{TiO}_2$  can be synthesised by hydrothermal reactions of titanium dioxide (anatase or rutile) powder with an aqueous NaOH solution.<sup>128–134</sup> For various tubes, the O : Ti atomic ratio differs from those observed in crystalline anatase or rutile.<sup>128</sup> Generally, multilayer tubes with an interlayer distance of  $\sim 0.75 \text{ nm}$  and an average diameter ( $D$ ) of  $\sim 9 \text{ nm}$  are produced.<sup>129</sup> The mechanism of their formation involves the rolling-up of the (100) plane of  $\text{H}_2\text{Ti}_3\text{O}_7$  about the [001] direction. The ends of the tubes are open and their walls are corrugated.<sup>134</sup> The morphology of the tubes depends on the size and structure of the starting  $\text{TiO}_2$  nanoparticles.<sup>130</sup>

Ultradispersed rutile with an average particle size of  $7.2 \text{ nm}$  gives longer nanotubes compared to those formed by anatase or large rutile particles. Nanotubes with  $D \approx 8–10 \text{ nm}$  and a length ( $L$ ) of  $\sim 100 \text{ nm}$  were synthesised<sup>131</sup> by keeping  $\text{TiO}_2$  with a specific surface area of  $50 \text{ m}^2 \text{ g}^{-1}$  in a  $10 \text{ M NaOH}$  solution at  $110^\circ\text{C}$  for 20 h. The morphology of the resulting samples depends on the  $\text{TiO}_2$  structure type, and their properties depend on subsequent acid and thermal treatment.<sup>132, 133</sup> For example, after treatment with a  $\text{H}_2\text{SO}_4$  solution followed by annealing at  $300^\circ\text{C}$ ,  $\text{TiO}_2$  nanotubes show high catalytic activity in esterification of cyclohexanol with acetic acid,<sup>132</sup> whereas the starting anatase is inactive in this catalytic process.

Hydrothermal treatment of  $\text{TiO}_2$  powders ( $4.0–18.5 \text{ nm}$ ) in a NaOH solution at  $110^\circ\text{C}$  for 20 h followed by washing with dilute  $\text{HNO}_3$  affords multilayer anatase nanotubes  $500 \text{ nm}$  in length.<sup>133</sup> The use of  $\text{HNO}_3$  instead of  $\text{HCl}$  results in the formation of more

**Table 2.** Main methods of synthesis and morphology of nanostructured transition metal oxides.

| Oxide                                                                                                        | Method of synthesis | Morphology                             | Oxide                                                                | Method of synthesis | Morphology                                |
|--------------------------------------------------------------------------------------------------------------|---------------------|----------------------------------------|----------------------------------------------------------------------|---------------------|-------------------------------------------|
| TiO <sub>2</sub>                                                                                             | chemical            | tubes with $D = 9-12$ nm               | Co <sub>3</sub> O <sub>4</sub>                                       | chemical            | tubes with $D = 200-400$ nm               |
| "                                                                                                            | "                   | rods with $D = (4-6)-(50-100)$ nm      | CoFe <sub>2</sub> O <sub>4</sub>                                     | template            | fibres                                    |
| "                                                                                                            | "                   | wire with $D = 20-200$ nm              | NiO                                                                  | "                   | wire with $D = 50$ nm                     |
| "                                                                                                            | "                   | ribbon with a width of $20-200$ nm     | "                                                                    | "                   | ribbon with a width of $4$ nm             |
| "                                                                                                            | "                   | needles and whiskers with $D = 5-8$ nm | CuO                                                                  | chemical            | wire with $D = 4$ nm                      |
| template                                                                                                     | template            | tubes with $D = 2-70$ nm               | "                                                                    | template            | rods with $D = 8$ nm                      |
| "                                                                                                            | "                   | hollow fibres with $D = 20-50$ nm      | "                                                                    | electrochemical     | tubes with $D = 20-90$ nm                 |
| "                                                                                                            | "                   | rods with $D = 20-30$ nm               | ZnO                                                                  | chemical            | fibres and whiskers with $D = 2-10$ nm    |
| electrochemical                                                                                              | electrochemical     | tubes with $D = 25-120$ nm             | "                                                                    | chemical            | rods with $D = 5-300$ nm                  |
| H <sub>2</sub> Ti <sub>3</sub> O <sub>7</sub>                                                                | chemical            | wire with $D = 40$ nm                  | "                                                                    | "                   | tubes                                     |
| K <sub>2</sub> Ti <sub>8</sub> O <sub>17</sub>                                                               | "                   | rods with $D = 9$ nm                   | "                                                                    | vapour phase        | chiral rods with $D = 500$ nm             |
| Na <sub>2</sub> Ti <sub>4</sub> O <sub>9</sub>                                                               | "                   | ribbons                                | "                                                                    | "                   | wire with $D = 15-80$ nm                  |
| SrTiO <sub>3</sub>                                                                                           | "                   | belts with a width of $100-500$ nm     | "                                                                    | "                   | rods with $D = 15-45$ nm                  |
| BaTiO <sub>3</sub>                                                                                           | "                   | tubes with $D = 8-15$ nm               | "                                                                    | "                   | whiskers with $D = 50-500$ nm             |
| Composite                                                                                                    | "                   | rods with $D = 5-60$ nm                | "                                                                    | "                   | belts                                     |
| TiO <sub>2</sub> /poly-pyrrole (poly-aniline)                                                                | "                   | tubes with $D = 90-130$ nm             | "                                                                    | "                   | bridges                                   |
| TiO <sub>2</sub> /SiO <sub>2</sub>                                                                           | "                   | tubes with $D = 13$ nm                 | "                                                                    | "                   | nails                                     |
| Composite                                                                                                    | template            | wire with $D = 210$ nm                 | "                                                                    | "                   | tadpoles                                  |
| Au/TiO <sub>2</sub>                                                                                          | "                   | tubes with $D = 15-150$ nm             | vapour phase combined with template synthesis                        | "                   | wire with $D = 30-200$ nm                 |
| VO <sub>x</sub> (C <sub>n</sub> H <sub>2n+4</sub> N) <sub>y</sub>                                            | chemical            | tubes with $D = 20-55$ nm              | electrochemical                                                      | "                   | wire with $D = 50$ nm                     |
| VO <sub>x</sub>                                                                                              | template            | tubes with $D = 30-100$ nm             | pyrolysis                                                            | "                   | cable with $D = 60$ nm                    |
| V <sub>0.99</sub> Mo <sub>0.01</sub> O <sub>2.49</sub> · (C <sub>16</sub> H <sub>36</sub> N) <sub>0.27</sub> | chemical            | rods with $D = 30-40$ nm               | composite Zn/ZnO                                                     | "                   | cable                                     |
| γ-LiV <sub>2</sub> O <sub>5</sub>                                                                            | "                   | rods                                   | composite Ga/Ga <sub>2</sub> O <sub>3</sub> /ZnO                     | "                   | "                                         |
| NaV <sub>2</sub> O <sub>5</sub>                                                                              | "                   | wire with $D = 20-200$ nm              | Y <sub>2</sub> O <sub>3</sub>                                        | template            | tubes                                     |
| β-Na <sub>x</sub> V <sub>2</sub> O <sub>5</sub>                                                              | vapour condensation | tubes with $D = 60-100$ nm             | ZrO <sub>2</sub>                                                     | "                   | tubes with $D = 40-50$ nm                 |
| Na <sub>0.26</sub> VO <sub>x</sub>                                                                           | ion exchange        | tubes with $D = 60-100$ nm             | "                                                                    | "                   | tubes with $D = 1.3-5.9$ μm               |
| K <sub>0.27</sub> VO <sub>x</sub>                                                                            | "                   | tubes with $D = 60-100$ nm             | "                                                                    | "                   | tubes with $D = 1.3-5.9$ μm               |
| Cu <sub>0.12</sub> VO <sub>x</sub>                                                                           | "                   | tubes with $D = 60-100$ nm             | Nb <sub>2</sub> O <sub>5</sub>                                       | chemical            | fibres with $D = 20-280$ nm               |
| Fe-VO <sub>x</sub>                                                                                           | "                   | tubes with $D = 60-100$ nm             | MoO <sub>3</sub>                                                     | template            | tubes with $D = 50-300$ nm                |
| Mn <sub>0.1</sub> VO <sub>2.5+δ</sub> · nH <sub>2</sub> O                                                    | "                   | tubes with $D = 60-100$ nm             | "                                                                    | electrochemical     | wire with $D = 40-60$ nm                  |
| CrO <sub>3</sub>                                                                                             | template            | tubes                                  | CdO                                                                  | template            | tubes                                     |
| α-MnO <sub>2</sub>                                                                                           | "                   | fibres                                 | Ta <sub>2</sub> O <sub>5</sub>                                       | "                   | tubes with $D < 2$ μm                     |
| α-Fe <sub>2</sub> O <sub>3</sub>                                                                             | chemical            | hollow fibres with $D = 4-10$ nm       | Sr <sub>0.8</sub> Bi <sub>2.2</sub> Ta <sub>2</sub> O <sub>9+y</sub> | vapour phase        | needles and whiskers with $D = 50-500$ nm |
|                                                                                                              |                     |                                        | WO <sub>x</sub>                                                      | "                   | rods with $D = 20$ nm                     |
|                                                                                                              |                     |                                        | WO <sub>2.9</sub>                                                    | template            | fibres with $D = 20$ nm                   |
|                                                                                                              |                     |                                        | WO <sub>3</sub>                                                      |                     |                                           |

dispersed NT powder. Titanium dioxide nanotubes prepared by the chemical method consist of 2–5 monolayers and have an inner diameter of 4.2–5.9 nm.<sup>135</sup> Such materials with a specific surface area of 379 m<sup>2</sup> g<sup>-1</sup> hold promise in photocatalysis.

Films of oriented TiO<sub>2</sub> NT were prepared by the hydrochemical method (titanium foil, which contained TiO<sub>2</sub> nanoparticles deposited from an aqueous suspension, was subjected to hydrothermal treatment in 10 M NaOH at 95–160 °C).<sup>136</sup> Most of these nanotubes are open and consist of several layers. The outer and inner diameters of NT are 12 and 3.7 nm, respectively. The distance between the layers is 0.78 nm. The nanotubes are characterised by the monoclinic unit cell of H<sub>2</sub>Ti<sub>3</sub>O<sub>7</sub> with the unit cell parameters  $a = 16.03$ ,  $b = 3.75$ ,  $c = 9.19$  Å,  $\beta = 101.45^\circ$ . The most probable<sup>137</sup> composition of these nanotubes is Na<sub>2</sub>Ti<sub>3</sub>O<sub>7</sub>; the Na<sup>+</sup> ions are removed by acid treatment. The distance between the layers in these nanotubes is independent of the number of layers and the inner and outer diameters of TiO<sub>2</sub> NT and is determined by OH<sup>-</sup> groups. Taking into account the Ti–OH bond lengths and the van der Waals radius of the O atom, the interlayer distance should be equal to

0.63 nm, but it increases to 0.8 nm due to repulsion between the OH<sup>-</sup> groups. The sodium cations play a decisive role in structure stabilisation.<sup>138</sup> Unmodified TiO<sub>2</sub> nanotubes exist only in an amorphous state<sup>139</sup> and are destroyed during crystallisation.

Anatase nanotubes prepared under hydrothermal conditions have a high capacity for lithium cations in electrochemical intercalation.<sup>140</sup> The insertion of Li<sup>+</sup> into TiO<sub>2</sub> NT occurs at a voltage of lower than 2.2 V. At a voltage of about 1.7 V, voltammetric curves have a plateau, which indicates that the electrochemical resistance reaches a minimum. These nanostructures were proposed as light-sensitive materials for solar batteries.<sup>141</sup>

Nanosized rods of rutile TiO<sub>2</sub> ( $D = 4-6$  nm,  $L = 50-150$  nm) were prepared<sup>142</sup> in air under atmospheric pressure by the reaction of 15 M HNO<sub>3</sub> with an aqueous TiCl<sub>4</sub> solution (3 mol litre<sup>-1</sup>) with stirring (100–250 °C, 6–24 h). The sizes of nanorods are independent of the temperature and time of hydrolysis. These nanorods belong to the rutile modification and are characterised by the [110] growth direction. Mixing of TiCl<sub>4</sub> and HNO<sub>3</sub> solutions leads to oxolation of the [TiO(OH<sub>2</sub>)<sub>5</sub>]<sup>2+</sup>

complex ion and isolation of rutile as brushes. The anisotropic growth was accounted for by selective absorption of  $\text{Cl}^-$  and  $\text{NO}_3^-$  anions and  $[\text{TiO}(\text{OH})_2]^{2+}$  cations on the (110) and (111) surfaces, respectively.

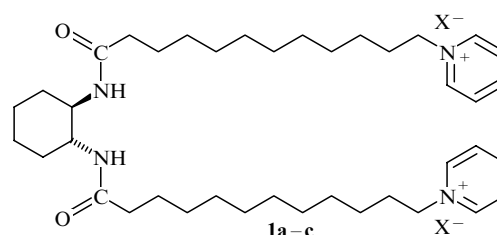
Thermolysis of titanium tetraisopropoxide  $[\text{Ti}(\text{OPr}^i)_4]$  vapour in the presence and in the absence of  $\text{NH}_3$  at 500 °C affords  $\text{TiO}_2$  nanowires ( $D = 50\text{--}100\text{ nm}$ ,  $L = 0.5\text{--}2\text{ }\mu\text{m}$ ) on the WC substrate.<sup>143</sup> Thermolysis at 600 and 400 °C gives nanoparticles and thin films, respectively, of the anatase modification. In the presence of  $\text{NH}_3$ , thinner and longer nanorods are produced. The formation of 1D structures of  $\text{TiO}_2$  is catalysed by cobalt admixtures.

A crystalline  $\text{TiO}_2$  nanowire was prepared<sup>144</sup> by annealing  $\text{TiS}_2$  in the presence of a flux (NaCl) and in the absence of a flux under an atmosphere of  $\text{NH}_3$ . In the former case, titanium disulfide was mixed with NaCl powder in a mass ratio of 1:3.5 and heated at 820 °C for 2.5 h. In the latter case,  $\text{TiS}_2$  was heated at 820 and 970 °C. The precipitates were washed with an HCl solution, water and ethanol and dried at 85 °C. Samples prepared in the presence of the flux crystallised in the anatase modification with the unit cell parameters  $a = 3.782$ ,  $c = 9.502\text{ }\text{\AA}$ , whereas samples synthesised in the absence of the flux crystallised in the rutile modification ( $a = 4.953$ ,  $c = 2.958\text{ }\text{\AA}$ ). Titanium dioxide nanoparticles are predominantly produced in the absence of NaCl. Anatase nanowires (smooth and straight) have a diameter of 20–200 nm and an  $L/D$  ratio of  $\approx 500$ . Rutile nanowires with  $D = 150\text{ nm}$  and a length of several micrometres were prepared at 970 °C. The formation of  $\text{TiO}_2$  nanostructures also occurs through the intermediate  $\text{Na}_2\text{TiO}_3$  phase during its exchange interaction with HCl.

An amorphous  $\text{TiO}_2$  gel prepared by hydrolysis of  $\text{Ti}(\text{OPr}^i)_4$  in an ethanolic solution was used as a precursor for the preparation of interconnected structured nanosized fibres.<sup>145</sup> The precursor (0.1–0.3 g) was mixed with a 5–15 M NaOH solution (20 ml) and subjected to hydrothermal treatment at 100–180 °C for 48 h. The powder that precipitated was filtered off, washed with water and 0.1 M HCl to pH < 7 and dried *in vacuo* at 100 °C for no less than 10 h. The resulting twisted fibres with a thickness of 5–30 nm and a length from tens to hundreds of micrometres, which are wrapped together to form superstructured materials, have a layered structure with an interlayer distance of 0.7 nm and contain defects and dislocations. Alkaline treatment of the precursor (at a temperature higher than 180 °C) afforded thin ribbon structures 30–200 nm in width and from a few to tens of micrometres in length. A change in the NaOH concentration has no effect on the morphology of the product. The specific surface area of the nanofibres was 267, 354 and 375  $\text{m}^2\text{ g}^{-1}$  at the synthesis temperatures of 100, 130 and 150 °C, respectively.

In the synthesis by the chemical method,  $\text{TiO}_2$  nanotubes are formed at the instant crystalline  $\text{TiO}_2$  reacts with a NaOH solution and transforms to the amorphous state. The reaction of an amorphous  $\text{TiO}_2$  gel with NaOH produces well-interconnected fibres, in which the Ti atoms are octahedrally coordinated by two types of oxygen atoms, *viz.*, the bridging  $\mu_2\text{-O}$  atoms, through which the Ti atoms of the adjacent octahedra are linked to each other, and the  $\text{OH}^-$  groups. The presence of hydroxyl groups is a distinguishing feature of the ' $\text{TiO}_2$ ' gel. The reaction of the latter with NaOH is accompanied by cleavage of some Ti–OH and Ti–O–Ti bonds, with the result that the  $\text{TiO}_6$  octahedra are linked into chains with long-range order, and the latter are partially transformed into layered structures. After lithium ion intercalation into nanofibres, the latter can be used as an electrode material in lithium cells and as atmospheric oxygen and nitrogen separators.

The template method has gained wide acceptance in the synthesis of  $\text{TiO}_2$  nanotubes.<sup>146, 147</sup> Chiral organic compounds **1a–c** can be used as templates.<sup>148, 149</sup>



$\text{X}^- = \text{PF}_6^-$ , (1*R*,2*R*) (**a**);  $\text{ClO}_4^-$ : (1*R*,2*R*) (**b**), (1*S*,2*S*) (**c**).

In alternative methods, a 25% aqueous  $\text{NH}_4\text{OH}$  solution or 2 M HCl was added to a solution of  $\text{Ti}(\text{OPr}^i)_4$  and compound **1a** in ethanol.<sup>148</sup> The resulting mixture was heated at 80 °C, homogenised, cooled to 25 °C, dried in air for 10 days and warmed at 50 °C *in vacuo* for 5 h. The dry sample was kept at 200 °C or 450 °C for 2 h. In the course of the sol–gel synthesis, template **1a** is self-organised to form a three-dimensional network of helical fibres ( $D = 50\text{--}300\text{ nm}$ ) stabilised by hydrogen bonds involving  $\text{NH}_2^+$  groups. The fibre structure was absent after heating of samples, which were pre-treated with an acid, at 450 °C. However, hollow fibres with an outer diameter of 150–600 nm and a length of up to 200  $\mu\text{m}$  are retained upon alkaline treatment. The inner diameter of  $\text{TiO}_2$  fibres (50–300 nm) is, apparently, dictated by the sizes of the template network.

The sol–gel synthesis with the use of chiral molecules **1b** and **1c** as templates produced chiral helical-like  $\text{TiO}_2$  NT (Fig. 1).<sup>149</sup> Derivatives of *trans*-(1*R*,2*R*)- and *trans*-(1*S*,2*S*)-1,2-diaminocyclohexane give left- and right-handed helical fibres stabilised by intramolecular hydrogen bonds between the amino groups. The synthesis was carried out by stirring a mixture of solutions of enantiomers (1 mol litre<sup>-1</sup>),  $\text{Ti}(\text{OPr}^i)_4$  (5 mol litre<sup>-1</sup>),  $\text{H}_2\text{O}$  (2.5 mol litre<sup>-1</sup>) and  $\text{NH}_4\text{OH}$  (0.4 mol litre<sup>-1</sup>) in ethanol at 0 °C followed by heating to 80 °C. The resulting transparent solution was slowly cooled to 25 °C and the resulting gel was dried

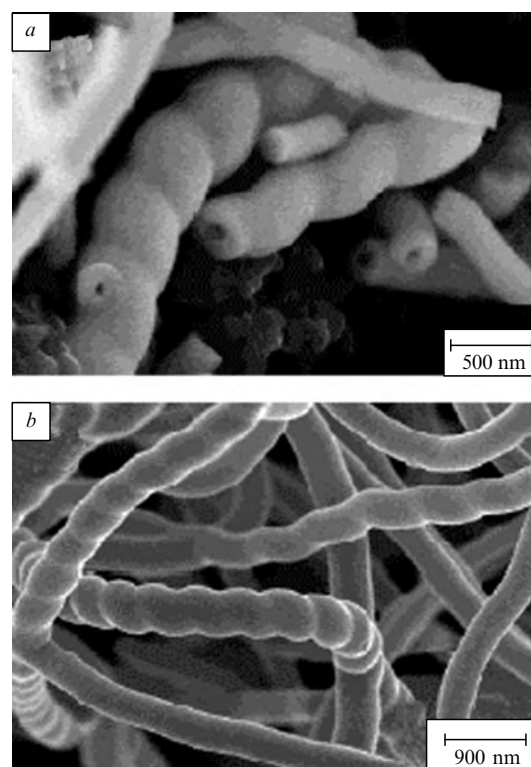


**Figure 1.** The SEM images of  $\text{TiO}_2$  fibres prepared from enantiomers **1b** (**a**) and **1c** (**b**).<sup>149</sup>

Hereinafter, SEM is scanning electron microscopy.

at 25 °C for 10 days and then kept at 50 °C *in vacuo* for 5 h. To remove the templates, the xerogel was washed with acetone and calcined at 200 °C for 2 h and at 450 °C for 24 h. The resulting fibres have an outer diameter of 100–600 nm, an inner diameter of 30–180 nm and a length of up to 30 µm. This method was used also to synthesise chiral vanadium and tantalum oxide nanotubes.

Well-ordered helical-like ribbons and nanotubes were prepared<sup>150</sup> by sol–gel polymerisation of  $\text{Ti}(\text{OPr})_4$  in template gels of neutral dibenzo-30-crown-10 bound to cholesterol. The synthesis successively produces  $\text{TiO}_2$  ribbons, twisted ribbons and open nanotubes with helical (right-handed) chirality ( $D \approx 500$  nm). After removal of the template by annealing under a nitrogen atmosphere at 500 °C for 4 h, hollow helical ribbons and hollow nanotubes with a distance of 8–9 nm between the walls were obtained. Apparently, oligomeric  $\text{TiO}_2$  particles are adsorbed on both sides of the corresponding structures from the template gel with a thickness of 8–9 nm and, consequently, the resulting tubes contain micro- and macropores. The mechanism of formation of helical ribbons and nanotubes involves adsorption of ‘oligomeric’ titanium dioxide particles on a tubular structure of an organic gel and their further growth through sol–gel polymerisation.

The use of laurylamine hydrochloride as a template and  $\text{Ti}(\text{OBu}^n)_4$  as a precursor made it possible to prepare  $\text{TiO}_2$  microtubes with mesoporous walls.<sup>151</sup> The outer diameter of the tubes was 2–8 µm. Their walls (0.2–2 µm in thickness) consist of cylindrical channels with the same diameter of 3.2 nm. These microtubes are thermally stable up to 773 K, have a specific surface area of 390 m<sup>2</sup> g<sup>−1</sup> and consist of anatase with a low degree of crystallinity. The pore volume is 0.586 ml g<sup>−1</sup>.

Ultrathin nanosized titanium dioxide layers were synthesised with the use of carboxylate latex and tobacco mosaic virus (TMV) particles as templates.<sup>152</sup> The latex and TMV particles on a substrate were coated with ultrathin  $\text{TiO}_2$  layers by the sol–gel method and subjected to plasma treatment. The resulting hollow titanium spheres were linked to form nanotubes. After oxidative removal of the template, a rod-like  $\text{TiO}_2$  structure with  $D = 20$ –30 nm was obtained. It is preferable to use oxygen plasma to retain the tubular structure after removal of the template.

Anatase nanoparticles prepared by gradual hydrolysis of a  $\text{TiF}_4$  solution (0.04 mol litre<sup>−1</sup>, pH 2) after the addition of  $\text{NH}_4\text{OH}$  (0.1 mol) were deposited on the surface of various templates,<sup>153,154</sup> such as organic (cotton, silk or wool) or polymeric<sup>155</sup> fibres, aluminium porous membranes, plant fibres, *etc.* After immersion of the template into a solution and storage at 60 °C for 1–48 h, the hydrolysis product undergoes dehydration, and an anatase layer appears on the surface. Organic compounds were removed by annealing in air at 500 °C, and aluminium metal was dissolved in ammonia water (pH 12). Traces of fluorine were removed by calcination in air at a temperature higher than 300 °C. The use of cotton threads as a template results in the formation of hollow  $\text{TiO}_2$  fibres consisting of anatase particles with a diameter of 20–50 nm; their inner diameter corresponds to the thread size. The wall thickness of  $\text{TiO}_2$  depends on the deposition time. The hollow structure is destroyed at sizes greater than 500 nm. The specific surface area of these nanotubes is 50–70 m<sup>2</sup> g<sup>−1</sup>, and their walls contain microscopic pores.

Studies of the photocatalytic activity of anatase as films and nanotubes formed on wool in oxidation reactions of NO demonstrated that the activity on nanotubes increases by a factor of almost nine. Anatase nanotubes with an inner diameter of 50–150 nm were prepared on an aluminium membrane with a channel diameter of ~200 nm. The specific surface area of the material is 100–140 m<sup>2</sup> g<sup>−1</sup>. The use of leaf fibres as a template gives rise to a honeycomb structure consisting of  $\text{TiO}_2$  nanotubes.

Nanosized crystalline anatase is generally prepared by the non-hydrolytic sol–gel method.<sup>156</sup> In a conventional method,  $\text{TiCl}_4$  is added with stirring to benzyl alcohol at room temperature, and then the mixture is warmed to 40 °C and subjected to

aging for 7–14 days. The resulting suspension is centrifuged and the precipitate consisting of  $\text{TiO}_2$  particles with a diameter of 4–5 nm is washed with ethanol and dried.

An anodised porous aluminium plate was used<sup>157</sup> as a template to prepare compact open anatase nanotubes with an inner diameter of 50–70 nm and a wall thickness of 3–10 nm. The pores of the  $\text{Al}_2\text{O}_3$  surface layer (70 nm in diameter and 10–12 µm in depth) were filled with liquid  $\text{Ti}(\text{OPr})_4$  and heated at 500 °C for 1 h under a stream of  $\text{O}_2$ . Decomposition of  $\text{Ti}(\text{OPr})_4$  on the surface of  $\text{Al}_2\text{O}_3$  afforded a  $\text{TiO}_2$  layer. Then anodised aluminium was partially and completely dissolved in a mixture of phosphoric (6 mass%) and chromic (1.5 mass%) acids. Etching at 80 °C for 15 min, as a rule, completely removed the template without destruction of  $\text{TiO}_2$  nanotubes.

Hydrolysis of  $\text{TiF}_4$  in an  $\text{HCl} + \text{NH}_4\text{OH}$  solution with pH 1.6 at 60 °C produced<sup>158</sup> single-crystalline  $\text{TiO}_2$  nanotubes on an anodised aluminium membrane with a pore diameter of 100 nm and a length of 60 µm. The product was washed with water and dried at 60 °C for 24 h. Nonuniformly distributed irregularly shaped columnar crystals of  $\text{TiO}_2$  containing straight  $\text{TiO}_2$  nanotubes with a cavity extended in the axial direction grew on the upper surface of the membrane. The outer and inner diameters of the nanotubes were 20–40 and 4–5 nm, respectively. The interlayer distances in the walls ( $3.6 \pm 0.1$  Å) corresponded to the interplanar distance  $d_{101}$  of anatase. Larger isolated tetragonal crystals of anatase appeared on the lower surface of the membrane.

Titanium dioxide nanotubes of the anatase modification were also prepared in nanosized channels of a porous aluminium membrane, which was stored in a  $\text{TiF}_4$  solution (0.04 mol litre<sup>−1</sup>, pH 2) at 60 °C for 24 h.<sup>159</sup> The template was dissolved in an aqueous ammonia solution (pH 12) at room temperature. The inner diameter of the nanotubes (Fig. 2) is 50–150 nm, the walls consist of  $\text{TiO}_2$  particles with a size of 10–20 nm and the pore diameter is smaller than 10 nm. The size of the inner channels in the tubes depends on the time of deposition of  $\text{TiO}_2$ . If the deposition time is longer than 12 h, compact rods grow. The morphology of the nanotubes is retained because they are prepared without calcination. This material is of interest for photocatalytic gas reactions and liquid filtration. The photoelectrochemical characteristics of  $\text{TiO}_2$  nanotubes and nanorods were studied,<sup>160</sup> and the dependence of the photocurrent on the potential was demonstrated to be analogous to that observed for nanocrystalline films.

The mechanism of formation and the microstructure of  $\text{TiO}_2$  nanotubes prepared according to the above-considered procedure<sup>159</sup> were investigated.<sup>161</sup> The outer and inner diameters of the

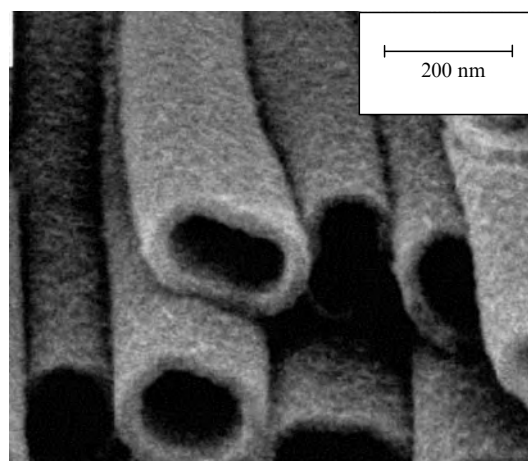


**Figure 2.** The SEM image of  $\text{TiO}_2$  nanotubes synthesised on anodised aluminium as a template.<sup>159</sup>



samples were 9 and 5 nm, respectively. These nanotubes with an interlayer distance of  $\sim 7.1$  Å, which is twice as large as the analogous distance along the [101] direction in anatase ( $a = b = 3.78$ ,  $c = 9.52$  Å), are structurally similar to carbon nanotubes and are formed by rolled-up planar  $\text{TiO}_2$  layers. Taking into account the crystallographic parameters of anatase and rutile ( $a = b = 0.459$ ,  $c = 0.295$  nm), it can be concluded that the anatase modification is more favourable for the formation of  $\text{TiO}_2$  nanotubes. This conclusion is supported by the fact that the surface energy of anatase is lower than that of rutile.<sup>161</sup>

The model of  $\text{TiO}_2$  nanotube formation can be represented by the 3D  $\rightarrow$  2D  $\rightarrow$  1D scheme. A three-dimensional (3D) anatase crystal reacts with a NaOH solution to form a laminar two-dimensional (2D) structure, which is bent so as to bind unsaturated bonds of the terminal atoms. Further rolling-up results in the formation of a tubular structure. There are two possible 2D  $\rightarrow$  1D transformations giving rise to concentric and non-concentric structures. Only non-concentric structures were experimentally observed.<sup>161</sup>

An ethanolic solution of  $\text{Ti}(\text{OPr}^i)_4$ , to which an HCl solution in ethanol is added at 15 °C, can be used as a precursor in the synthesis of  $\text{TiO}_2$  nanotubes.<sup>162</sup> An aluminium membrane was placed in the resulting sol for 5–60 s. Then the membrane was dried and annealed at 400 °C for 6 h. Immersion of the membrane into the sol for 5 and 60 s affords nanotubes and nanofibres, respectively. In the case of an intermediate immersion time (25 s), nanotubes with thick walls grow. The sol temperature and the time of membrane immersion also influenced the morphology of nanostructures and the wall thickness of  $\text{TiO}_2$  nanotubes. In membrane pores with a size of 22 nm, bundles of 2–4, 10 or a larger number of fibres grow as long prismatic crystals with the rare and metastable anatase-like orientation of the (001) plane with the [110] direction. After irradiation with sunlight, fibrillar  $\text{TiO}_2$  exhibits high catalytic activity in decomposition of salicylic acid, which is associated with its larger specific surface area. This method can also be used to prepare photocatalytically active  $\text{TiO}_2$  nanowires.<sup>163</sup>

In the synthesis of  $\text{TiO}_2$  NT by colloidal heterocoagulation, carbon nanotubes (C-NT) were used as a template. A  $\text{TiO}_2$  gel with an admixture of NaOH was added dropwise to an aqueous suspension of carbon nanotubes, which were pre-treated with ammonia, and polyethyleneamine  $(\text{CH}_2\text{CH}_2\text{NH})_n$  at pH 8. The negatively charged  $\text{TiO}_2$  particles were deposited on the walls of the carbon nanotubes and cover them uniformly. The resulting composite contained  $\sim 1.5$  mass% C-NT, had a low specific gravity, was easily separated from the reaction mixture and possessed photocatalytic properties.<sup>164–166</sup>

Nanoparticles of anatase  $\text{TiO}_2$  were prepared on carbon nanotubes<sup>167</sup> in water by hydrolysis of dihydroxy titanium bis(ammonium lactate)  $[\text{MeCH}(\text{O}^-)\text{CO}_2\text{NH}_4]_2\text{Ti}(\text{OH})_2$  and dispersion of C-NT (90–100 °C, 20 h). Carbon nanotubes coated with titanium dioxide and ultradispersed  $\text{TiO}_2$  were separated by centrifugation and dried *in vacuo*; the size of the resulting particles was in a range of 2–10 nm.

The  $\text{TiO}_2$ – $\text{SiO}_2$  nanotube composite with a coaxial structure was synthesised on anodised aluminium.<sup>168</sup> In the first step,  $\text{SiO}_2$  nanotubes were obtained in pores (with a size of 200–250 nm) of anodised aluminium. Then  $\text{TiO}_2$  nanotubes grew on their inner shell. The formation of this nanotube composite depends on the presence of Ti–O–Si bonds and the amorphous character of the  $\text{SiO}_2$  layer. This method allows one to prepare tubes with the more complex  $\text{TiO}_2$ – $\text{SiO}_2$ – $\text{TeO}_2$  composition.<sup>169</sup>

Silicon-containing titanium dioxide nanotubes can be prepared by the sol–gel method in the absence of a template.<sup>170</sup> For this purpose, butanediol,  $\text{Si}(\text{OEt})_4$  and  $\text{Ti}(\text{OPr}^i)_4$  in ratios of 2: (0 at.%–10 at.% Si): 1 were stirred at room temperature and kept for several days until a dry gel was obtained. The dry gel, which was pre-heated with a rate of 5 K min<sup>−1</sup>, was crystallised at 400–600 °C for 1 h to form nanotubes and nanoparticles (for pure  $\text{TiO}_2$  and  $\text{TiO}_2$  + 10 at.% Si, only nanoparticles were

prepared). The inner and outer diameters of  $\text{TiO}_2$  NT containing 5 at.% Si were 3 and 13 nm, respectively. The amount of silicon plays an important role in the nanotube formation. The specific surface area of the samples prepared at 600 °C increases with increasing amount of silicon from 1.6 ( $\text{TiO}_2$ ) to 110.66 m<sup>2</sup> g<sup>−1</sup> ( $\text{TiO}_2$  + 10 at.% Si). In this case, the pore size decreases, which is associated with suppression of growth of  $\text{TiO}_2$  nanoparticles in the presence of silicon.

Iron-doped  $\text{TiO}_2$  nanotubes with a diameter of up to 10 nm and a length of 200 nm were synthesised<sup>171</sup> by the hydrothermal method in an alkaline medium. Iron-containing anatase and rutile powders with a particle size of 30 and 42 nm, respectively, were used as precursors. A procedure was developed<sup>172</sup> for the synthesis of a nanocomposite in the form of Au/ $\text{TiO}_2$  nanowires 60 µm long. These nanowires contain the smooth surface formed by anatase and the gold core ( $D = 210$  nm, which corresponds to the pore diameter of an aluminium membrane). The thickness of the shell consisting of  $\text{TiO}_2$  particles with sizes 10–15 nm is 40 nm. The ordered structure of the composite was achieved by layer-by-layer deposition of cationic polyelectrolytes and a titanium-containing precursor on gold nanowires.

A semiconductor/metal nanocomposite was prepared<sup>173</sup> from semiconducting  $\text{TiO}_2$  nanotubes filled with polypyrrole nanowires (the latter were grown by chemical polymerisation<sup>174</sup>). This nanocomposite is as an efficient photocatalyst, because it has a large specific surface area and the conducting core.

A composite consisting of polyaniline (PAni) nanotubes ( $D = 90$ –130 nm) filled with  $\text{TiO}_2$  nanoparticles ( $\sim 10$  nm) was synthesised in the presence of  $\beta$ -naphthalenesulfonic acid ( $\beta$ -NSA) as an admixture.<sup>175</sup> Titanium dioxide powder was added to a  $\beta$ -NSA solution ( $10^{-3}$  mol litre<sup>−1</sup>), the mixture was treated ultrasonically until a homogeneous suspension was prepared, an aniline and water mixture ( $10^{-3}$  mol litre<sup>−1</sup>) was added, and oxidative polymerisation was carried out by adding  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  ( $2 \times 10^{-3}$  mol). The precipitate of the PAni– $\beta$ -NSA– $\text{TiO}_2$  nanotube composite that formed was filtered off, washed with water and ethanol and dried *in vacuo* at 20 °C. The morphology, size, conductivity and hydrophobicity of the composite are determined by the amount of  $\text{TiO}_2$  nanoparticles in the tubes. At a  $\text{TiO}_2$  concentration lower than 0.08 mol litre<sup>−1</sup>, the resulting amorphous composite consisted of hollow fibres. In the concentration range of 0.04–0.06 mol litre<sup>−1</sup>, the composite consisted of nanotubes. At a concentration of 0.12 mol litre<sup>−1</sup>, the composite contained granules. X-ray powder diffraction study revealed an impurity of crystalline  $\text{TiO}_2$ .

The conductivity of the composite depends on its morphology and the percentage of  $\text{TiO}_2$ . The conductivity is  $4.4 \times 10^{-3}$  and  $1.2 \times 10^{-1}$  S cm<sup>−1</sup> for granules and nanotubulenes, respectively. The conductivity decreases with increasing  $\text{TiO}_2$  concentration. The temperature dependence of the conductivity of the composite in the range of 300–77 K is typical of semiconductors with the hopping charge-transfer mechanism. The hydrophilicity of the composite can be varied by varying the  $\text{TiO}_2$  content in the composite.

Nanowires of the anatase/poly(vinylpyrrolidone) (PVP) composite with a porous structure were prepared<sup>176</sup> by electrocentrifugation.<sup>177</sup> Titanium tetraisopropoxide was mixed with acetic acid and ethanol, PVP was added, and the mixture was homogenised for 1 h. Then the mixture was placed in a centrifuge and nanofibres were collected on an aluminium foil at 30 kV. Traces of PVP were removed from the nanofibres by heating them in air at 500 °C for 3 h, which led to a decrease in the diameter of nanofibres from  $78 \pm 9$  to  $53 \pm 8$  nm.

The fibre thickness of the  $\text{TiO}_2$ /PVP composite and anatase nanofibres can be varied in the ranges of  $(52 \pm 11)$ – $(374 \pm 66)$  and  $(33 \pm 6)$ – $(192 \pm 69)$  nm, respectively. Their sizes depend on the parameters of electrocentrifugation, the  $\text{Ti}(\text{OPr}^i)_4$  concentration and the rate at which PVP is added in the course of preparation of the precursor. Titanium dioxide nanoparticles are involved in the formation of composite fibres with a size of  $\sim 10$  nm. The surface



porosity of  $\text{TiO}_2$  nanofibres can be varied as desired by changing the rate of hydrolysis of  $\text{Ti}(\text{OPr})_4$  in fibres through changes in atmospheric humidity. Composite fibres up to several centimetres in length are prone to form a nonwoven structure, which can be used as a sensor after deposition on a substrate. When annealed, this structure is transformed into a ceramic membrane without deterioration of porosity. In this case, fibres can partially melt, which enhances the mechanical strength of the membrane.

Noteworthy is the electrochemical method for the preparation of  $\text{TiO}_2$  nanotubes by anodic oxidation of titanium metal strips in an aqueous electrolyte containing 0.5 mass %–3.5 mass % HF.<sup>178</sup> A porous  $\text{TiO}_2$  layer that appeared on the metal surface represents a high-density homogeneous lattice consisting of parallel tubes. The upper ends of the tubes are open, whereas the lower ends are closed. The average diameter of the tubes (25–65 nm) increases with increasing voltage of anodic oxidation, but the length of the tubes is determined by the thickness of the oxide layer and is independent of the electrolysis time.

Amorphous  $\text{TiO}_2$  nanotubes can be prepared by anodic oxidation of a titanium foil in 0.5% HF at a potential of 12–20 V using a platinum cathode.<sup>179</sup> The length of nanotubes is  $\sim 400$  nm,  $D = 46$ –76 nm, and the wall thickness is 17–27 nm. Annelation of these nanotubes at 500 °C under an oxygen stream affords the anatase and rutile modifications. The former modification is concentrated on the walls of nanotubes, whereas the second modification is concentrated on the barrier layer. The nanotubes are stable up to 600 °C and are of interest as materials for resistive hydrogen sensors.<sup>180, 181</sup> A  $\text{TiO}_2$ -NT-based sensor has the highest sensitivity for hydrogen at 375 °C, which increases with decreasing diameter of the tubes. The hydrogen sensor is completely reversible, its response time is 150 s, the hysteresis is absent, and the sensitivity threshold is  $10^{-4}$ . The sensor is highly selective for hydrogen compared to  $\text{CO}$ ,  $\text{CO}_2$  and  $\text{NH}_3$ , but is responsive also to  $\text{O}_2$  at the high concentration of the latter.

Electrochemical oxidation of a TiN layer on a silicon substrate with the use of a nanoporous anodised  $\text{Al}_2\text{O}_3$  film as a template afforded nanosized  $\text{TiO}_x$  crystallites<sup>182</sup> with  $D \approx 60$  nm belonging to the hexagonal system. This method is suitable also for the preparation of nanocrystallites of other semiconducting oxides.

Titanium dioxide nanoparticles were synthesised in mesopores of  $\text{Al}_2\text{O}_3$  with the use of a new precursor, *viz.*, bis(tolueno)-titanium, which served as a molecular source of  $\text{Ti}^{IV}$ .<sup>183</sup> Insertion of the precursor into mesopores of an aluminium template leads to elimination of titanium metal, which is oxidised to  $\text{TiO}_2$  (anatase) with a particle size of  $\sim 2$  nm. This material readily adsorbs UV radiation.

Various geometric structures can be prepared from  $\text{TiO}_2$  nanoparticles.<sup>184–189</sup> A simple chemical method for the synthesis of needle-like samples<sup>184</sup> consists in mixing  $\text{Ti}(\text{OPr})_4$  and  $\text{Si}(\text{OEt})_4$  solutions in ethanol with admixtures of HCl and  $\text{H}_2\text{O}$  to prepare a composite with the molar ratio  $\text{TiO}_2:\text{SiO}_2 = 4:1$ . Hydrolysis and gel formation in moist (70%) air at 40 °C for 5 days followed by annealing at 600 °C (2 h) and storage of anatase that formed in an autoclave in an aqueous NaOH solution (a Teflon vessel) at 20, 60 or 110 °C for 20 h afforded well-crystallised  $\text{TiO}_2$  with a specific surface area of  $400 \text{ m}^2 \text{ g}^{-1}$ . After washing with 0.1 M HCl and water, the product exhibited high photocatalytic activity. The synthesis with the use of 10 M NaOH at 60–110 °C for 20 h produced ‘needles’ with a tubular structure ( $D \approx 8$  nm,  $L \approx 100$  nm). Analogous anatase samples were also prepared without the addition of  $\text{SiO}_2$  to the starting reaction mixture.

Ultrasonic treatment allows one to prepare nanotube forms of  $\text{TiO}_2$  not only as nanotubes but also as whiskers.<sup>185</sup> Particles ( $D \approx 20$  nm) prepared by thermal treatment of titanium hydroxide at 650 °C for 1 h (17% of anatase and 83% of rutile) serve as a precursor. To produce whiskers, a sample was placed in a 10 M NaOH solution, heated to 80 °C and subjected to ultrasonic treatment at an output power of 560 W for 80 min (treatment at an output power of 280 W for 60 min gave nanotubes). The

precipitate that formed was washed with 0.1 M  $\text{HNO}_3$  and water, kept at 110 °C for 4 h on an oil bath, washed once again and dried *in vacuo* (12 h). The sizes and composition of the whiskers depend on the time of washing with water in the first step. After 6 h,  $L \approx 1 \mu\text{m}$ ,  $D \approx 60$  nm, and the composition is  $\text{H}_2\text{Ti}_3\text{O}_7 \cdot 0.5 \text{H}_2\text{O}$ . An increase in the washing time to 8 h leads to a decrease in the diameter of whiskers to 5 nm and the  $\text{TiO}_2$  composition (the so-called B modification).<sup>186</sup> Storage of a sample at 110 °C for 4 h followed by washing with 0.1 M  $\text{HNO}_3$  for 2 h and with water for 14 h results in the formation of open sodium-free nanotubes with  $D \approx 5$  nm,  $L \approx 200$ –300 nm and the ratio  $\text{Ti}:\text{O} = 1:2$ .

Titanium dioxide whiskers cannot be prepared without ultrasonic treatment. Treatment of a  $\text{TiO}_2$ -containing NaOH solution affords sodium titanate consisting of layers of  $\text{TiO}_6$  octahedra, between which alkali metal cations are located. In an  $\text{HNO}_3$  solution, ion exchange occurs to give  $\text{H}_2\text{Ti}_3\text{O}_7 \cdot 0.5 \text{H}_2\text{O}$ . Ultrasonic treatment not only accelerates the reaction between the starting components but also facilitates a particular orientational growth of titanate layers. After washing of the sample with water, the resulting  $\text{TiO}_2$  layers increase in size and roll up into nanotubes.

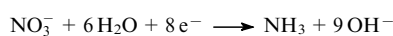
Titanium dioxide whiskers can also be prepared by treating a  $\text{TiOCl}_2$  precipitate, which is prepared by the reaction of  $\text{TiCl}_4$  with a 5 M aqueous ammonia solution, in an autoclave.<sup>187</sup> To prepare anatase and rutile whiskers, titanium oxochloride is pre-calcinated at 450 and 800 °C, respectively. Whiskers ( $D < 20$  nm) as bundles are produced under hydrothermal conditions at 100 °C for 12 h along with  $\text{TiO}_2$  nanotubes 60–100 nm in length and 10–30 nm in diameter. An increase in the temperature leads to an increase in the amount of nanotubes in the samples, their length becomes as large as 150 nm, and the diameter is 15–20 nm. At 200 °C, the amount of tubes is larger than the amount of spherical particles (which are always present in samples), their length increases to 200–500 nm, and the inner diameter is 7–8 nm. An increase in the temperature leads to an increase in the size of the tubes, but the rate of their formation decreases. This is associated with the predominant formation of less soluble spherical particles ( $\text{TiO}_2$  crystal nuclei). Since the lattice parameter of anatase  $c \gg a$ , its powder more easily forms nanotubes, which is attributed to the anisotropy of growth of  $\text{TiO}_2$  particles during the autoclave treatment.

Nanosized  $\text{TiO}_2$  ribbons with a length from a few to tens of micrometres, a thickness of several nanometres and a width of 30–200 nm were prepared by the hydrothermal method from titanium dioxide powder in a NaOH solution.<sup>188</sup> A  $\text{TiO}_2$  gel, crystalline anatase or an anatase and rutile mixture were used as the starting titanium compound. The precursor (0.3 g) was mixed with a NaOH (5–15 M) solution (20 ml) and subjected to hydrothermal treatment at 180–240 °C for 1–2 days, and the products were washed with water and 0.1 M HCl. It was found that the temperature and the alkali concentration have no effect on the morphology of ribbons, which can roll up about the [001] direction. The corrugated surface of such ribbons results from cluster condensation. These thin ( $\leq 5$  nm) ribbons can be doped with various elements, which is of considerable importance in the synthesis of functional materials.

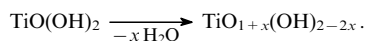
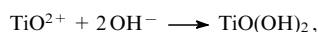
The sol–gel method is most widely used in the synthesis of nanotube forms of  $\text{TiO}_2$  with different geometry. The drawbacks of this method as applied to the preparation of nanorods are that the template pores are difficult to fill with a high-concentration gel and that the use of dilute gels leads to the formation of cracks and defects. The template pores can be filled using electrophoresis of sol–gel nanocomposites. However, this procedure is unsuitable for the preparation of nanorods with  $D < 20$ –50 nm.

The synthesis of single-crystalline  $\text{TiO}_2$  nanorods by the sol–gel method was performed under cathodically induced conditions.<sup>189</sup> The electrolyte was prepared by dissolving titanium metal powder in  $\text{H}_2\text{O}_2$  and ammonia, the resulting yellow gel was dissolved in 4 M  $\text{H}_2\text{SO}_4$ , and then  $\text{KNO}_3$  was added to the

solution to pH 2–3. The pores (12–50 nm) of an anodised aluminium membrane were filled using the electrochemical method at room temperature at potentials ( $V$ ) from  $-0.9$  to  $-1.2$  V. At  $V < -0.9$  V, electroreduction of nitrate ions occurred at the cathode

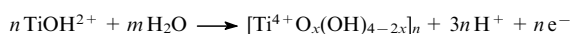


which was accompanied by the formation of titanium hydroxide sol and gel



Annelation of a sample (450 °C, 24 h) gave  $\text{TiO}_2$  nanowires of the anatase modification with  $D \approx 40$  nm and a length of 2–10  $\mu\text{m}$  depending on the electrolysis time (0.5–3 h). A high gel density in template pores prevents the formation of defects and cracks during heating.

Electrochemical deposition of a titanium hydroxide gel in pores of poly(methyl methacrylate) using gold electrodes afforded  $\text{TiO}_2$  nanotubes.<sup>190</sup> An electrolyte with pH 2.5 was prepared under nitrogen from  $\text{NaHCO}_3$  and a  $\text{TiCl}_3$  solution in hydrochloric acid. The electrochemical reaction



was carried out at an anode potential of +0.5 V. Amorphous  $\text{TiO}_2$  nanotubes were prepared by removing the polymer using dissolution in acetone at 40 °C. Heating of these nanotubes at 450 °C for 1 h afforded intergrown anatase nanotubes with an outer diameter of 120 nm and a wall thickness of 25 nm. At short distances between the pores of the polymer, a compact porous  $\text{TiO}_2$  film was obtained.<sup>190</sup>

The influence of the molar ratio of the starting components on the morphology of  $\text{TiO}_2$  nanorods and nanotubes, which were synthesised from a sol by the template method on anodised aluminium, was studied.<sup>191</sup> The sol was prepared by adding a  $\text{Ti}(\text{OPr}^i)_4$  solution in ethanol to an ethanol, water and acetylacetone mixture. The amount of perfect nanorods ( $D = 200$ –250 nm) formed by particles with a size of  $\sim 20$  nm can be increased by increasing the percentage of ethanol in the sol. This can be achieved with the use of the starting molar ratio  $\text{Ti}(\text{OPr}^i)_4$ :acetylacetone: $\text{H}_2\text{O}$ :EtOH = 1:1:3:(20–40). An increase in the percentage of acetylacetone in the  $\text{TiO}_2$  sol (1:2:3:20) results in the formation of  $\text{TiO}_2$  nanotubes with thin walls (15–20 nm), which are easily broken and cracked.

Titanium dioxide nanowires were synthesised by deposition of a precursor on the corrugated surface of a polymeric template (based on azobenzene-functionalised epoxide resin) or silicon dioxide followed by calcination at 500 °C in air for 3 h.<sup>192</sup> The precursor was prepared as a sol by hydrolysis of a  $\text{Ti}(\text{OPr}^i)_4$  solution in isopropanol in a moist air atmosphere. Nanowires grow on a polymer template but do not grow on  $\text{SiO}_2$ . An increase in the isopropanol concentration in the sol results in the formation of cracks parallel to grooves in the template.

Considerable progress was made in the synthesis of nanostructures of complex titanium oxides.<sup>193–198</sup> For example, nanorods of titanic acid  $\text{H}_2\text{Ti}_3\text{O}_7$  were synthesised by the hydrothermal method<sup>193</sup> involving mixing of anatase with 10 M NaOH and heating at 130 °C for 72 h. The precipitate that formed was washed with water to prepare tubular particles 9 nm in diameter and hundreds of nanometres in length. Alkaline treatment of  $\text{TiO}_2$  gives rise to Ti–O–Na bonds, which are cleaved in water due to the replacement of  $\text{Na}^+$  ions with  $\text{H}^+$  ions. This results in the formation and subsequent rolling-up of laminar particles. In an acidic medium, the formation of nanotubes is not accelerated, but the resulting nanotubes contain numerous defects.

The formation of a disordered intermediate phase containing sodium ions is an important step in the formation of these nanotubes. The synthesis with the use of amorphous  $\text{TiO}_2$  as a precursor does not afford nanotubes, because  $\text{TiO}_2$  is recrystal-

lised into needle-like brookite. The use of KOH or LiOH instead of NaOH leads to the formation of nanorods and platelets or nanoparticles, respectively. Therefore, a high concentration of  $\text{Na}^+$  cations and a strongly alkaline medium are essential conditions for the nanotube formation. All  $\text{H}_2\text{Ti}_3\text{O}_7$  nanotubes are open and are formed by rolling up  $\text{TiO}_2$  layers with an interlayer distance of  $\sim 7.8$  Å.

The  $\text{H}_2\text{Ti}_3\text{O}_7$  phase belongs to the monoclinic system with the unit cell parameters  $a = 16.03$ ,  $b = 3.75$ ,  $c = 9.19$  Å and  $\beta = 101.45^\circ$ . The formula of this weak acid is generally represented as hydroxide  $\text{Ti}_3(\text{OH})_2\text{O}_5$  stable in an alkaline medium. Its monolayer is formed by corrugated ribbons consisting of  $\text{TiO}_6$  octahedra sharing edges (three octahedra in width), which form stepwise planes separated by  $\text{H}^+$  ions. In the polymeric titanate ion  $(\text{Ti}_3\text{O}_7^{2-})_n$ , the atomic layers roll up about the [001] direction of the crystal structure of  $\text{H}_2\text{Ti}_3\text{O}_7$ . An interesting feature of these nanotubes is the simultaneous presence of an interlayer space and a quasi-one-dimensional inner channel. Titanate  $\text{H}_2\text{Ti}_3\text{O}_7$  is a potential protonic electrolyte for fuel cells. In a concentrated NaOH solution, the nanotube material  $\text{Na}_2\text{Ti}_2\text{O}_4(\text{OH})_2$  was produced from polycrystalline  $\text{TiO}_2$  at 110 °C for 20 h.<sup>194</sup> Treatment of this material with an HCl solution at pH 1 gives rise to the orthorhombic tubular structure of  $\text{H}_2\text{Ti}_2\text{O}_4(\text{OH})_2$ .

The reaction of nanodispersed  $\text{TiO}_2$  (4 nm) with a 4–10 M KOH solution in an autoclave at 160–180 °C for 48 h affords the monoclinic  $\text{K}_2\text{Ti}_8\text{O}_{17}$  phase.<sup>195</sup> This phase consists of nanostructures analogous to twisted and bent ribbons (a few micrometres in length and tens of nanometres in width and thickness) extended along the [010] direction. The synthesis by this method in a NaOH solution produced nanosized belts of titanate  $\text{Na}_2\text{Ti}_4\text{O}_9$  with a width of 100–500 nm and a thickness of 30 nm. In these structures, the  $\text{Na}^+$  ions can be replaced by most cations. Potassium titanate shows chemoluminescence at 270 °C, which is 140 °C lower compared to that observed for  $\text{TiO}_2$  nanopowders. For this phase, photoluminescence at an excitation wavelength of 401 nm and an emission wavelength of 612 nm was observed for the first time.

The low-temperature hydrochemical method afforded  $\text{SrTiO}_3$  and  $\text{BaTiO}_3$  nanotubes with an outer diameter of 8–15 nm, an inner diameter of 4–7 nm and a length of 50–500 nm.<sup>196</sup> They have a cubic perovskite structure with the unit cell parameter  $a$  of 3.889 and 3.975 Å for  $\text{SrTiO}_3$  and  $\text{BaTiO}_3$ , respectively. The samples contain impurities of an amorphous product, the starting reagents and carbonates. The synthesis was carried out by stirring  $\text{SrCl}_2$  or  $\text{Ba}(\text{OH})_2$  and  $\text{TiO}_2$  NT solutions under argon or nitrogen for 6–20 h. Then pH of the suspension was brought to 12 and 10 by the addition of NaOH or HCl, respectively, and the precipitate was separated by decantation, washed with water and dried. Crystalline  $\text{SrTiO}_3$  and  $\text{BaTiO}_3$  nanorods (the unit cell parameter  $a$  is 3.90 and 4.03 Å, respectively) can also be prepared by thermolysis of  $\text{Sr}(\text{OPr}^i)_2$  and  $\text{Ba}(\text{OPr}^i)_2$  in the presence of oleic acid at 280 °C for 6 h.<sup>197</sup> Isolated nanorods have a diameter of 5–60 nm and a length of 10  $\mu\text{m}$ . These materials can be used as nanosized ferroelectrics and memory elements.<sup>198</sup>

## b. Vanadium oxides

The first vanadium(V) oxide nanotubes have been synthesised only recently.<sup>199</sup> The sol–gel method giving rise to xerogels with a pronounced quasi-one-dimensional structure proved to be efficient in the synthesis of such nanotubes.<sup>200</sup> A combination of the sol–gel process with hydrothermal treatment at 180 °C for 5 h produced nanowires of composition  $\text{V}_2\text{O}_5 \cdot n\text{H}_2\text{O}$  ( $0.3 \leq n \leq 1.7$ ) with the [010] growth axis.<sup>201,202</sup>

Extensive experimental data<sup>203</sup> on the chemistry of intercalates based on the  $\text{V}_2\text{O}_5 \cdot n\text{H}_2\text{O}$  xerogel provided the basis for developing new procedures for the synthesis of nanotube forms of vanadium oxide.<sup>204</sup> Evidently, the layered structure of a xerogel, in which the distances between the V–O layers are controlled by organic molecules, plays the key role in the design of vanadium

oxide nanotubes. Organic guest molecules serve as templates, thus determining the structure of a multilayer nanotube composite.

Primary amines  $C_nH_{2n+1}NH_2$  ( $4 \leq n \leq 22$ ) and  $\alpha,\omega$ -diamines  $H_2N(CH_2)_nNH_2$  ( $14 \leq n \leq 20$ ) were proposed as templates for these syntheses.<sup>204–208</sup> An ethanolic solution of vanadium(V) triisopropoxide  $VO(OPr^i)_3$  and amine in a molar ratio of 2:1 was stirred for 1 h under an inert atmosphere and then subjected to hydrolysis. After 12–96-h aging of the system, an orange composite was obtained, which was subjected to hydrothermal treatment in an autoclave at 180 °C for 2–7 days to prepare a black product, *viz.*, single-phase nanotubes with a length of up to 15  $\mu m$ , an outer diameter of 15–150 nm and an inner diameter of 5–50 nm. The walls of these tubes consisted of 2–30 layers of crystalline vanadium oxide, between which intercalated amine and diamine molecules are located. The distance between the layers (1.7–3.8 nm) is proportional to the length of the guest molecule. The general formula of such nanotubes can be represented as  $VO_xO_{y/2}(C_nH_{2n+4}N)_y$  or  $VO_x(C_nH_{2n+4}N)_y$ , where  $2.30 \leq x \leq 2.47$  and  $0.25 \leq y \leq 0.30$ , respectively. In the case of diamines, the tubes have thicker walls and a smaller inner diameter.

Vanadium–oxygen layers of the nanotubes under consideration consist of  $VO_4$  tetrahedra and  $VO_5$  tetragonal pyramids. The vanadium oxide tubes are stable after removal of amines but decompose at a temperature above 250 °C. Unlike mesoporous metal oxides with a laminar structure, these composites are characterised by a tubular morphology and well-structured walls. It is believed<sup>201</sup> that twisted layers of vanadium oxides are very flexible, and they can be stretched and involved in numerous exchange reactions.

In the above-described procedure for the synthesis of nanotubes, vanadium(V) oxochloride and oxide are also used as precursors.<sup>209</sup> In the first step,  $VOCl_3$  or  $V_2O_5$  is mixed with primary amine  $C_nH_{2n+1}NH_2$  under an inert atmosphere, and the mixture is hydrolysed with an acetate buffer (pH 7) or water. The next step involves hydrothermal treatment at 180 °C for 7 days. Elemental analysis demonstrated that the composition of the nanotubes synthesised from  $VOCl_3$  corresponded to the formula  $VO_{2.45 \pm 0.05}(C_nH_{2n+4}N)_{0.27 \pm 0.01}$  ( $11 \leq n \leq 16$ ). The tubes prepared from  $V_2O_5$  had the composition  $VO_{2.43 \pm 0.03} \cdot (C_nH_{2n+4}N)_{0.27 \pm 0.01}$  ( $11 \leq n \leq 20$ ).

The morphological characteristics of vanadium oxide nanotubulenes depending on the type of the precursor and the nature of the template are given in Table 3. The multilayer walls of these well-crystallised open tubes consist of rolled-up vanadium–oxygen layers built from  $VO_4$  squares with the unit cell parameter  $a = 6.1$  Å.<sup>210</sup> The tubes composed of ideal cylindrical layers are rarely produced (< 1%), and these tubes contain no more than six layers. Nanotubes of  $VO_x$  are more often composed of rolled-up layers and are characterised by the roll morphology.

The majority of vanadium oxide tubes contain various defects. An isolated layer forms an inner part of the tube, whereas its outer surface is generally transformed into a roll of two layers between which amine molecules are located. These tubes are characterised

by the formation of bundles and intergrowths. A roll of one  $VO_x$  layer can go to the adjacent tube with a change in the direction of rolling. This pair of tubes sharing layers is often observed in  $VO_x$  nanotubes with intercalated diamines after ion exchange. Aromatic amines can also be used as templates in the synthesis of  $VO_x$  nanotubes.<sup>211</sup> For example, the reaction of  $VO(OPr^i)_3$  with 3-phenylpropylamine followed by hydrolysis and hydrothermal treatment of the product affords nanotubes containing defects in the structure of the walls.

The structural characteristics of nanotubes can be varied as desired by changing the pH of the  $V_2O_5$  gel through the addition of ammonia.<sup>212</sup> In a neutral or weakly acidic medium, nanotubes with an interlayer distance proportional to the length of the  $(CH_2)_n$  chain are produced. The nanotubes synthesised at pH 9–10 have a unique structure of the walls, which consist of  $VO_x$  layers regularly alternating with intercalated amine and ammonia molecules (interlayer distances are 20 and 9 Å, respectively). The tubes formed in the presence of ammonia have a much larger outer diameter (larger than 250 nm) and smaller length (2–5  $\mu m$ ) compared to the nanotubes prepared at pH 4–8 (Fig. 3). The general formula of these nanotubes can be represented as  $[(NH_4)_yVO_x][(RNH_3)_xVO_x]$  (R is a hydrocarbon fragment).

Derivatives of *trans*-(1*R*,2*R*)- and *trans*-(1*S*,2*S*)-1,2-diamino-cyclohexane were proposed<sup>49</sup> as templates for the synthesis of the helical chiral structure of  $VO_x$  NT. The *R,R*- and *S,S*-enantiomers always give the left- and right-handed helices, respectively.

The synthesis of  $VO_x$  nanotubes from a  $V_2O_5 \cdot nH_2O$  gel ( $n \approx 300$ ), which was prepared by dissolution of vanadium(V) oxide in hydrogen peroxide, was documented.<sup>213,214</sup> A solution of hexadecylamine ( $0.45 \text{ g ml}^{-1}$ ) in acetone (the molar ratio V : amine = 2 : 1) was added to this gel, the mixture was stirred at room temperature for 16 h, and the composite was subjected to hydrothermal treatment at 150 or 180 °C for 2–10 days. The resulting black powder was washed with ethanol and cyclohexane and dried *in vacuo* at 80 °C for 5 h. The interlayer distance in  $VO_x$  NT decreases from 37 to 32 Å with increasing temperature and time of the hydrothermal process.

The X-ray powder diffraction patterns of the resulting nanotubes are typical of layered compounds. They contain intense 00*l* reflections (reflections from atomic planes) and weak *hk*0 reflections determined by a two-dimensional structure of the layer. The alkylamine molecule is perpendicular to the planes of  $VO_x$ , because the interlayer distance is close to the chain length of the amine (33 Å). Water molecules located between the layers along

**Table 3.** Morphological characteristics of V–O nanotubulenes ( $C_nH_{2n+1}NH_2$  template).<sup>209</sup>

| Precursor     | <i>n</i>           | Outer diameter of NT /nm | Inner diameter of NT /nm | Number of layers | Length of NT / $\mu m$ |
|---------------|--------------------|--------------------------|--------------------------|------------------|------------------------|
| $VO(OPr^i)_3$ | $4 \leq n \leq 22$ | 15–150                   | 5–50                     | 2–30             | 1–15                   |
| $VOCl_3$      | 11                 | 50–100                   | 15–35                    | 10–20            | 1.5–5                  |
|               | 16                 | 80–100                   | 20–35                    | 11–14            | 0.8–1.5                |
| $V_2O_5$      | 11                 | 70–140                   | 20–35                    | 9–13             | 2–12                   |
|               | 12                 | 50–90                    | 15–35                    | 7–13             | 1–3                    |
|               | 16                 | 70–100                   | 20–45                    | 6–13             | 1–2                    |
|               | 20                 | 60–90                    | 20–45                    | 6–10             | 1–3                    |

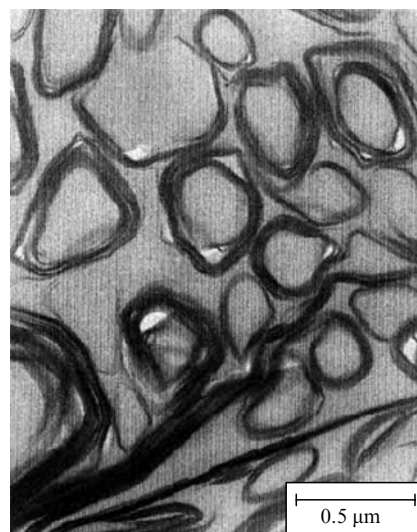


**Figure 3.** The TEM image of cross-sections of  $VO_x$  NT.<sup>212</sup> Hereinafter, TEM is transmission electron microscopy.

with protonated amines increase this distance to 37 Å. The inner and outer diameters of the nanotubes are 30–40 and 50–130 nm, respectively, the length is 1–10 µm, and the number of the layers varies from 5 to 25.

Vanadium(V) oxide powder can be used as a precursor in the synthesis of VO<sub>x</sub> nanotubes.<sup>215–217</sup> In this case, V<sub>2</sub>O<sub>5</sub> and hexadecylamine are mixed in water, the mixture is heated in an autoclave at 140 or 180 °C for 24 h or 3 days, respectively, and the resulting black product is washed with water and dried at 70 °C. The product consists of nanotubes with a length of 1–10 µm and a diameter of 30–100 nm depending on the conditions of the synthesis, the template type, the precursor concentration and the reaction time. The walls of these nanotubes are formed by 3–10 VO<sub>x</sub> layers with interlayer distances of 35.3 Å. The ESR spectra of these samples contain a single line without hyperfine structure, which is typical of interacting V<sup>4+</sup> ions. This is indicative of the close arrangement of paramagnetic centres (*d* < 0.7 nm) and the occurrence of spin–spin coupling interaction. The *g* factor (1.961) is equal to that of the VO(H<sub>2</sub>O)<sub>5</sub><sup>2+</sup> ion (1.962).

Hydrothermal treatment of a V<sub>2</sub>O<sub>5</sub>, MoO<sub>3</sub> and hexadecylamine mixture (180 °C) for one week afforded V<sub>0.99</sub>Mo<sub>0.01</sub>O<sub>2.45</sub>(C<sub>16</sub>H<sub>36</sub>N)<sub>0.27</sub> nanotubes with a diameter 30–10 nm and a length of 2–8 µm.<sup>217</sup> The interlayer distance in these nanotubes determined by X-ray and electron diffraction is 34 and 29.3 Å, respectively. The unit cell parameter *a* of the two-dimensional tetragonal unit cell in the layer is 6.23 Å.

Manganese-containing VO<sub>x</sub> nanotubes of composition Mn<sub>0.1</sub>VO<sub>2.5+δ</sub>·*n*H<sub>2</sub>O were synthesised by the ion exchange method from the layered V<sub>2</sub>O<sub>5+δ</sub>(C<sub>12</sub>H<sub>25</sub>NH<sub>3</sub><sup>+</sup>) precursor.<sup>218</sup> Their largest diameter is 100 nm and the length is 1.3 µm. The nanotubes contain defects as partially broken zigzag layers with a tetragonal structure (*a* = 6.157(3) and *c* = 10.52(3) Å). This compound with a tubular morphology was tested as a cathode material for electrochemical lithium intercalation. At a potential of ~2 V, 0.5 mol of Li per mole of V<sub>2</sub>O<sub>5</sub> are reversibly inserted into VO<sub>x</sub> nanotubes. The cell capacity is 140 A h kg<sup>-1</sup>.

Reaction products of multilayer VO<sub>x</sub> nanotubes, which contain α-monoamines with a chain length of 4–22 carbon atoms between the layers (for example, C<sub>12</sub>-VO<sub>x</sub> contains alkylamine with 12 carbon atoms), with salt solutions were studied.<sup>219</sup> This process was demonstrated to be accompanied by intercalation of alkali (Na<sup>+</sup>, K<sup>+</sup>), alkaline earth (Mg<sup>2+</sup>, Ca<sup>2+</sup>, Sr<sup>2+</sup>) and transition metal (Fe<sup>2+</sup>, Co<sup>2+</sup>, Ni<sup>2+</sup>, Cu<sup>2+</sup>, Sm<sup>3+</sup>, Tb<sup>3+</sup>) cations with a decrease in the interlayer distance in the tubes to 0.9–1.2 nm. The intercalated K<sup>+</sup> cations bound to crown ether can be partially replaced with dodecylamine with the result that the initial interlayer distance is restored. The reactions with RbCl, CsCl, AgNO<sub>3</sub>, SrCl<sub>2</sub> and BaCl<sub>2</sub> solutions lead to destruction of nanotubes, whereas ZnCl<sub>2</sub> and Pb<sup>2+</sup> salts are not intercalated. The largest atomic cation : V ratio in the insertion compounds is as high as 0.27.

Nanotubes intercalated with Na<sup>+</sup>, K<sup>+</sup> and Cu<sup>2+</sup> ions were prepared by the ion exchange method at the molar ratio VO<sub>x</sub> : MCl<sub>*n*</sub> = 1 : 4.<sup>220</sup> These cations in the samples account for 0.26, 0.27 and 0.12, respectively. The unit cell parameters for the intercalated tubes are as follows (the parameters of the starting nanotubes are given for comparison):

|                                    | <i>a</i> /Å | <i>c</i> /Å |
|------------------------------------|-------------|-------------|
| C <sub>12</sub> -VO <sub>x</sub>   | 6.12(1)     | 27.1(2)     |
| Na <sub>0.26</sub> VO <sub>x</sub> | 6.05(1)     | 9.2(1)      |
| K <sub>0.27</sub> VO <sub>x</sub>  | 6.11(1)     | 9.6(1)      |
| Cu <sub>0.12</sub> VO <sub>x</sub> | 6.08(2)     | 10.6(2)     |

The Raman spectra of VO<sub>x</sub> nanotubes show a broad low-intensity band at 995 cm<sup>-1</sup> (V=O) and two broad bands at 800–600 and 500–200 cm<sup>-1</sup> (V–O–V). These broad bands are associated with high disorder of the atomic structure of the tubes.<sup>220</sup> Galvanostatic studies of these materials provided evidence that the redox process is reversible (more than 100 cycles) in

current sources with a lithium anode. The discharge capacity is 120–150 A h g<sup>-1</sup> and the maximum lithium content is 0.5 Li<sup>+</sup> per vanadium atom.

Multilayer Cu–VO<sub>x</sub> and Fe–VO<sub>x</sub> nanotubes were prepared<sup>221</sup> by stirring (20 h) a dodecylamine–VO<sub>x</sub> NT suspension in aqueous-alcoholic CuCl<sub>2</sub> and FeCl<sub>3</sub> solutions followed by filtration, washing and drying in air at 60 °C. The starting nanotubes (primarily, open) have an outer diameter of 60–100 nm, an inner diameter of 15–40 nm and a length of 1–3 µm. Their walls consisted of 6–12 rolled-up layers of vanadium oxides with cracks and dislocations; the average interlayer distance (~30.2 Å) is indicative of the perpendicular arrangement of the dodecylamine molecules. The starting dodecylamine–VO<sub>x</sub> nanotubes are characterised by the tetragonal unit cell (*a* = 6.12, *c* = 33.71 Å). The Cu- and Fe-containing nanotubes have the same structure, the interlayer distances are 10.9 and 10.5 Å, respectively, the inner diameter varies in the range of 40–65 nm and the outer diameter varies in the range of 60–80 nm.

The structural changes resulting from the transformation of a dodecylamine–VO<sub>x</sub> xerogel into nanotubes followed by intercalation with Cu<sup>n+</sup> and Fe<sup>n+</sup> cations were studied by IR spectroscopy. The main absorption bands for the dodecylamine–VO<sub>x</sub> composite are observed at 998, 957, 733, 531 and 838, 809, 635 cm<sup>-1</sup>, and the main absorption bands for the dodecylamine–VO<sub>x</sub> nanotubes are observed at 1001, 792, 721, 573 and 487 cm<sup>-1</sup>. The spectra of the nanotubes also show the shift of the N–H stretching band from 3049 to 3127 cm<sup>-1</sup> and changes in the 1600–1500 cm<sup>-1</sup> region of bending vibrations associated with the difference in the environment about the NH<sub>3</sub><sup>+</sup> groups. After ion exchange (Cu–VO<sub>x</sub> NT), new bands appear at 3571, 3440 and 1615 cm<sup>-1</sup>, which correspond to O–H stretching vibrations and H–O–H bending vibrations. In the region of V–O bonds, two new bands at 755 and 526 cm<sup>-1</sup> (a shoulder at 590 cm<sup>-1</sup>) correspond to V–O–V and V–O–Cu bending vibrations, and the V=O band is shifted from 1001 to 1007 cm<sup>-1</sup>. For the Fe–VO<sub>x</sub> nanotubes, the shifts of the bands are insignificant (997, 576, 495 cm<sup>-1</sup> and 3384, 3203 and 1614 cm<sup>-1</sup>). This indicates that the Fe<sup>n+</sup> cations are bound to the VO<sub>x</sub> layers.

X-ray photoelectron spectroscopy demonstrated<sup>221</sup> that intercalated nanotubes contain a large amount of tetravalent vanadium. Copper atoms exist primarily in the monovalent state, and Cu<sup>2+</sup> cations and copper clusters are also present in small amounts. In Fe–VO<sub>x</sub> nanotubes, iron atoms exist in the Fe<sup>0</sup>, Fe<sup>2+</sup> and Fe<sup>3+</sup> states. Analysis of the N1s band shows that trace amounts of amines are present in the samples. The compositions of NT were represented as VO<sub>2.3</sub>(C<sub>12</sub>H<sub>25</sub>NH<sub>3</sub>)<sub>0.38</sub>, VO<sub>1.53</sub> < *x* < 2.1(C<sub>12</sub>H<sub>25</sub>NH<sub>3</sub>)<sub>0.21</sub>Cu<sub>0.08</sub>(H<sub>2</sub>O)<sub><0.56</sub> and VO<sub>2.08</sub> < *x* < 2.68(C<sub>12</sub>H<sub>25</sub>NH<sub>3</sub>)<sub>0.13</sub>Fe<sub>0.19</sub>(H<sub>2</sub>O)<sub><0.33</sub>. The chlorine content in the intercalates was lower than 0.01 mol.

Upon heating in air to 180 °C, Cu–VO<sub>x</sub> NT remain unchanged. The weight loss (~9%) occurs due to elimination of water coordinated to copper cations. At about 350 °C, the weight loss is 17%, residual water and organic molecules are eliminated, and the tubular structure is destroyed to form the unstructured V<sub>2</sub>O<sub>5-x</sub>/CuO composite. Under nitrogen, the weight loss in Cu–VO<sub>x</sub> NT occurs in the temperature range of 180–650 °C, and thermolysis affords Cu and V<sub>2</sub>O<sub>3</sub>. The process gives rise to V<sub>2</sub>O<sub>3</sub> nanotubes consisting of V<sub>2</sub>O<sub>3</sub> crystallites with a size of 3–5 nm. These nanotubes are thermally stable under nitrogen up to 650 °C, and copper metal nanoparticles are present inside the nanotubes. The Cu–VO<sub>x</sub> nanotubes are catalytically active in decomposition of HCN giving rise to Cu(CN)<sub>2</sub>. Additional data on copper-containing VO<sub>x</sub> nanotubes were reported in the study.<sup>222</sup>

The VO<sub>x</sub> nanotubes are structurally related to BaV<sub>7</sub>O<sub>16</sub>·*n*H<sub>2</sub>O<sup>223</sup> and (en)V<sub>7</sub>O<sub>16</sub>.<sup>224</sup> The (V<sub>7</sub>O<sub>16</sub>)<sub>*n*</sub> layers form a framework of the tube, whereas the amine molecules are inserted between the layers. These isotropic layers formed by the equivalent planes, which are composed of VO<sub>5</sub> square pyramids on

both sides of the layer, roll up to compensate free bonds of the terminal atoms giving rise to a tubular morphology.

The (en)V<sub>7</sub>O<sub>16</sub> compound is an example of structures characterised by strong electrostatic interactions between the negatively charged VO<sub>x</sub> layers and the ethylenediamine cations. This compound crystallises in the triclinic system with the unit cell parameters  $a = 6.161(2)$ ,  $b = 6.170(2)$ ,  $c = 19.111(7)$  Å,  $\alpha = 96.138(9)$ ,  $\beta = 92.819(9)$ ,  $\gamma = 90.067(9)^\circ$ . (In an independent electron diffraction study, the following unit cell parameters were determined:  $a \approx b \approx 6.15$ ,  $c \approx 18.5$  Å,  $\alpha \approx 98$ ,  $\beta \approx 93$ ,  $\gamma \approx 90^\circ$ .) Each V<sub>7</sub>O<sub>16</sub> layer consists of two planar sheets, which, in turn, are composed of VO<sub>5</sub> square pyramids linked *via* VO<sub>4</sub> tetrahedra. However, (en)V<sub>7</sub>O<sub>16</sub> was not prepared in pure form, and the NH<sub>2</sub> groups in this compound are protonated. The model of intercalated vanadium oxide nanotubes can be derived from the (en)V<sub>7</sub>O<sub>16</sub> structure. The unit cell parameters for C<sub>12</sub>-VO<sub>x</sub> nanotubes are  $a = 6.152$ ,  $c = 54.80$  Å, the space group is  $P4_2/m$ . The nanotube formation is favoured by a large interlayer distance (larger than 1.6 nm), as well as by the presence of amines and diamines containing long alkyl chains, which are inserted in the nanotubes.

Nanostructured vanadium oxide was synthesised using carbon nanotubes as a template.<sup>225,226</sup> The procedure involves coating of carbon NT with a V<sub>2</sub>O<sub>5</sub> gel followed by removal of carbon by calcination in air at 700 °C. To create acid centres on the surface of C-NT, the pre-treatment with boiling HNO<sub>3</sub> was carried out for 24 h. The diameter of the nanotubes thus prepared was 20–55 nm and the length was 2–3 µm. The orthorhombic system and the unit cell parameters  $a = 11.44$ ,  $b = 3.54$ ,  $c = 4.35$  Å were determined by electron diffraction.

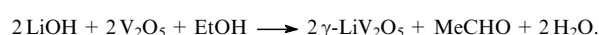
Oxide  $\gamma$ -V<sub>2</sub>O<sub>5</sub> forms a layered orthorhombic structure with the unit cell parameters  $a = 9.946$ ,  $b = 3.585$ ,  $c = 10.042$  Å. The shortest interatomic distances (in Å) in the VO<sub>5</sub> pyramids of vanadium oxides are as follows:

| Oxide                                                     | V=O   | V–O(–V) | O...O        |
|-----------------------------------------------------------|-------|---------|--------------|
| $\gamma$ -V <sub>2</sub> O <sub>5</sub> (V <sub>1</sub> ) | 1.547 | 1.726   | 1.891, 1.986 |
| $\gamma$ -V <sub>2</sub> O <sub>5</sub> (V <sub>2</sub> ) | 1.581 | 1.848   | 1.898, 1.967 |
| $\alpha$ -V <sub>2</sub> O <sub>5</sub>                   | 1.576 | 1.778   | 1.878, 2.018 |

Nanorods and nanowires of  $\gamma$ -V<sub>2</sub>O<sub>5</sub> were synthesised<sup>227</sup> under mild conditions using the micelle method. The average lengths of the nanorods and nanowires were 90 nm and 1 µm, respectively. The sizes of these nanostructures depend on the time during which particles are kept in a micellar solution. The syntheses were carried out in a colloidal sodium bis(ethyl-2-hexyl)sulfosuccinate–isooctane–H<sub>2</sub>O solution, where the first component served as a stabilising surfactant, to which a solution of VO(OPr<sup>i</sup>)<sub>3</sub> in isooctane ( $5 \times 10^{-3}$  mol litre<sup>-1</sup>) was added at 20 °C for 24 h and 100 days, respectively. Well-crystallised nanorods, whose axes are parallel to the [101] direction, and nanowires extended along the [100] direction were synthesised.

The IR spectra of the nanorods are similar to those of the nanowires. The 1750–1000 cm<sup>-1</sup> region shows bands assigned to surfactants and bending vibrations of water molecules (1630 cm<sup>-1</sup>). The V–O stretching vibrations are observed at 1022, 1000, 963, 745 and 537 cm<sup>-1</sup>. X-ray photoelectron spectroscopy demonstrated that vanadium in these nanostructures exists in the pentavalent state; the bond energies of the 2p doublet are 518.8 and 525 eV.

Nanorods of  $\gamma$ -LiV<sub>2</sub>O<sub>5</sub>, which crystallise in the orthorhombic system and have a diameter of 30–40 nm and a length of 0.4–2 µm, were synthesised by the solvothermal method<sup>228</sup> with the use of ethanol as the solvent, which served simultaneously as a reducing agent:



A 1:1 LiOH and V<sub>2</sub>O<sub>5</sub> mixture in ethanol was kept in an autoclave at 160 °C for 24 h, and the precipitate was filtered off,

washed with ethanol and dried at 100 °C. The nanorods thus prepared were tested as a cathode material in a cell with a lithium anode. In the potential range of 1.5–4.2 V, the discharge capacity of the cell was 259 mA h g<sup>-1</sup>. In the first five charge–discharge cycles, the discharge capacity rapidly decreased and then remained constant (199 mA h g<sup>-1</sup> after 20 cycles).

Nanosized crystalline mixed-oxidation-state vanadium oxide was prepared by the addition of VOCl<sub>3</sub> to benzyl alcohol at room temperature and heating of a solution to 120 °C.<sup>156</sup> After aging, the precipitate was separated by centrifugation, washed with ethanol and dried.

Nanorods of NaV<sub>2</sub>O<sub>5</sub> (the orthorhombic system, the unit cell parameters  $a = 11.293$ ,  $b = 3.606$ ,  $c = 4.798$  Å) were produced by the hydrothermal method.<sup>229</sup> Their geometric parameters are determined primarily by pH and the concentration of the reducing agent (NH<sub>2</sub>OH). The magnetic properties of the samples were determined in the temperature range from 2 K to room temperature.

Single-crystalline samples of tubes with composition Na<sub>2</sub>V<sub>3</sub>O<sub>7</sub> were grown *in vacuo* from a Na<sub>1.9</sub>V<sub>2</sub>O<sub>5</sub> melt as black fibres several millimetres in length.<sup>230,231</sup> Fibre bundles can be easily separated into individual crystalline fibres with  $D < 100$  µm. The crystals belong to the trigonal system,  $a = 10.886$ ,  $c = 9.538$  Å,  $Z = 6$ , and consist of VO<sub>5</sub> square pyramids sharing edges and vertices to form parallel tubes with an inner diameter of  $\sim 0.5$  nm. The Na ions are located along the axis of the tube and between the tubes. This material should have an unusual ionic conductivity and properties of a low-dimensional quantum magnet and can be involved in ion-exchange reactions. The electronic and vibrational characteristics of Na<sub>2</sub>V<sub>3</sub>O<sub>7</sub> NT were studied.<sup>231</sup> The electronic structure of Na<sub>2</sub>V<sub>3</sub>O<sub>7</sub> is similar to that of nanotubular vanadates. The optical absorption spectrum shows a band at  $\sim 1.2$  eV, which was assigned to V(d → d) transitions, and bands at 3.3 and 3.9 eV assigned to O2p → V3d transitions.

Chemical vapour deposition from a  $\beta$ -diketonate complex and vanadyl acetylacetonate mixture on a glass substrate afforded nanowires of the  $\beta$  phase of Na<sub>x</sub>V<sub>2</sub>O<sub>5</sub> with  $D = 20$ –200 nm and  $L = 10$ –30 nm.<sup>232</sup> A single-phase sample of  $\beta$ -Na<sub>x</sub>V<sub>2</sub>O<sub>5</sub>, in which the growth orientation along the  $[h0l]$  direction prevails, was prepared only at 550 °C. A decrease in the temperature to 540 °C results in the appearance of an impurity as V<sub>2</sub>O<sub>5</sub> platelets.

Complex manganese vanadium oxide Mn<sub>7-2/3x</sub>(OH)<sub>3</sub>·(VO<sub>4</sub>)<sub>4-2x</sub>(V<sub>2</sub>O<sub>7</sub>)<sub>x</sub>, where  $x = 0.2$ , with a hexagonal structure also exhibits a tubular morphology (Fig. 4).<sup>233</sup> This oxide was synthesised by hydrothermal treatment of an alkaline solution (pH 10.2) containing V<sub>2</sub>O<sub>5</sub>, MnSO<sub>4</sub> and tetrabutylammonium cations (the template) in a molar ratio of 1:1:4 at 165 °C for 72 h.

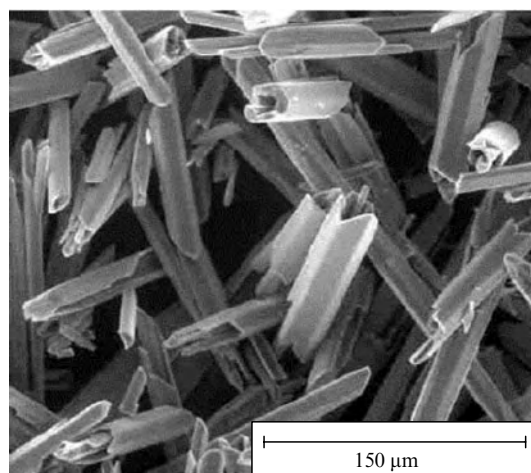


Figure 4. The SEM image of (Mn,V)O<sub>x</sub> NT.<sup>232</sup>

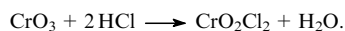
Nowadays, most studies of  $\text{VO}_x$  nanotubes are aimed at developing procedures for the synthesis and investigating the morphology of samples. Data on their physicochemical properties are scarce.<sup>234</sup> The prospects of the use of vanadium oxide tubulenes as cathode materials for lithium cells,<sup>235–238</sup> semiconductors for the production of FET transistors<sup>239</sup> and catalysts for oxidation<sup>227</sup> were estimated. Studies of the cathode properties of  $\text{VO}_x$  nanotubes in chemical current sources with a lithium anode demonstrated that vanadium (which initially consisted of 60% of  $\text{V}^{5+}$  and 40% of  $\text{V}^{4+}$ ) is reduced to the tetra- and trivalent states.<sup>240</sup> The theoretical cathode capacitance is  $240 \text{ mA h g}^{-1}$  and the experimental capacitance is  $210 \text{ mA h g}^{-1}$ . During the first twenty discharge cycles (5 h), the discharge capacity increased.

At a potential below 2 V, the cathode material contains  $\text{V}^{5+}$ ,  $\text{V}^{4+}$  and  $\text{V}^{3+}$  derivatives. Consequently, vanadium can be reduced further, which accounts for the observed increase in the discharge capacity. When charging the current source, the charge is localised in the  $\text{V}(3d)$  band.<sup>241</sup> The C-NT/aerogel/ $\text{V}_2\text{O}_5$  nanocomposite exhibits good cathode properties at a high discharge rate.<sup>242</sup> At a current density of  $112 \text{ mA g}^{-1}$ , the discharge capacity of this cathode is higher than  $560 \text{ mA h g}^{-1}$ . For the graphite/aerogel/ $\text{V}_2\text{O}_5$  composite, the discharge capacity is  $450 \text{ mA h g}^{-1}$ . The resistance of electrodes composed of the C-NT/aerogel/ $\text{V}_2\text{O}_5$  composite is four times lower, which is primarily responsible for the improvement of their characteristics.

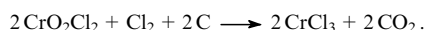
Nanosized oxide tubes and rods are promising modules for nanotechnologies.<sup>243</sup> Nanowires prepared on a  $\text{Si}/\text{SiO}_2$  substrate have a symmetric nonlinear voltammetric parameter and high resistance.<sup>244</sup> Measurements performed in the temperature range of 100–300 K provided evidence for the hopping mechanism of conductivity. Small-radius polarons migrate between  $\text{V}^{4+}$  and  $\text{V}^{5+}$  with an activation energy of 0.11 eV. The electrical characteristics of  $\text{V}_2\text{O}_5$  nanowires with a ribbon structure formed on a  $\text{Si}/\text{SiO}_2$  substrate were studied<sup>240, 244, 245</sup> (the length of the ribbons is a few micrometres, the width is 10 nm and the thickness is 1.5 nm). The conductivity of the fibres from such ribbons is  $20.5 \text{ S cm}^{-1}$  and the contact resistance between the fibres is 62 M $\Omega$ . In strong electric fields ( $E > 10^5 \text{ V cm}^{-1}$ ), the conductivity depends nonlinearly on the length of nanofibres. An analogous dependence has been observed earlier for  $\text{V}_2\text{O}_5$  films. In the region adjacent to the electrodes ( $L < 300 \text{ nm}$ ), non-Ohmic transport can occur.

### c. Chromium oxides

A composite consisting of carbon nanotubes filled with chromium oxide  $\text{CrO}_3$  was synthesised in air at room temperature.<sup>246</sup> For this purpose, C-NT were treated with a paste consisting of  $\text{CrO}_3$  and  $\text{HCl}$  (12 M) in a molar ratio of 2 : 1. The tubes were filled over a period of time from 3 h to 2 days. The material is formed by the following reaction of  $\text{CrO}_3$  with  $\text{HCl}$ :



Initially, chromium oxochloride and unconsumed  $\text{CrO}_3$  are inserted between bundles of carbon nanotubes to form intercalation compounds. The  $\text{CrO}_2\text{Cl}_2$  compound is sensitive to light, gradually decomposes, releases chlorine and oxidises carbon:



Oxidation of carbon atoms is induced by defects and impurities on the surface of C-NT, due to which the tubes contain pores. As a result, concentrated  $\text{CrO}_3$  solutions can penetrate into their inner cavity. The latter reaction competes with filling of the tubes. The structure of C-NT remains intact upon mild oxidation of carbon. Chromium trichloride was washed with water. The resulting composite is stable *in vacuo* under ion bombardment, as well as in air and in polar solvents, such as water, ethanol and acetone.

### d. Manganese oxides

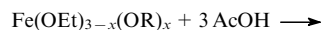
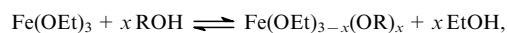
Nanoribbons of complex manganese magnesium oxide of composition  $\text{Mg}_{2.11}\text{Mn}_{5.46}\text{O}_{12} \cdot x\text{H}_2\text{O}$ , with a length varying from a few to tens of micrometres, a width of 20–100 nm and a specific surface area of  $81 \text{ m}^2 \text{ g}^{-1}$  were synthesised.<sup>247</sup> The compound crystallises in the pseudoorthorhombic (monoclinic) system with the unit cell parameters  $a = 9.7$ ,  $b = 2.9 \text{ \AA}$ ,  $\beta = 90^\circ$ ; the parameter  $c$  was not determined. The average oxidation state of Mn is +3.62. The nanosized crystalline ribbons contain tunnels with equal diameter extended along the  $a$  axis, which are arranged in an ordered fashion about the  $b$  axis. The size of the framework of the tunnel structure is  $6.9 \times 6.9 \text{ \AA}$ . The synthesis was carried out in an autoclave at 120, 150 and  $200^\circ\text{C}$  using layered microporous  $\text{MgO}$  and a  $(\text{Et}_4\text{N})_x\text{MnO}_y$  gel as precursors. Heating of the nanoribbons at 40–130  $^\circ\text{C}$  was accompanied by elimination of physically adsorbed water (5%). Water located in the tunnels was removed ( $\sim 11\%$ ) in the temperature range of 130–420  $^\circ\text{C}$ , and destruction accompanied by elimination of coordinated water and oxygen occurred at 420–560  $^\circ\text{C}$ . Relatively active oxygen chemisorbed in tunnels was eliminated at 480  $^\circ\text{C}$ , and oxygen involved in the crystal structure was eliminated at 550  $^\circ\text{C}$ . The catalytic activity of the nanoribbons in oxidation of benzyl alcohol to benzaldehyde was studied; the degree of conversion was as high as 45%.

Nanofibres of nanostructured  $\alpha\text{-MnO}_2$  were synthesised<sup>248</sup> by the template method. An aluminium membrane was placed in a sol (which was prepared by stirring fumaric acid,  $\text{KMnO}_4$  and a  $\text{H}_2\text{SO}_4$  solution for 10 min) for 10 s. Then the membrane was dried and heated in air at 500  $^\circ\text{C}$  for 24 h. The resulting manganese dioxide layers were separated and treated with a 6 M  $\text{NaOH}$  solution to remove the residual aluminium template.

### e. Iron oxides

Macroscopic hollow fibres of hematite ( $\alpha\text{-Fe}_2\text{O}_3$ ) with a diameter of 4–10  $\mu\text{m}$ , a wall thickness of 1–2  $\mu\text{m}$  and a length of up to 20 cm were synthesised.<sup>249</sup> Reduction of hematite with hydrogen affords hollow fibres of  $\alpha\text{-Fe}$ . Iron alkoxide  $\text{Fe}(\text{OEt})_3$ , which was dissolved in ethanol and mixed with 2-methoxyethanol (MOE) in the molar ratio  $\text{Fe}^{3+} : \text{MOE} = 1 : 3$ , was used as a precursor in the synthesis. Within 2 h after dissolution of the red precipitate in acetic acid ( $\text{Fe}^{\text{III}} : \text{AcOH} = 1 : 10$ ), a sol appeared. The sol was transformed into green fibres of the gel at 40  $^\circ\text{C}$  during several days. After removal of organic components at 200  $^\circ\text{C}$ , amorphous fibres were obtained. At 300 and 400  $^\circ\text{C}$ , the fibres were transformed into  $\beta\text{-Fe}_2\text{O}_3$  and  $\alpha\text{-Fe}_2\text{O}_3$ , respectively. Final thermal treatment of the fibres was carried out at 500–700  $^\circ\text{C}$ .

The mechanism of formation of hollow fibres can be represented by the following sequence of transformations:



The ROH (MOE) molecules form hydrogen bonds with the polymeric  $\text{Fe}(\text{OAc})_3$  units, resulting in the formation of an ethanol sol. Further polymerisation affords fibres containing large amounts of ethanol and acetate anions. Heating of the composite leads to diffusion of sol particles, evaporation of organic compounds and formation of tubes, which are transformed into hollow polycrystalline fibres by thermal decomposition of acetate with elimination of  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . Hollow fibres were observed also after storage of gels in air for one month.

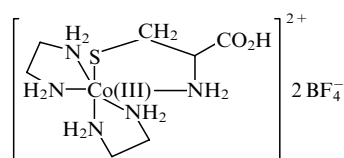
Nanoparticles of  $\alpha\text{-Fe}_2\text{O}_3$  with a size of smaller than 100 nm were deposited<sup>250</sup> as round-shaped particles with a size of  $\sim 1 \mu\text{m}$  on the (001) crystallographic face of silicon from a ferrocene, xylene and water vapour mixture at 1000  $^\circ\text{C}$ . In the absence of water vapour, carbon nanotubes are produced. Water vapour reacts with silicon of the substrate giving rise to round-shaped templates to which  $\text{Fe}_2\text{O}_3$  nanoparticles are bound as a result of selective etching and oxidation of  $\text{Fe}^0$  with  $\text{H}_2\text{O}$  vapour. It was also found<sup>251</sup> that  $\gamma\text{-Fe}_2\text{O}_3$  nanoparticles ( $\sim 5 \text{ nm}$ ) prepared by

hydrolysis of  $\text{FeCl}_3$  in the presence of *n*-octylamine undergo aggregation. Highly crystalline  $\alpha\text{-Fe}_2\text{O}_3$  nanotubes were prepared<sup>252</sup> by hydrothermal treatment of  $\text{Fe}(\text{NO}_3)_3$  in cavities of C-NT and in a NaOH solution.

Nanowires of cobalt ferrite  $\text{CoFe}_2\text{O}_4$  with an average diameter of 50 nm and a length of up to a few micrometres were synthesised under mild conditions inside C-NT.<sup>253</sup> Carbon nanotubes with an outer diameter of 120 nm and an inner diameter of 60 nm were filled with aqueous  $\text{Co}(\text{NO}_3)_2$  and  $\text{Fe}(\text{NO}_3)_2$  solutions in a molar ratio of 1 : 2 and heated in air at 100 °C. The amount of cobalt and iron salts recalculated for the metals accounts for 30% of the mass of C-NT. Thermal treatment of long-fibre  $\text{CoFe}_2\text{O}_4$  nanowires (with a diameter of ~60 nm, which is equal to the inner diameter of the template tube) at 450 °C afforded cobalt ferrite nanoparticles as capsules 10 nm in size. Biological macromolecules, for example, hollow protein tubes of tobacco mosaic virus, can also be used as a template for the preparation of iron oxide nanotubes.<sup>254</sup>

#### f. Cobalt oxides

It was found<sup>255</sup> that the trivalent cobalt complex  $\text{CoL}(\text{en})_2(\text{BF}_4)_2$



[where  $\text{L} = \text{NH}_2\text{CH}(\text{CO}_2\text{H})\text{CH}_2\text{S}$ ] can be readily inserted into polyelectrolyte (PE) layers of colloidal particles, is deposited on these particles and serves as a precursor of  $\text{CoO}$  NT. The starting composite was prepared by the addition of poly(diallyldimethylammonium chloride) (PDADMAC) to an aqueous suspension of polystyrene particles (PS) with stirring followed by centrifugation to remove an excess of PDADMAC and layer-by-layer deposition of poly(sodium 4-styrenesulfonate) (PSS) and  $\text{CoL}(\text{en})_2(\text{BF}_4)_2$  onto PS particles. After drying at room temperature in air, spherical particles of modified PS form a necklace-like structure (Fig. 5). [In the absence of the cobalt(III) complex, this structure is not formed, because hydrogen bonds of the cobalt-containing precursor in the composite play the key role.] The use of Co complexes, which are not involved in hydrogen bonding, led to the formation of hollow spheres. Calcination of modified PS particles at 385 °C under nitrogen and oxygen for 2 and 6 h, respectively, afforded  $\text{Co}_3\text{O}_4$  tubulenes with  $D = 200\text{--}400$  nm and  $L = 3\text{--}4$   $\mu\text{m}$ .

The necessary condition for the nanotube formation is the presence of ten alternating PDADMAC and PSS layers on PS particles. If the number of layers is smaller than six, nanotubes are not produced. The amount of the precursor in multilayer polyelectrolyte particles and the time of their heating under a stream of nitrogen and oxygen play an important role in the synthesis of  $\text{Co}_3\text{O}_4$  nanotubes. The morphology of nanostructures also depends substantially on the type of hydrogen-containing  $\text{Co}^{3+}$  complexes inserted into a multilayer polyelectrolyte on the surface

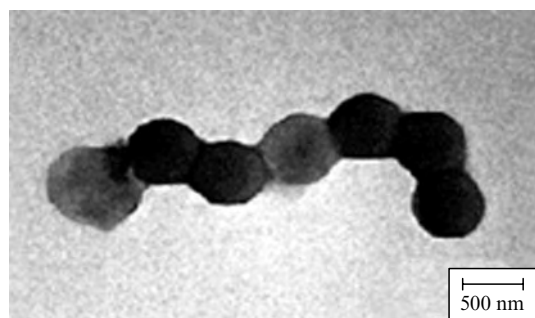


Figure 5. The TEM image of  $\text{CoO}_x$  NT.<sup>255</sup>

of colloidal particles.<sup>256</sup> Cobalt complexes with strong intermolecular hydrogen bonds form one-dimensional  $\text{Co}_3\text{O}_4$  nanotube structures. Complexes, in which hydrogen bonds are weak, if at all present, give rise to short defect-containing nanotubes and destroyed balls.

Nanostructures of  $\text{Co}_3\text{O}_4$  with a large specific surface area are of practical interest, because this  $\text{Co}^{2+}$ - and  $\text{Co}^{3+}$ -containing oxide with the spinel structure serves as a good catalyst for oxidation of CO. Nanosized  $\text{Co}_3\text{O}_4$  fibres can be prepared by the template sol–gel method.<sup>248</sup> An aqueous solution of  $\text{Co}(\text{NO}_3)_2$  (0.3 mmol litre<sup>-1</sup>) and citric acid (0.05 mmol litre<sup>-1</sup>) was subjected to hydrolysis for 1 h, the resulting sol was incorporated into an aluminium template membrane for 10 s, and the membrane was dried in air and annealed at 500 °C for 24 h. Then the membrane was dissolved in alkali to prepare individual  $\text{Co}_3\text{O}_4$  fibres.

#### g. Nickel oxides

Nickel-containing tubulenes can be synthesised by the template method.<sup>257</sup> For example, nickel nanowires were grown starting from C-NT, which were prepared by decomposition of propene on an anodised aluminium membrane.<sup>257</sup> The tubes were filled with nickel metal by decomposition of nickelocene under a stream of hydrogen at 105 °C. Then the aluminium membrane was removed by dissolution in 10 M NaOH at 150 °C in an autoclave. The length of the nickel nanowires thus prepared varies from tens to hundreds of nanometres, the diameter is 4 nm, and the inner size of C-NT is 20 nm, which is uncharacteristic of the template method. The latter usually gives nanowires with a length that coincides with the inner diameter of the channels in the template. The growth of nanowires occurs predominantly along the (111) plane of the crystal structure of nickel metal. The formation of the latter in the vicinity of the open ends of C-NT was not observed. Nickel nanowires are produced inside C-NT by vacuum evaporation of nickelocene.<sup>258</sup>

Decomposition of nickelocene at 275 °C under a water vapour atmosphere followed by deposition of nickel on a carbon film afforded a Ni–C composite.<sup>257</sup> Treatment of the latter with 10 M NaOH at 150 °C in an autoclave produced C-NT with inclusions, which are analogous to nanosized NiO ribbons 4 nm in width and 10–800 nm in length, and nickel metal particles (larger than 10 nm, Fig. 6). The upper and lateral surfaces of the nanoribbons are parallel to the (111) and (202) crystallographic planes, respectively, of NiO, if its axis is oriented along the [211] direction.

The formation of NiO results from oxidation of nickel with atmospheric oxygen, which occur during alkaline treatment of the composite in an autoclave. In the cavity of C-NT with an inner diameter of 20 nm, NiO crystals grow along the tube axis. In

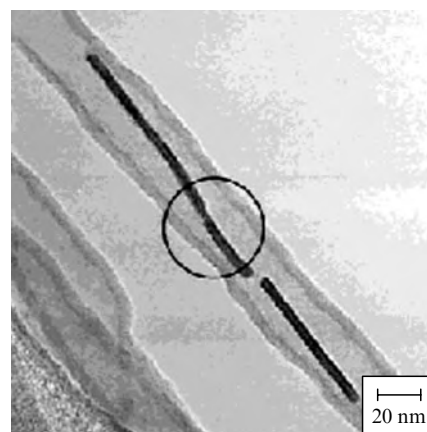


Figure 6. The TEM image of a NiO nanoribbon intercalated into a carbon nanotube.<sup>257</sup>



C-NT with  $D > 20$  nm, platelets with sizes (in the plane) of hundreds of nanometres can be produced. The complete filling of the cavities in C-NT with NiO crystals is needed for the synthesis of nanowires or nanorods. However, this does not occur due to the growth of a thin crystalline NiO plate along the tube axis. The NiO–C-NT nanocomposite can also be prepared by filling carbon nanotubes, which are pre-treated with nitric acid followed by annealing under a stream of argon at 450 °C for 5 h, with nickel nitrate.<sup>259</sup> In this case, nickel oxide completely fills the inner cavity of the tube ( $\sim 3$ –6 nm in diameter) to form elongated nanoparticles (10–40 nm in length). This composite can be used as a catalyst in organic synthesis.

#### h. Copper oxides

Nanosized CuO rods were synthesised<sup>260</sup> according to a rather simple procedure by stirring  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  and NaOH in the presence of polyethylene glycol (PEG). Then the composite was washed with water and EtOH and dried in air at 60 °C for 3 h. The final product consisted of identical CuO nanorods 8 nm in diameter and 40 nm in length. The type of the nanostructures is determined by PEG, which forms chain aggregates in water. The synthesis of bamboo-like CuO nanoparticles ( $D = 20$ –90 nm,  $L = 250$ –700 nm) was documented.<sup>261</sup> Templates of multilayer C-NT were treated with boiling  $\text{HNO}_3$  (68%) for 24 h, stirred with a  $\text{Cu}(\text{NO}_3)_2$  solution for 48 h, filtered, washed with water and dried at 60 °C for 12 h. Heating under a stream of argon at 450 °C (5 h) followed by burning up of C-NT in air (750 °C, 1 h) afforded copper oxide with the parameters of the monoclinic unit cell  $a = 4.697$ ,  $b = 3.425$ ,  $c = 5.130$  Å,  $\beta = 99.67^\circ$ . The average size of the crystallites was 37 nm (calculated from the width of the (110) reflection), and the crystallites are oriented predominantly along the [101] direction. It should be noted that the sizes of the CuO nanoparticles are much larger than those of the template, which is attributable to the tendency of the system to decrease the surface energy and to the intergrowth of the adjacent CuO nanostructures upon burning up of carbon tubes.

One-dimensional well-ordered CuO nanofibres are produced during autocatalytic growth.<sup>262</sup> Copper nuclei with sizes equal to the pore diameter of the membrane (50–60 and 100–150 nm) were deposited on a copper plate having a polycarbonate (PC) membrane as a template from a  $\text{CuSO}_4$  solution in the electric field of  $15 \text{ V cm}^{-1}$ . Heating of Cu crystallites under an oxygen atmosphere results in their transformation into nanocrystalline CuO fibres with an average length of 2  $\mu\text{m}$  and a packing density of  $10^7$ – $10^8 \text{ cm}^{-2}$ . The diameter of nanofibres corresponds to the average size of copper particles. The solid-phase synthesis of nanosized whiskers ( $D = 2$ –10 nm,  $L > 100$  nm) in the presence of the non-ionic surfactant polyethylene glycol (PEG-400) was also documented.<sup>263</sup>

The CuO/C-NT composite with the mass ratio CuO:C = 3:2, which was prepared by oxidation of Cu/C-NT by heating to 160 °C in air for 12 h, was studied as a cathode material in current sources with a lithium anode.<sup>264</sup> Lithium (1.88 g-at of Li per 6 g-at of C) was inserted into C-NT by the electrochemical method. This amount of lithium corresponds to the capacity of 700 mA h  $\text{g}^{-1}$ . For CuO/C-NT layers, the capacity is 268 mA h  $\text{g}^{-1}$ . Lithium is inserted into the CuO structure at a potential of 1.7–1.0 V and is eliminated at 2.3–2.5 V. The stable operating time of the CuO/C-NT cathode material during cycling is determined by stability of the intercalation compound  $\text{Li}_x\text{CuO}$ , which decomposes into Cu,  $\text{Cu}_2\text{O}$  and  $\text{Li}_2\text{O}$ . In this case, the microstructure of C-NT is of considerable importance. Intercalation and deintercalation of lithium causes destruction of C-NT.

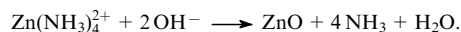
#### k. Zinc oxides

Nanostructured ZnO has attracted considerable attention,<sup>265</sup> because materials based on this compound are widely used in electronics, optoelectronics, optics, solar batteries and sensors and also serve as photocatalysts. Zinc oxide nanorods and nanofibres

were prepared by the hydrothermal method.<sup>266–269</sup> The simplest microemulsion method is the reverse of the micelle formation.<sup>266</sup> Cetyltrimethylammonium bromide (CTAB) was used as a micro-emulsifying agent. Sodium hydroxide was added to a solution of zinc acetate in n-hexanol and n-heptane to pH 14. The mixture was stirred until a  $\text{Zn}(\text{OH})_4^{2-}$  emulsion was formed and then heated in an autoclave at 140 °C for 13 h. The white precipitate that formed was washed and dried *in vacuo* at 60–70 °C. The product consisted of nanowires of hexagonal ZnO ( $D = 30$ –150 nm,  $L$  to 3  $\mu\text{m}$ ) with the growth direction along the ZnO (110) crystallographic plane. Single-crystalline ZnO nanowires ( $D = 80$ –100 nm,  $L \approx 10 \mu\text{m}$ , the [0110] growth direction) were also synthesised by hydrothermal treatment of  $\text{Zn}_4\text{CO}_3(\text{OH})_6 \cdot \text{H}_2\text{O}$ .<sup>269</sup>

Hydrothermal oxidation of zinc metal in the presence of CTAB (180 °C, 20 h) affords ZnO nanorods.<sup>268</sup> Surfactants, such as CTAB and n-hexanol, play an important role in the formation of ZnO nanowires. These surfactants facilitate the orientational growth of ZnO. In the synthesis with the use of zinc metal as a precursor, the surfactants promote erosion of ZnO. Ultrasonic pre-treatment of the reaction mixture before hydrothermal treatment facilitates nucleation and gives rise to a unified morphology of ZnO nanorods in an alkaline solution in the ratio  $\text{Zn}^{2+}:\text{OH}^- = 1:20$  in the presence of ethanol and ethylenediamine.<sup>267</sup> Intergrowths of ZnO rods with a diameter 30–40 nm, a length of 1.5  $\mu\text{m}$  were prepared (the unit cell parameters  $a = 3.25$ ,  $c = 5.21$  Å). These rods exhibit photoluminescence at 385 and 485 nm under excitation with a He–Cd laser at a wavelength of 325 nm.<sup>266</sup>

A zinc oxide tubular material with an outer diameter 450 nm, an inner diameter of 250 nm and an average length of 4  $\mu\text{m}$  was synthesised<sup>270</sup> under hydrothermal conditions (180 °C, 13 h) from an ethanolic solution containing  $\text{Zn}(\text{NH}_3)_4^{2+}$  cations by the reaction



Ammonia that is eliminated plays an important role in the formation of the tubular morphology of ZnO. The reaction performed at a temperature below 180 °C with the use of methanol or propanol instead of ethanol produces the final product consisting only of ZnO nanoparticles.

Zinc oxide nanorods can be prepared by simple thermal decomposition of hydrated zinc acetylacetonate  $\text{Zn}(\text{acac})_2 \cdot n\text{H}_2\text{O}$  in an atmosphere of a  $\text{N}_2$  and  $\text{O}_2$  mixture at a pressure of  $5 \times 10^{-3} \text{ mm Hg}$  and at 130–140 °C on silicon [(100) plane] and sapphire substrates.<sup>271</sup> The ordered ZnO structure ( $D = 60$ –80 nm,  $L = 450$ –500 nm) is prepared on the silicon (100) plane, whereas ZnO nanorods, which are oriented along the  $c$  axis and arranged in an ordered fashion along the  $a$  axis, were grown only on the sapphire (110) plane. Zinc oxide nanorods were grown also on an amorphous  $\text{SiO}_x$  layer of a Si(100) plate heated to 500 °C. These rods show emission and absorption in the UV region at 386 nm and are characterised by a low concentration of oxygen vacancies. The synthesis of high-quality well-oriented nanorods with a controlled diameter (45, 60 or 90 nm) was carried out by varying the vapour temperature (135–138 °C), the flow rate of a  $\text{N}_2/\text{O}_2$  mixture and the substrate temperature. The synthesis at 130–200 °C from  $\text{Zn}(\text{acac})_2$  vapour and products of its partial decomposition [for example,  $\text{Zn}(\text{acac})$ ] affords zinc metal, which is oxidised on the substrate surface followed by the growth of nanostructured ZnO.

Zinc oxide nanowires and nanorods can also be prepared in aqueous solutions of zinc salts.<sup>272, 273</sup> The oppositely charged  $\text{Zn}(\text{NH}_3)_4^{2+}$  and  $\text{Zn}(\text{OH})_4^{2-}$  micelles act as microreactors, resulting in the anisotropic growth of ZnO during a simple solvothermal process.

Nanostructured ZnO was synthesised<sup>274</sup> at room temperature by adding 0.02 M NaOH to a mixture of solutions of  $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$  (0.01 mol litre<sup>-1</sup>) and triethanolamine (TEA) (0.07 mol litre<sup>-1</sup>), which was used as a surfactant, and stirring for

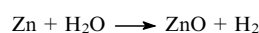


30 min. The composite was washed with water and ethanol using ultrasonic treatment and dried at 80 °C. The final product consisted of hexagonal nanorods (the hexagonal system,  $a = 3.249$ ,  $c = 5.209$  Å) with a diameter of 20 nm and a length of up to 200 nm. In the absence of TEA, ZnO nanoparticles were prepared. The optimum TEA:Zn<sup>2+</sup> ratio is smaller than (0.1–1):1.

The solid-phase synthesis of hexagonal ZnO nanorods ( $a = 3.250$ ,  $c = 5.207$  Å;  $D = 40$ –120 nm,  $L$  is up to several micrometres)<sup>275</sup> was carried out with the use of a ZnCl<sub>2</sub>, Na<sub>2</sub>CO<sub>3</sub> and KCl mixture, which was prepared with poly(oxyethylene)-5-nonylphenol or poly(oxyethylene)-9-nonylphenol ether in cyclohexane, as a precursor. The latter gave a precipitate, which was washed with acetone, separated by centrifugation, dried, annealed in air (770 °C, 3 h) and washed with water. The use of NaCl instead of KCl (as a flux), an increase in the temperature to 820 °C or an increase in the annealing time led to the formation of larger nanorods.

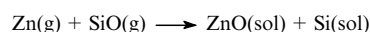
The growth of perfect individual ZnO nanorods with  $D = 150 \pm 10$  nm and  $L = 2.17 \pm 0.13$  µm was observed upon decomposition of amorphous tubular Zn(OH)<sub>2</sub> as a precursor.<sup>276</sup> Good reproducibility of the sizes was achieved with the use of sodium dodecylbenzenesulfonate (DBS) as a modifying and protecting agent.

Zinc oxide nanorods with a diameter of 5–300 nm and a length of up to several hundreds of micrometres can be synthesised by the reaction



in the gas phase at 730–1000 °C.<sup>277–280</sup> The growth of ZnO occurs along the  $c$  axis (the [001] direction). For nanostructures synthesised at 1000 °C under argon for 30 min, the following three luminescence bands are observed:<sup>280</sup> a strong band in the UV region (379 nm), a blue band (466 nm with a shoulder at ~452 nm) and a weak yellow band (612 nm). The UV emission is induced by direct exciton recombination, and the blue band appears due to the imperfect ZnO structure. After annealing under oxygen at 500 °C, the blue and yellow luminescence bands are substantially weakened due to a decrease in the concentration of O and Zn defects.

A modification of the chemical vapour-phase synthesis of ZnO nanowires is based on the reaction



at 900 °C under a stream of argon.<sup>281</sup> Oxidation of zinc vapour in the temperature range of 850–925 °C affords high-quality ZnO nanostructures as intergrowths of four nanorods (Fig. 7).<sup>282</sup> The morphology of the particles depends on the conditions of the process.<sup>283</sup> Tetrahedral intergrown T-ZnO nanorods are produced in air (see Table 1), whereas individual nanorods are formed under wet argon and nitrogen. The T-ZnO structure consists of tetrahedrally shaped intergrowths with four 'legs'

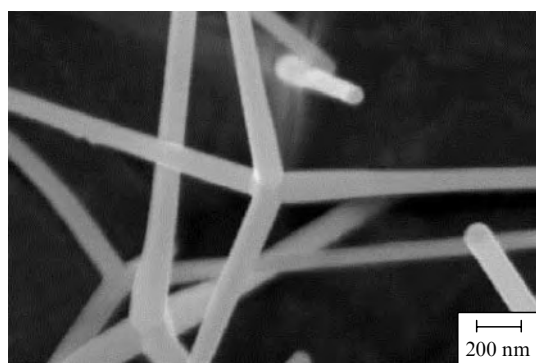


Figure 7. The SEM image of an intergrowth of T-ZnO nanorods.<sup>282</sup>

2–3 µm in length and the central core with a size of 70–200 nm.<sup>284</sup>

Oxidation of an aluminium-based melt containing 6% Si, 2% Zn and 0.8% Fe (mass %) produced relatively linear ZnO whiskers 50–500 nm in diameter.<sup>285</sup> The process was carried out at 1100 °C for 1 h under oxygen. The melt was oxidised to form Al<sub>2</sub>O<sub>3</sub> microchannels on the surface. These channels were filled with a liquid alloy, and zinc metal was oxidised to ZnO on the surface of the alloy, resulting in the growth of nanowhiskers tens of micrometres in length. In this example, iron serves as a catalyst, and silicon acts as a promoter of growth of ZnO nanowhiskers.

Zinc oxalate, which was prepared in cyclohexane in the presence of a surfactant, was used as a precursor to prepare ZnO nanowires.<sup>286</sup> Zinc oxalate with an admixture of a flux (NaCl) was heated at 920 °C under a stream of argon. Thermolysis of ZnC<sub>2</sub>O<sub>4</sub> afforded ZnO, which was reduced with carbon of the surfactant to Zn, and the latter went to the gas phase. Zinc and zinc oxide vapours were deposited on the walls of the reactor to form zinc oxide nuclei containing defects in the oxygen sites. Zinc oxide nanowires ( $a = 3.249$ ,  $c = 5.206$  Å,  $D = 15$ –80 nm) were grown when air was passed through the mixture. Depending on the flow rate of argon, either nanowires or nanowhiskers grow on the (101) surface. The addition of a NaCl flux facilitates the formation and nucleation of nanostructured ZnO, hinders particle agglomeration and promotes evaporation of Zn and ZnO.

Crystalline nanowhiskers of hexagonal ZnO were prepared by reduction of ZnS with hydrogen (5% H<sub>2</sub> under argon) at 1300 °C to give Zn followed by oxidation to ZnO in an Ar + 5% O<sub>2</sub> gas mixture.<sup>287,288</sup> The process is autocatalytic and occurs by the vapour–liquid–solid mechanism. The growth of ZnO occurs along the [0001] direction. The outer diameter, the length and the wall thickness of the whiskers range up to 400 nm, 15 µm and 100–150 nm, respectively.<sup>288</sup> The photoluminescence spectrum of the whiskers shows a strong emission band in the UV region (381 nm) and a broad band at 583 nm (green luminescence).

Zinc oxide forms unusually extended and oriented chiral nanostructures.<sup>289</sup> Such nanorods and nanocolumns grow in the presence of citrate ions that control the crystal growth due to adsorption on the (002) surface. The synthesis was carried out with the use of oriented ZnO nanorods, which were grown on a glass substrate in a solution of Zn(NO<sub>3</sub>)<sub>2</sub> (0.03 mol litre<sup>-1</sup>) and hexamethylenetetramine (HMT) (0.03 mol litre<sup>-1</sup>) at 60 °C for 3 days. To grow helical ZnO nanostructures, the substrate was placed in a solution containing Zn(NO<sub>3</sub>)<sub>2</sub> (0.03 mol litre<sup>-1</sup>), HMT (0.01 mol litre<sup>-1</sup>) and sodium citrate (0.001 mol litre<sup>-1</sup>) and the mixture was kept at 95 °C for 1 day. The process was repeated by adding small amounts of sodium citrate. Chiral nanorods 1 µm in length were prepared. The base and top diameters were 500 and 30 nm, respectively. The nanorods were composed of helically arranged platelets with a step height of ~15 nm.

The microwave-induced plasma method was used<sup>290,291</sup> to synthesise ZnO structures with different morphologies (nanowires, nanocables, nanotubes) and specified sizes. Zinc or zinc oxide powder was placed in a quartz tube furnace, through which hydrogen was passed. Microwave heating of the precursor (400 W, 2.45 MHz) up to the plasma formation (1000 °C) led to condensation of Zn vapour in the furnace region with a temperature 500 °C. After evaporation for 30 min, hydrogen flow was terminated, and zinc was oxidised by passing a 1 : 50 oxygen and argon mixture for 15–30 min. Zinc nanowires formed under hydrogen served as a template in the synthesis of nanosized Zn/ZnO cables involving partial oxidation of zinc with oxygen followed by the formation of ZnO NT. The wall thickness of the tubes depends on the time of oxidation occurring along the [001] direction. The average outer and inner diameters of nanotubes were 40 and 10 nm, respectively, and the length was 1 µm. The sizes of the tubes can be varied depending on the conditions of the microwave-induced plasma process, the flow rate of hydrogen and the oxidation time. The microwave-induced plasma method

combined with heating in a furnace allows one to prepare also nanostructured ZnO as aggregates consisting of four nanorods with a diameter of 10–25 nm and a length of up to 160 nm.<sup>291</sup> Cathode luminescence of such structures is characterised by strong UV radiation at 385 nm.

Nanosized whiskers of oxalate  $\text{ZnC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$  can be prepared by a chemical method.<sup>292</sup> For this purpose, the  $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$  precursor was dispersed in xylene with an admixture of sodium DBS as a template. An ethanolic solution of  $\text{H}_2\text{C}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$  was added to the resulting suspension, and the white precipitate consisting of nanosized whiskers ( $D = 200\text{--}300\text{ nm}$ ,  $L$  up to  $20\text{ }\mu\text{m}$ ) was separated by centrifugation, washed and dried *in vacuo* at  $60\text{ }^\circ\text{C}$ . Some whiskers were obtained as tubes with a wall thickness of  $\sim 30\text{ nm}$ . Heating of these nanostructures at  $180$  and  $427\text{ }^\circ\text{C}$  was accompanied by elimination of  $\text{H}_2\text{O}$  and  $\text{CO}_2$ , respectively. The resulting nanostructured ZnO powder ( $50\text{--}60\text{ nm}$ ) was stable up to  $1280\text{ }^\circ\text{C}$ . At a temperature below  $280\text{ }^\circ\text{C}$ ,  $\text{ZnC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$  was transformed into  $\beta\text{-ZnC}_2\text{O}_4$  nanowhiskers. The  $\text{ZnC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$  nanoparticles prepared from an aqueous solution had a size and shape, which were determined by a microreactor composed of the surfactant (DBS).

Considerable progress was made in the synthesis of nanostructured ZnO by evaporation of zinc metal and its compounds. Zinc oxide nanowires ( $D < 50\text{ nm}$  and up to tens of micrometres in length) were prepared by heating Zn under a stream of nitrogen or argon in the absence of a catalyst (zinc metal serves as the catalyst, which is then oxidised to ZnO).<sup>293</sup> Heating of a zinc plate at  $900\text{ }^\circ\text{C}$  affords ZnO nanostructures exhibiting a tetrahedral morphology (see Fig. 7).<sup>294</sup> Evaporation of Zn powder at  $800\text{ }^\circ\text{C}$  under argon gives rise to the hexagonal phase of ZnO as wires with a diameter of  $0.2\text{--}0.4\text{ }\mu\text{m}$  and a length of several tens of micrometres.<sup>295</sup> This material exhibits strong green luminescence at  $520\text{ nm}$  and relatively weak UV luminescence near  $370\text{ nm}$ . The former appears due to electron–hole recombination with the involvement of electrons of the charged oxygen vacancies in the ZnO structure. Zinc oxide nanowires ( $30\text{--}60\text{ nm}$  in diameter and tens of micrometres in length), which were prepared by heating Zn powder in the presence of Au nanoparticles as the catalyst at  $900\text{ }^\circ\text{C}$ , also show a strong green emission.<sup>296</sup>

Evaporation of zinc oxide at  $1380\text{ }^\circ\text{C}$  under a stream of argon or *in vacuo*<sup>297–299</sup> affords single-crystalline ZnO nanowires ( $D = 15\text{--}60\text{ nm}$ ,  $L = 10\text{--}70\text{ }\mu\text{m}$ ) with the  $[110]$  growth direction.<sup>298</sup> Samples synthesised *in vacuo* hold promise as materials for short-wavelength nanolasers.<sup>299</sup> Condensation of ZnO vapour in the temperature range of  $900\text{--}1030\text{ }^\circ\text{C}$  gave a mixture of nanosized rods and belts of nanometre to micrometre diameter (width).<sup>300</sup> In the temperature range of  $650\text{--}700\text{ }^\circ\text{C}$ , rods and belts with  $D = 70\text{--}300\text{ nm}$  were grown. More homogeneous materials were produced at  $350\text{--}450\text{ }^\circ\text{C}$  as wires  $15\text{--}40\text{ nm}$  in diameter and  $10\text{--}70\text{ }\mu\text{m}$  in length. The growth direction of ZnO crystals is perpendicular to the  $(01\bar{1}0)$ ,  $(0001)$  and  $(11\bar{2}0)$  planes for the belts, rods and wires, respectively. Crystalline ZnO nanobelts, which were prepared<sup>301</sup> by thermal evaporation of ZnO in pores of an aluminium membrane, had a length of  $10\text{--}100\text{ }\mu\text{m}$ , a width of  $30\text{--}300\text{ nm}$  and a thickness of  $6\text{--}30\text{ nm}$  and contained a smaller number of oxygen defects than powders synthesised under analogous conditions.

Additives of oxides<sup>302</sup> or low-melting point metals<sup>303</sup> in the synthesis of nanostructures from ZnO vapour increase the evaporation rate of the latter and influence the morphology of the final product. Nanosized bridges and nails can be prepared from ZnO on a graphite, silicon or  $\text{SrTiO}_3$  substrate by varying the conditions of the synthesis. Nanobridges are produced by the addition of  $\text{In}_2\text{O}_3$  to zinc oxide at  $1000\text{ }^\circ\text{C}$  and an air pressure of 2 Torr, and nanonails grow at  $950\text{--}970\text{ }^\circ\text{C}$  and  $0.5\text{--}1.0$  Torr. A typical bridge (Fig. 8) is tens of micrometres in length and up to several micrometres in height and width;<sup>302</sup> it consists of a ZnO belt and nanorods ( $50\text{--}200\text{ nm}$  in diameter and up to  $2\text{ }\mu\text{m}$  in length) located at the edges of the belt. Each nanorod belonging to the hexagonal system grows epitaxially along the  $[0001]$  or  $[000\bar{1}]$

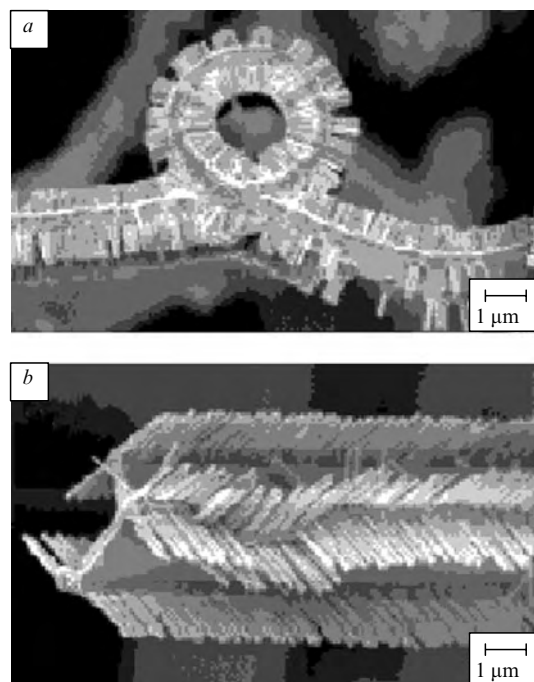


**Figure 8.** The SEM images of different types of ZnO bridges; (a) coiled; (b) doubled.

direction. The rows of nanorods are parallel to the  $[01\bar{1}0]$  direction of the belt, which forms a ring in the centre of the bridge (Fig. 8a). Two belts can be linked together perpendicular to each other (Fig. 8b). The epitaxial growth of ZnO nails along the  $c$  axis occurs on a graphite substrate (Fig. 9). These structures are

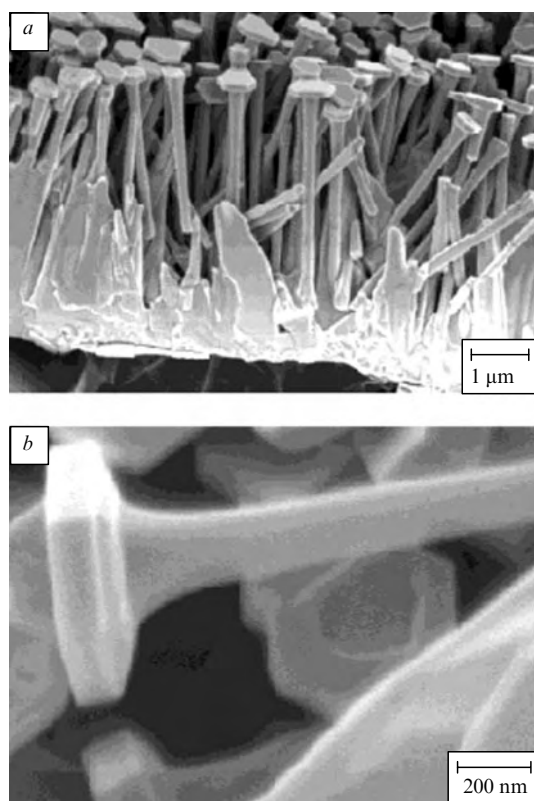


**Figure 9.** The SEM images of ZnO nanonails.<sup>302</sup>

several micrometres in length, the diameters of the rods are in a range of 150–200 nm, and the diameter and thickness of the hexagonal nail-heads are  $\sim 1\ \mu\text{m}$  and 50–100 nm, respectively.

The characteristic feature of ZnO nanostructures formed in the presence of low-melting point elements is the growth of attached branches of various shapes. In this case, the surface segregation of low-melting point elements plays an important role due to enrichment of the tops of nanostructures in these elements. A three-dimensional self-organised nanosized ZnO-based heterostructure doped with In or Sn was synthesised by condensation from a vapour phase on a graphite substrate.<sup>303</sup> A ZnO,  $\text{In}_2\text{O}_3$  (or  $\text{SnO}_2$ ) and graphite mixture was heated at 1000 °C and condensed at 850 °C by oxidation with atmospheric oxygen to form nanosized In- or Sn-doped ZnO ribbons. Indium-containing comb-shaped heterostructures have a core composed of nanowires ( $D = 10\text{--}15\ \text{nm}$ ) grown along the  $[01\bar{1}0]$  direction. The  $\pm(2\bar{1}\bar{1}0)$  faces of the core are covered with nanoribbons located perpendicular to this face. The chemical composition of the core is described by the formula  $(\text{ZnO})_{11}\text{In}_2\text{O}_3$ . At a higher percentage of indium in the starting mixture, an additional growth of ZnO nanorods with a length of 100–3000 nm on both sides of the nanowires (perpendicular to the ribbon plane) is observed. These nanorods form a straight row. Therefore, the nanorods and nanoribbons grow epitaxially on the core formed by nanowires.

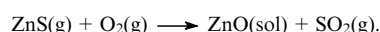
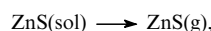
A further increase in the percentage of indium in the starting mixture leads to the formation of nanostructures as four- or six-blade rotors (Fig. 10). The length of such rotors along the central axis is equal to tens of micrometres, and the length of the nanorods forming the blades varies from 200 nm to several micrometres. The terminal blades of the nanorods are ordered in a line and are hexagonal in shape. The core of the rotors consists of  $\text{In}_2\text{O}_3$  belonging to the cubic system with the unit cell parameters  $a = 10.118\ \text{\AA}$ . If the growth of the core occurs along the  $[001]$  direction, there are four equivalent (100) planes, on which ZnO nanorods grow to form a four-blade rotor. If the  $\text{In}_2\text{O}_3$  core grows along the  $[111]$  direction, the resulting nanorotor has six symmetrical blades corresponding to six equivalent (110) planes.

The growth of nanoribbons with a length of 1–20  $\mu\text{m}$  and a width of  $\sim 1\ \mu\text{m}$ , which cover the core of the nanostructure, occurs also in the presence of tin. The core of the structure consists primarily of ZnO and grows in the  $[01\bar{1}0]$  direction, while the

ribbons grow in the  $[2\bar{1}\bar{1}0]$  direction. The Sn:Zn ratio increases from the centre to the ends of the structure, where it is  $\sim 8\%$ .

The self-organised type of the structural configuration of ZnO nanowires and nanoribbons butt-joined together was obtained<sup>304</sup> by thermal evaporation of a ZnO and  $\text{SnO}_2$  mixture in a mass ratio of 1:1 at 1300 °C under a stream of argon (300–400 Torr). Nanostructured oxide ZnO is produced in a furnace in the upper part of the alundum tube at 700–800 °C. Tin particles reduced from  $\text{SnO}_2$  serve as the catalyst for this process. The morphology of the resulting structures appears like a liana: Sn balls are attached to the axial ZnO nanowire ( $D \approx 30\ \text{nm}$ ) by nanoribbons (Fig. 11). The junctions of the ribbons with the axial nanowire are tens of nanometres at size, the width of the ribbons varies from 100 to 200 nm, and the ribbons are arranged about the axial nanowire at approximately 60 degree intervals. In the first step of formation of this configuration, the axial ZnO nanowire rapidly grows along the  $[0001]$  direction under the catalytic action of tin. Then particles of tin melt on the surface of the nanowire and initiate nucleation and epitaxial growth of nanoribbons. In this slower step, tin particles at the ends of the nanoribbons grow in size to form a tadpole-shaped structure (Fig. 11b). The growth of ZnO nanoribbons along six directions,  $\pm[10\bar{1}0]$ ,  $\pm[01\bar{1}0]$  and  $\pm[\bar{1}100]$ , give rise to six symmetrically arranged tadpoles with an angle between the adjacent tadpoles of  $\sim 60^\circ$ .

Semiconducting single-crystalline ZnO wires were synthesised by thermal evaporation of ZnS on a Si(100) substrate in the presence of Au as the catalyst<sup>305</sup> at 1223 K under argon (150 Torr) according to the reactions



The nanowires 20–60 nm in diameter and tens of micrometres in length grow along the  $[001]$  direction and contain a high density of structural defects. Evaporation of a ZnS and  $\text{Fe}(\text{NO}_3)_3$  mixture in

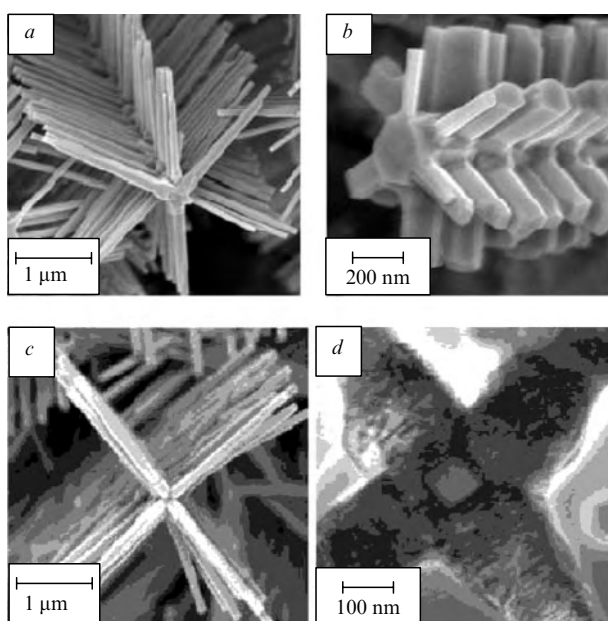


**Figure 10.** The SEM (a and c) and TEM images (b and d) of ZnO nanorotors with six (a and b) and four (c and d) blades.<sup>303</sup>

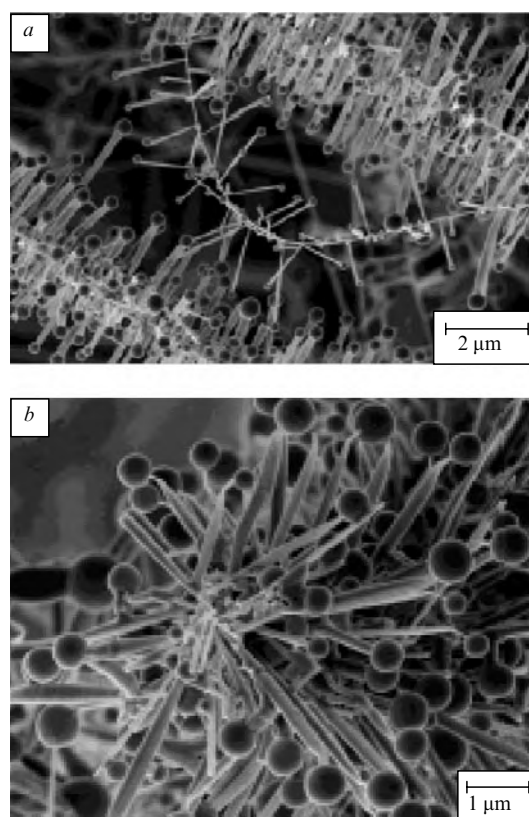
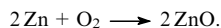
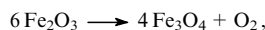
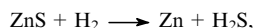
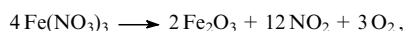


**Figure 11.** The SEM images of nanosized liana-shaped (a) and tadpole-shaped (b) ZnO heterostructures.

a molar ratio of 1 : 2 (1300 °C, 12 h) under argon containing 5% H<sub>2</sub> (350 Torr) affords whiskers with a diameter of 200–500 nm and tens of micrometres in length.<sup>306</sup> Zinc oxide whiskers do not grow under pure argon or nitrogen. In oxygen, micronic-size ZnO particles are produced by the reactions



Thermolysis of Fe<sub>2</sub>O<sub>3</sub> occurs very slowly, due to which a low O<sub>2</sub> concentration in the gas phase leads to the formation of nanosized ZnO nuclei and growth of oxygen-defect whiskers. Zinc oxide nanobelts, which grew along the [01 $\bar{1}$ 0] direction and were bounded by the  $\pm(0002)$  and  $\pm(01\bar{1}0)$  planes, were synthesised by evaporation of ZnCl<sub>2</sub> in an Ar and O<sub>2</sub> gas mixture in a ratio of 10 : 1 at 700 °C.<sup>307</sup> The resulting material is intended for use in light-emitting and laser diodes.

In the Et<sub>2</sub>Zn and N<sub>2</sub>O vapour phase (1 : 3 ratio, 200 Torr), high-quality ZnO nanorods and layered structures were grown epitaxially.<sup>308</sup> Nanorods with a diameter of 10–50 nm and a height of 0.5–1 µm grow on a sapphire substrate at 500 °C, whereas ZnO layers of identical shape grow at 800 °C. Three-dimensional structures are generally synthesised when the temperature of a sapphire<sup>308</sup> or silicon<sup>309,310</sup> substrate is lower than 700 °C, whereas two-dimensional layered structures grow at higher temperatures.

Evaporation of Zn(acac)<sub>2</sub>·*n*H<sub>2</sub>O at 130–140 °C under an atmosphere of an N<sub>2</sub> and O<sub>2</sub> mixture (in a ratio of 1 : 1, 200 Torr)<sup>311</sup> and with the use of a Si(001) substrate heated to 450 °C produced nanorods with *D* = 45 nm and *L* = 200 nm. The diameter of the nanorods increased with increasing temperature. The epitaxial growth of ZnO nanorods from an organometallic phase occurs also on an Al<sub>2</sub>O<sub>3</sub>(001) substrate at 400 °C.<sup>312</sup> Nanorods of equal length and density and with *D* ≈ 25 nm grow perpendicular to the substrate along the *c* axis of the ZnO lattice.

The growth of nanosized ZnO wires, rods and whiskers on a sapphire substrate by evaporation of zinc oxide was documented.<sup>313–316</sup> Analogous structures were also grown on a silicon substrate.<sup>317–322</sup> A substrate imperfection influences the selectivity of the initial growth of nanowires.<sup>318</sup> On an imperfect Si(100) face consisting of terraces separated by steps, nuclei of ZnO nanowires appear at the edges of the steps along the [01 $\bar{1}$ ] direction and grow perpendicular to the support. Zinc oxide nanowires virtually do not grow on a defect-free Si(100) substrate. Twinned ZnO nanowires, in which the boundary between single-crystalline domains is parallel to the growth axis, grow on a Si substrate during evaporation of Zn under an atmosphere with a low oxygen content.<sup>319</sup> The components of the twin, which have no dislocations and amorphous regions, are parallel to the (0 $\bar{1}$ 14) plane and grow along the [0 $\bar{1}$ 1 $\bar{1}$ ] direction and the (2 $\bar{1}$ 10) plane. The distance between the adjacent planes of the crystal lattice (2.60 ± 0.05 Å) corresponds to the distance between the (0002) planes. This unusual structure serves as a model for studying the electrical charge transport and mass transfer along a single planar defect.

Single-crystalline ZnO nanobelts were prepared<sup>320</sup> on a Si substrate by infrared heating of a Cu–Zn melt under moderate vacuum. Nanostructures grow along the [0001] direction, and their length is twice as large as their width. Long ZnO nanowires can be prepared catalytically on a Si substrate partially covered with gold under an atmosphere of an Ar and H<sub>2</sub>S mixture at a low partial pressure of hydrogen sulfide.<sup>321</sup> A vapour phase was prepared by carbon thermal reduction of ZnO. Nanowires grown under these conditions show blue-green luminescence, whose intensity increases with increasing H<sub>2</sub>S partial pressure in the synthesis of this material.

A substrate and a template composed of anodised aluminium are widely used to grow ZnO nanostructures with different morphologies.<sup>322–325</sup> Polycrystalline ZnO nanowires were prepared on anodised aluminium by vacuum evaporation of ZnO.<sup>322</sup> Nanosized tower-shaped ZnO columns were produced by pyrolysis and oxidation of ZnS.<sup>323</sup> Apparently, these columns grow by layering nanocrystalline zinc oxide. Zinc oxide nanowires (*D* = 40–200 nm) containing a low concentration of oxygen vacancies were also grown on an aluminium substrate by heating a 1 : 1 mixture of ZnO and Zn powders to 500 °C in the presence of water vapour as an oxidiser.<sup>324</sup>

The synthesis of ZnO nanowires with a high degree of crystallinity was carried out on an aluminium substrate in the presence of the NiO catalyst.<sup>325</sup> Zinc metal was evaporated at 450–950 °C under argon. The samples thus prepared have a hexagonal structure, a diameter of 55 nm and a length of 2.6 µm (Fig. 12). At a growth temperature of 500 °C, the nanowires are characterised by the perfect hexagonal morphology. All ends of nanowires are well-formed and can serve as mirror planes for a laser matrix.

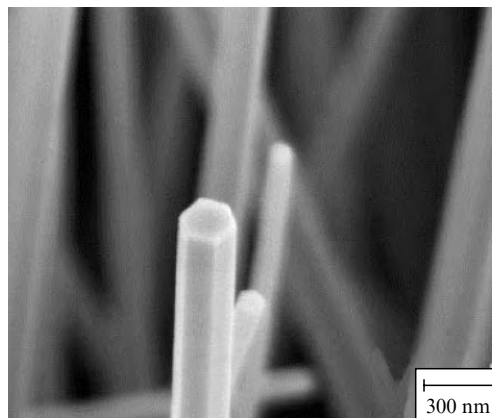


**Figure 12.** The SEM image of ZnO nanowires prepared on an aluminium membrane.<sup>325</sup>

Electrochemical deposition using an anodised aluminium template membrane also allows one to prepare ZnO nanomaterials with different morphologies.<sup>326–328</sup> Zinc oxide nanowires consisting of individual crystalline particles were prepared in hexagonal channels of the membrane by electrochemical deposition in a 0.1 M Zn(NO<sub>3</sub>)<sub>2</sub> solution at a voltage of 1 V using a zinc electrode.<sup>327</sup> The composite can be used in optical, electrical and sensor nanodevices. Well-ordered high-density ZnO nanowires with constant dimensions were prepared by electrochemical deposition on a Si substrate using a template composed of anodised aluminium.<sup>329</sup> Electrolysis was carried out in an aqueous Zn(NO<sub>3</sub>)<sub>2</sub> solution, and the membrane pores were filled with the sol that formed upon its hydrolysis.<sup>330</sup> Then the template was successively annealed at 200 °C (1 h) and 400 °C (2 h) and dissolved in 1 M NaOH at 60 °C using ultrasonic stirring to prepare well-crystallised nanowires. The X-ray diffraction pattern of the latter has the (100), (002) and (101) reflections corresponding to the interplanar distances of 2.8, 2.6 and 2.5 Å, respectively.

Treatment of multilayer C-NT with zinc vapour on outer graphite layers afforded ZnO ultrathin films, nanocrystallites (quantum dots), nanowires and nanorods.<sup>331</sup> Nanowires with an average diameter of 30 nm and a length of up to 1.5 µm were grown at 600 °C on the surface of a carbon tube in the absence of a catalyst. Zinc oxide nanorods with a diameter of 80–150 nm and a length of 0.5–1 µm were produced at 800 °C.

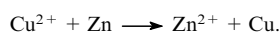
Considerable progress was made in the synthesis of composite heterostructured nanomaterials of applied importance. The synthesis of metal–semiconductor heterostructures as nanorods and

nanocables was documented.<sup>332–335</sup> Evaporation followed by condensation of zinc metal vapour on vertically arranged ZnO nanorods afforded a Zn/ZnO composite.<sup>332</sup> In this case, Zn is localised primarily at the tips of nanorods. Gold-coated heterostructured ZnO nanorods had the pronounced Au/ZnO interface.

Pyrolysis of zinc acetylacetonate produced a Zn/ZnO coaxial cable ( $D \approx 30$  nm) with a zinc core and a ZnO shell.<sup>333</sup> The latter has a crystal structure and is transformed into ZnO nanotubes with a wall thickness of 4 nm, which appear due to evaporation of Zn from the cable core. Zinc oxide nanotubes and Zn/ZnO coaxial nanocables were also prepared by thermal reduction of ZnS (1300 °C) under a stream of an Ar + H<sub>2</sub> gas mixture at 300 Torr.<sup>334</sup> The nanocables are several micrometres in length, the core diameter is  $\sim 50$  nm, and the thickness of the outer shell is 5 nm. Hollow ZnO samples with an outer diameter  $\sim 60$  nm and a wall thickness of  $\sim 10$  nm were also synthesised. There is a good epitaxial relationship between the zinc core and the ZnO shell. However, dislocations occur at the Zn/ZnO interface due to incommensurability in the crystal structures of the components. The use of ZnO nanobelts as templates made it possible to synthesise ZnO/ZnS nanocables by a chemical method.<sup>335</sup>

Coaxial structures of more complex composition were prepared<sup>336</sup> by the thermal reaction combined with physical evaporation. A three-layer coaxial nanocable had a gallium core, a Ga<sub>2</sub>O<sub>3</sub> inner layer and an outer shell composed of ZnO. The mechanism of formation and the luminescent properties of this composite were studied. It was suggested that an Al<sub>2</sub>O<sub>3</sub> coating be used to protect ZnO nanorods against contamination and corrosion.<sup>337</sup> The coating was prepared with the use of water vapour and AlMe<sub>3</sub> as a precursor. The reagents were fed into a furnace containing ZnO nanotubes grown on silicon (300 °C, 250–280 Torr) under a stream of argon. The resulting nanotubes have a shell composed of amorphous oxide Al<sub>2</sub>O<sub>3</sub> 46 nm in thickness.

Doping of Zn/ZnO nanocables with copper<sup>338</sup> using CuSO<sub>4</sub> (0.01–0.5 mol litre<sup>-1</sup>) and Cu(NH<sub>3</sub>)<sub>4</sub><sup>2+</sup> (0.1 mol litre<sup>-1</sup>) solutions occurs according to the reaction



Depending on the concentration of the solution, copper-containing clusters are produced, which can form larger structural networks. In the presence of the complex cations Cu(NH<sub>3</sub>)<sub>4</sub><sup>2+</sup>, copper nanorods grow on the surface of cables. This redox reaction occurs both on the damaged surface of Zn/ZnO nanocables and on its ZnO shell.

Considerable progress was made in the practical application of zinc-containing nanostructures.<sup>339–354</sup> It was suggested that well-crystallised ZnO nanowires be used in planar displays.<sup>339</sup> The emission current density of the material is as high as 1 mA cm<sup>-2</sup> at an electric field strength of 11 V  $\mu\text{m}^{-1}$ , which provides sufficient brightness of FET emitters based on this material. The turn-on voltage of glow of these wires is 6 V  $\mu\text{m}^{-1}$  at a current density of 0.1  $\mu\text{A cm}^{-2}$ . For nanosized ZnO needles with tips several nanometres in diameter, the emission current density is as high as 2.4 A cm<sup>-2</sup> at an electric field strength of 7 V  $\mu\text{m}^{-1}$ .<sup>340</sup> Due to a very stable emission current density and a low turn-on field (2.4 V  $\mu\text{m}^{-1}$ ), this nanomaterial holds considerable promise for the construction of field emission displays.

Zinc oxide nanowires with a diameter of 60 nm are highly sensitive to UV radiation, due to which they can be used in optical switching devices.<sup>341</sup> Samples of ZnO nanorods synthesised from an organozinc vapour phase in the absence of a catalyst are characterised by high optical quality.<sup>342</sup> Poly(vinylpyrrolidone)-capped ZnO nanorods are of interest as an optical material.<sup>343</sup> Luminescence of this nanocomposite is observed at a temperature below 50 K.

A nanosized field-effect transistor (FET) was constructed based on ZnO nanobelts 10–30 nm in thickness with gold electrodes.<sup>344</sup> At a threshold input voltage of 15 V, the ratio of the turn-on current to the turn-off current is  $\sim 100$ , and the maximum

conductivity is  $1.25 \times 10^{-3}$  S cm<sup>-1</sup>. Comparative characteristics of diodes composed of ZnO nanorods and Au/ZnO heterostructures were given in the study.<sup>345</sup> Both diodes have nonlinear and asymmetric voltammetric characteristics. However, the Au/ZnO heterostructure is characterised by a higher puncture potential (8 V) compared to that of ZnO nanorods (3 V). Zinc oxide nanowires are of interest as a material for frequency converters in optical chains and logical components in nanosized optoelectronic devices.<sup>346</sup>

A procedure for the design of the nanosized Au(MEA)/(ZnO/PSS)<sub>19</sub>ZnO/Ag device [MEA is mercaptoethylamine and PSS is poly(sodium 4-styrenesulfonate)], which can rectify the current, and its electronic properties were described, and the mechanism of current rectification was proposed.<sup>347</sup> Single ZnO nanobelts can be used as resonators, whose mechanical resonance is induced by an alternating electric field.<sup>348</sup> It was suggested<sup>349</sup> that the Rh–ZnO/C-NT nanocomposite be used as a highly active catalyst for the methanol synthesis (the yield of MeOH with respect to the catalyst is 411.4 mg g<sup>-1</sup> h<sup>-1</sup>, the selectivity is 96.7% at 250 °C). The activity of this material is higher than that of the known Cu–ZnO/Al<sub>2</sub>O<sub>3</sub> catalyst (for the latter, the yield of MeOH is 213.6 mg g<sup>-1</sup> h<sup>-1</sup>). The multilayer structure of a C-NT substrate facilitates rapid transport and proton and electron binding. Zinc oxide nanowires with a large specific surface area is of importance for photocatalysis.<sup>350</sup> The ZnO nanoparticles–acrylic resin composite prepared by ultrasonic stirring of tetrahedral and usual ZnO nanoparticles in a surfactant-containing solution possesses antistatic and antibacterial properties.<sup>351</sup>

## 2. Nanostructures of 4d-metal oxides

### a. Yttrium oxides

Yttrium oxide was prepared<sup>258</sup> as the Y<sub>2</sub>O<sub>3</sub>/C-NT nanocomposite. Carbon nanotubes, which were pre-treated with nitric acid, were filled with yttrium nitrate and heated at 450 °C for 5 h under a stream of argon. X-ray diffraction study of bulky samples determined  $d = 2.65$  Å for the Y<sub>2</sub>O<sub>3</sub> (400) planes.

### b. Zirconium oxides

Hollow zirconium dioxide nanotubes were synthesised<sup>355</sup> using C-NT as a template. Carbon tubes were treated with a 16 M HNO<sub>3</sub> solution, mixed with Zr(OPr<sup>i</sup>)<sub>4</sub> under argon, subjected to ultrasonic treatment for 2 min, washed and dried. Annealing at 450 °C in air afforded the ZrO<sub>2</sub>/C-NT composite. Carbon was removed by heating the product at 700 °C. Zirconium dioxide nanotubes thus prepared had a diameter of 40 nm and a wall thickness of 6 nm (Fig. 13). Electron diffraction study demonstrated that these nanotubes consisted of a 1:1 mixture of the monoclinic and tetragonal phases. Heating of the samples led to their destruction. The problem of the preparation of single-phase nanotubes was resolved by preparing yttrium-stabilised ZrO<sub>2</sub> nanotubes (0.92 ZrO<sub>2</sub> · 0.08 Y<sub>2</sub>O<sub>3</sub>). The latter were synthesised as follows: NH<sub>4</sub>OH was added to a mixed ZrOCl<sub>2</sub> and Y(NO<sub>3</sub>)<sub>3</sub> solution to pH 9, and the resulting gel was mixed with C-NT, dried in air and annealed successively at 450 °C (12 h) and 700 °C (48 h). This method was used to synthesise hollow nanotubes belonging to the cubic system ( $a = 5.116$  Å) with an outer diameter of 40–50 nm and a wall thickness of 6 nm.

Hollow tubes of amorphous ZrO<sub>2</sub> with a length of 40–200  $\mu\text{m}$ , a wall thickness of 0.2–0.7  $\mu\text{m}$  and an outer diameter of 1.3–5.9  $\mu\text{m}$  were prepared with the use of needle-like crystals of ammonium tartrate as a template.<sup>356</sup> Zirconium dioxide was deposited on the surface of these crystals from an ethanolic solution upon the addition of zirconium alkoxide. The template was removed by dissolving in water. The specific surface areas and the pore size of these tubes depend on the alkoxide used, the conditions of deposition of ZrO<sub>2</sub> and the amount of water. Both open and closed composite BN nanotubes, which were filled with nanorods composed of monoclinic ZrO<sub>2</sub>, were synthesised.<sup>357</sup> The diameter of the latter (20–40 nm) corresponds to the inner diameter of BN nanotubes.

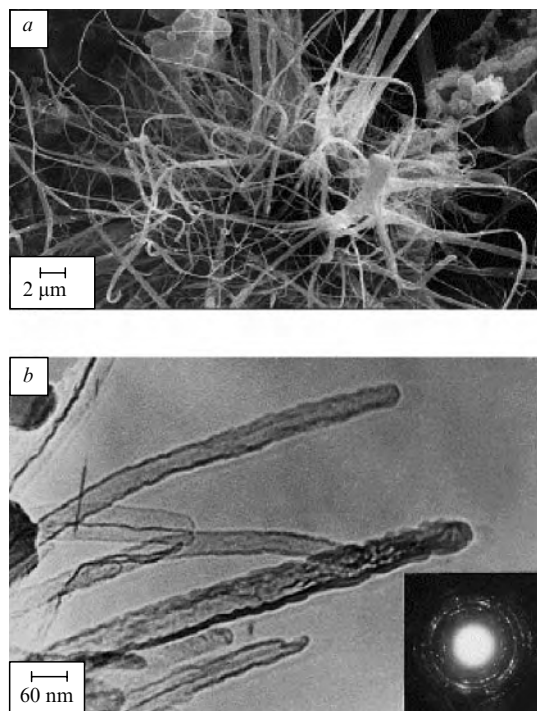


**Figure 13.** Images of a hollow  $\text{ZrO}_2$  nanotube;<sup>355</sup> (a) SEM, (b) TEM. The electron diffraction pattern of the sample is shown in the inset.

#### c. Niobium oxides

Hollow amorphous rectangular-shaped  $\text{Nb}_2\text{O}_5$  tubes were prepared analogously to  $\text{ZrO}_2$  tubes using ammonium tartrate as a template.<sup>356</sup> The length and width of the tubes varied in ranges of 40–200 and 1.3–5.9  $\mu\text{m}$ , respectively, the channel size was 1.0–4.9  $\mu\text{m}$ , and the wall thickness was 0.2–0.7  $\mu\text{m}$ . The specific surface area and the pore size of the tubes depend on the composition of niobium alkoxide, and the microporous structure depends on the conditions of its hydrolytic polycondensation.

#### d. Molybdenum oxides

Molybdenum trioxide has attracted interest because of its catalytic, photochromic and electrochromic properties. The composite consisting of carbon nanotubes filled with  $\text{MoO}_3$  single crystals was prepared<sup>358</sup> by heating the corresponding mixture in a quartz tube at 800 °C (3 h). The yield of the target product was ~50%. Infrared heating of a molybdenum foil under moderate vacuum (950–1000 °C, 5 Torr, 1 h) on a tantalum substrate afforded a pale-blue film consisting of quasi-linear  $\text{MoO}_3$  tubes (the orthorhombic system,  $a = 3.95$ ,  $b = 13.88$ ,  $c = 3.70$  Å) with a length of 5–8  $\mu\text{m}$ , an outer diameter of 50–300 nm and an inner diameter of 20–150 nm. Compared to crystalline  $\text{MoO}_3$ , the unit cell parameter  $a$  is smaller by 0.3%, whereas the unit cell parameters  $b$  and  $c$  are larger by 0.16 and 0.1%, respectively, due to the influence of a tubular structure. The nanotubes grow predominantly along the [100] direction. Disturbance of the ordered arrangement of the tubes along the [010] direction due to weak interactions between the oxide (020) planes gives rise to a three-dimensional structure. Nucleation and growth of  $\text{MoO}_3$  nanotubes rather than nanorods or nanobelts was associated with a layered structure and a low concentration of molybdenum trioxide vapour.

Nanosized  $\text{MoO}_3$  fibres were synthesised<sup>358, 359</sup> by the sol–gel method in three steps. The reaction of molybdic acid  $\text{H}_2\text{MoO}_4 \cdot \text{H}_2\text{O}$  with amine  $\text{C}_n\text{H}_{2n+1}\text{NH}_2$  (in a molar ratio of 2:1) in ethanol followed by the addition of water produced the  $\text{MoO}_3$ /amine composite, which was subjected to hydrothermal

treatment in an autoclave at 120 °C for 3–5 days. The product was filtered off, washed with ethanol and diethyl ether and stirred in 33%  $\text{HNO}_3$  at 20 °C for 48 h to prepare fibrous molybdenum trioxide. The  $\text{MoO}_3$ /amine composite  $(\text{C}_{12}\text{H}_{28}\text{N})_{0.5}\text{MoO}_{3.25}$  was prepared using components in a ratio of 3:1. This composite has a laminar structure and contains template molecules between the layers. The morphology of the product is independent of the reaction time (1–14 days) at 100–120 °C, but it strongly depends on the reaction time at 150 °C. Hydrothermal treatment at 180 °C for 7 days led to destruction of the laminar structure and the formation of a black crystalline powder. The template was removed by treatment of the composite with  $\text{HNO}_3$ , which was accompanied by the transformation of the laminar structure into quasi-one-dimensional  $\text{MoO}_3$ , viz., planar-needle- or cylinder-shaped fibres (with a diameter 20–280 nm and a length varying from 350 nm to 15  $\mu\text{m}$ ) formed by threads with  $D = 20$ –50 nm. The morphology of the  $\text{MoO}_3$  fibres remained unchanged upon annealing at 400 °C in air for several hours, and these fibres are of interest as catalysts for oxidation of ethanol and methane.

Calcination of  $\text{MoO}_3(4,4'\text{-bipy})_{0.5}$  single crystals with a layered structure ( $d = 11.2$  Å) in the temperature range of 300–450 °C afforded molybdenum trioxide plates (60–100 nm).<sup>360</sup> In the temperature range of 320–350 °C, the metastable  $\beta$ - $\text{MoO}_3$  phase was prepared. At 380 °C, the latter was transformed into the orthorhombic  $\alpha$ - $\text{MoO}_3$  phase. Nanoplates of these oxides were packed in stacks 50–250  $\mu\text{m}$  in height.

#### e. Cadmium oxides

Cadmium oxide is an n-type semiconductor, which is of interest in the fabrication of light-emitting diodes, diode lasers and field emission displays. Cadmium oxide nanowires were prepared by electrochemical deposition of cadmium metal from the aqueous electrolyte  $\text{CdCl}_2$  (40 g litre<sup>-1</sup>) and  $\text{H}_3\text{BO}_3$  (30 g litre<sup>-1</sup>) on an anodised aluminium membrane at a current density of 1 mA cm<sup>-2</sup> followed by oxidation of Cd in air at 400 °C and dissolution of the membrane in a NaOH solution.<sup>361</sup> Cadmium oxide nanowires had an ordered structure. The diameter of the nanowires was equal to the channel size of the membrane (~60 nm).

Single-crystalline CdO nanowires several micrometres in length (the cubic system,  $a = 4.569$  Å,  $D = 40$ –60 nm) were prepared by oxidation of a mixed Cd (70%) and Te (30%) film electrochemically deposited on an aluminium substrate from a  $\text{CdCl}_2$  and  $\text{TeO}_2$  solution (0.1 and 0.2 mol litre<sup>-1</sup>, respectively, pH 10, 0.2 mA), at 450 °C under an atmosphere of  $\text{O}_2$  and Ar (1:9).<sup>362</sup> Tellurium served as a flux, which facilitates growth of CdO nanowires. Nanostructured oxide CdO was grown as needles by vapour deposition.<sup>363</sup> Single needles with high conductivity were proposed as a material for highly sensitive IR photoprotectors and  $\text{NO}_2$  gas sensors. Semiconducting CdO nanowires hold promise for electronics, optics, sensors and optoelectronic nano-devices.<sup>364</sup>

### 3. Nanostructures of 5d-metal oxides

#### a. Tantalum oxides

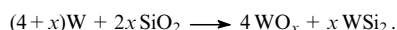
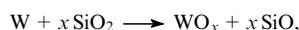
Tubulenes of  $\text{Ta}_2\text{O}_5$  were synthesised analogously to  $\text{Nb}_2\text{O}_5$  nanotubes.<sup>356</sup> Nanotubes of complex oxide of composition  $\text{Sr}_{0.8}\text{Bi}_{2.2}\text{Ta}_{2.0}\text{O}_{9+y}$  were also prepared by the template method.<sup>365</sup> A protonated silicon membrane with hexagonal pores having diameters of 2  $\mu\text{m}$  and 800 nm and a depth of 100  $\mu\text{m}$  was used as a template. The precursor was deposited on the template from a solution of Sr, Bi or Ta ethylhexanoate (0.1 mol litre<sup>-1</sup>) in toluene. After two-step pyrolysis of the composite at 100 and 300 °C, the membrane was subjected to thermal treatment in air at 850 °C for 30 min and then the template was removed by dissolving in a HF and  $\text{HNO}_3$  mixture (15 mol.% and 50 mol.%, respectively). Nanotubes of identical shape with a wall thickness smaller than 100 nm, a diameter of up to 2  $\mu\text{m}$  and a length of 100  $\mu\text{m}$  were prepared. Partial removal of the template gives rise to a periodic structure consisting of isolated



nanotubes. Such nanotubes exhibiting both ferroelectric and piezoelectric properties can be used in memory elements.

### b. Tungsten oxides

Heating of a tungsten foil, which contained a SiO<sub>2</sub> plate on its surface, at 1600 °C under argon ( $p_{Ar} = 100$  Torr) afforded a nanostructured WO<sub>x</sub> material ( $x = 0-3$ ).<sup>366</sup> Ultrasonic treatment of the latter led to its decomposition to give needles (5–50 nm in thickness and 20–200 nm in length) and planar polyhedral nanoparticles (10–50 nm in cross-section). The nanoneedles consisted primarily of oxide W<sub>18</sub>O<sub>49</sub>, and nanoparticles contained primarily WO<sub>3</sub>. The process of their formation can be described by the reactions



The epitaxial growth of monoclinic oxides WO<sub>x</sub> (WO<sub>3</sub>, W<sub>18</sub>O<sub>49</sub> and W<sub>3</sub>O) occurs from the gas phase at the W (foil)–SiO<sub>2</sub> plate interface along the [010] crystallographic axis.

Hollow fibres of crystalline oxide W<sub>18</sub>O<sub>49</sub> forming a pine-needle-shaped structure were synthesised<sup>367</sup> by heating WS<sub>2</sub> powder on a tungsten foil at 1300–1400 °C under an atmosphere of argon and oxygen ( $p_{Ar} = 490 \pm 90$ ,  $p_{O_2} = 10$  Torr). The outer diameter of the fibres is 3–10 μm and the length is 0.1–2 mm. The fibres consist of thin whiskers 50–500 nm in diameter (Fig. 14). The formation of hollow W<sub>18</sub>O<sub>49</sub> fibres is attributed to their single-crystalline axial growth, which provides efficient scattering of released heat.

The synthesis of W<sub>18</sub>O<sub>49</sub> nanorods and their optical properties were documented.<sup>368</sup> The starting compounds [W(CO)<sub>6</sub>, Me<sub>3</sub>NO·2H<sub>2</sub>O and oleylamine] were stirred and heated to 270 °C for 2 h. After aging for 24 h, the mixture became viscous and turned bright-blue. This composite was dissolved in toluene, ethanol was added, and a blue precipitate was separated by

centrifugation and purified by reprecipitation with ethanol from toluene. The final powder consisted of nanorods  $4 \pm 1$  nm in diameter and  $75 \pm 20$  nm in length. The electron diffraction pattern of the sample has two intense rings corresponding to  $d = 3.78$  and 1.89 Å, which is indicative of the predominant growth of nanorods in one direction. X-ray diffraction study demonstrated that these nanorods have a structure of W<sub>18</sub>O<sub>49</sub> with the [010] growth direction. The length of the nanorods depends on the temperature of the synthesis ( $25 \pm 6$  nm at 250 °C and  $130 \pm 30$  nm at 270 °C). At temperatures below 250 °C, nanorods do not grow.

Thermal oxidation of tungsten<sup>369</sup> produced WO<sub>2.9</sub> nanorods on Si(001), Si(111) and SiO<sub>2</sub>/Si plates and silver-coated glasses. A tungsten coil was heated to 600–2000 °C by passing current *in vacuo* ( $3 \times 10^{-2}$  Torr). Tungsten oxide vapour was condensed on plates, whose temperature was lower than 200 °C. Single-crystalline WO<sub>2.9</sub> nanorods with a diameter of 20 nm and a length of 400 nm were arranged in an ordered fashion on substrates. For the majority of nanorods, the WO<sub>2.9</sub> [010] crystallographic axes are almost parallel and coincide with their growth direction. There are orientational relationships not only between the nanorods but also between the nanorods and the substrate. Thus, the WO<sub>2.9</sub> [010] axis is parallel to the Si (001) plane. At the tungsten coil temperature of 850 °C, WO<sub>2.9</sub> nanorods were deposited. At a temperature above 1100 °C, WO<sub>2</sub> nanorods began to grow, and these nanorods prevailed at 1450 °C. These results are attributed to the difference in the degree of oxidation of the coil under an atmosphere with a constant concentration of oxygen.

The template method was used to grow WO<sub>3</sub> fibres with a diameter of 20 nm and a length of 50 μm inside the pores of an anodised aluminium membrane.<sup>162</sup> Tungsten hexachloride was dissolved in ethanol and an aqueous pentane-2,4-dione solution was added. Then the membrane was immersed in this mixture for 1 min, dried in air and annealed at 550 °C for 6 h. Hydrated oxide WO<sub>3</sub>·H<sub>2</sub>O was prepared as two-dimensional plates with an average size of 30–100 nm using benzyl alcohol as a template.<sup>156</sup> A WCl<sub>6</sub> and C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>OH mixture was heated at 100 °C for 48 h, and the precipitate of WO<sub>3</sub>·H<sub>2</sub>O nanoplates that formed was separated by centrifugation, washed with ethanol and dried.

## III. Computer design of structures and electronic properties of oxide nanotubes

### 1. Structural models of inorganic nanotubes

Most of the known inorganic nanotubes were prepared (or predicted) for layered substances and compounds with layered (graphite-like) structures,<sup>31–38</sup> due to which the models of their atomic structures can be constructed and their geometry can be described using approaches and the classification developed for carbon tubes.<sup>2–7</sup>

Models of ideal carbon nanotubes can be built by wrapping atomic ribbons, which are cut out from a hexagonal graphite sheet (the so-called graphene sheet), and cross-linking the broken bonds of the terminal atoms in such a way as to form a cylinder. Depending on the mode of wrapping (the type of graphene-like ribbons), two main types of tubes (chiral and achiral) are constructed. In turn, the latter are divided into the so-called zigzag and armchair NT.

The modes of construction of NT are illustrated in Fig. 15. The **a**<sub>1</sub> and **a**<sub>2</sub> basis vectors of the hexagonal graphene network specify the chiral vector **C**<sub>h</sub> = *n***a**<sub>1</sub> + *m***a**<sub>2</sub>, which lies in the plane of the network and links two crystallographically equivalent positions. The scalar of vector **C**<sub>h</sub> is equal to the cylinder perimeter (the tube cross-section). The diameter (*D*) and the chiral angle (*α*) between the **C**<sub>h</sub> and **a**<sub>1</sub> vectors, which is uniquely related to the **a**<sub>1</sub> and **a**<sub>2</sub> vectors by the *n* and *m* indices, respectively, are the main geometric characteristics of the tubes. The notations (*n,m*)-NT are used in the classification of nanotubes. According to this classification, all (*n,m*)-NT with *n* ≠ *m* ≠ 0 belong to chiral (helical) nanotubes with 0 < *α* < 30°. Achiral (*n,0*)-NT (zigzag) and (*n,n*)-

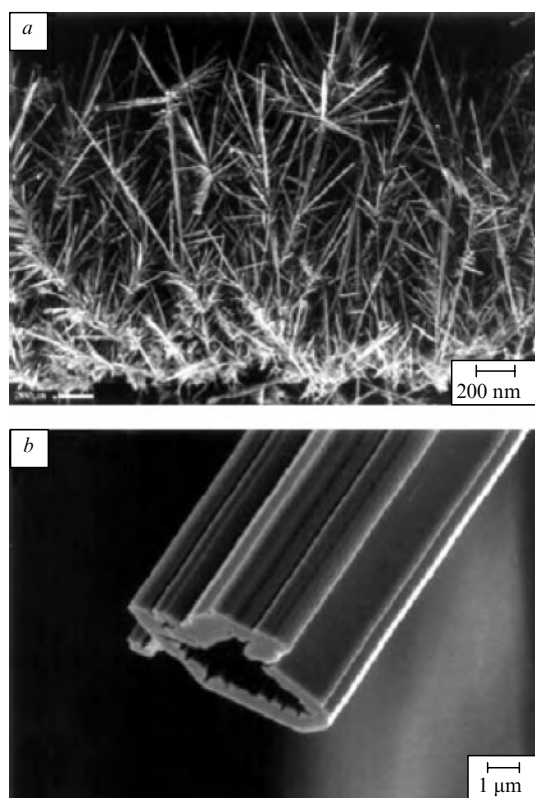


**Figure 14.** The SEM images of crystalline (a) and hollow (b) W<sub>18</sub>O<sub>49</sub> fibres with a pine texture.<sup>367</sup>

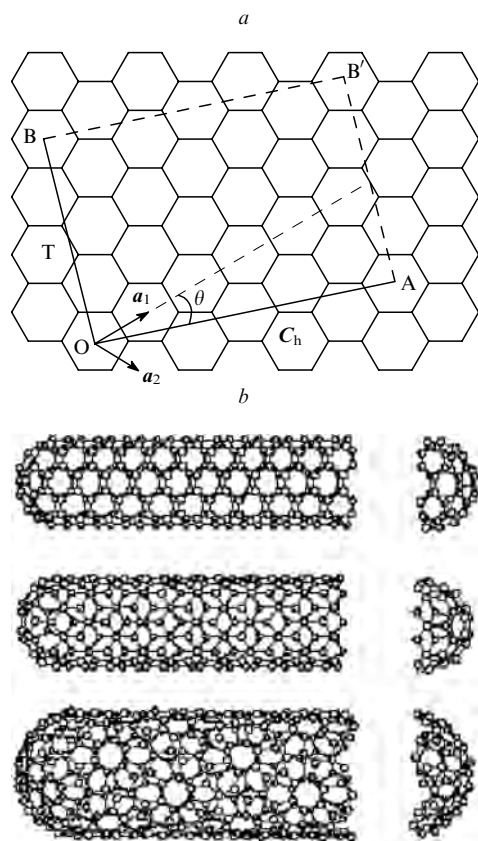


**Figure 15.** Models of the construction (a) and types of carbon nanotubes (b) formed by wrapping a graphene sheet into a cylinder. Terminal structures of achiral armchair, achiral zigzag and chiral nanotubes.

NT (armchair) have  $\alpha = 30$  or  $\alpha = 0^\circ$ , respectively. These tubes are called in accordance with the structure of their cross-sections (zigzag or armchair; see Fig. 15).

This approach can be applied to the construction of atomic structures of nanotubes for typical representatives of layered inorganic compounds. Both homo- and heteroatomic networks (for example, Si or BN) and molecular layers consisting of two (metal diborides), three (d-element dichalcogenides,  $\text{NiCl}_2$ ) or more ( $\text{Bi}_2\text{S}_3$ ) atomic networks can serve as monolayers of the starting crystalline phases, which form NT. A network or a molecular layer can be either planar ( $\text{BC}_x$ ,  $\text{CN}_x$ ,  $\text{B}_x\text{C}_y\text{N}_z$ , etc.) or corrugated (for example, a network of black phosphorus).<sup>36–38</sup>

Tubes of the layered modifications of carbon nitride ( $\text{CN}_x$ ), boron nitride (BN) or boron carbonitrides ( $\text{B}_x\text{C}_y\text{N}_z$ ) isostructural with graphite are the simplest analogues of carbon NT.<sup>31, 369–375</sup> Their atomic structures (taking into account the differences in the interatomic distances in graphite and the above-mentioned B–C–N phases) are analogous to those of C-NT, and the distinguishing features depend on the structural type, the ratio of the elements and the mutual arrangement of their atoms in the cell, i.e., the atomic ordering in the walls of the tubes.

Tubes of hexagonal metal diborides  $\text{MB}_2$  are structurally more complex. Their structures ( $\text{AlB}_2$ , space group  $P6/mmm$ ) consist of the alternating hexagonal networks of metal M and graphite-like boron networks.<sup>106–110, 376</sup> The atomic models of single-layer tubes with formal stoichiometry  $\text{MB}_2$  are derived by wrapping the atomic bilayer  $(\text{MB}_2)_\infty$  of the crystal. These models consist of two coaxial cylinders formed by a planar hexagonal metal network and a planar graphite-like boron network linked to each other. Chiral and achiral  $\text{MB}_2$  NT can be constructed analogously to carbon tubes. In addition, two other configuration types of such tubes can in principle, exist. In these tubes, a

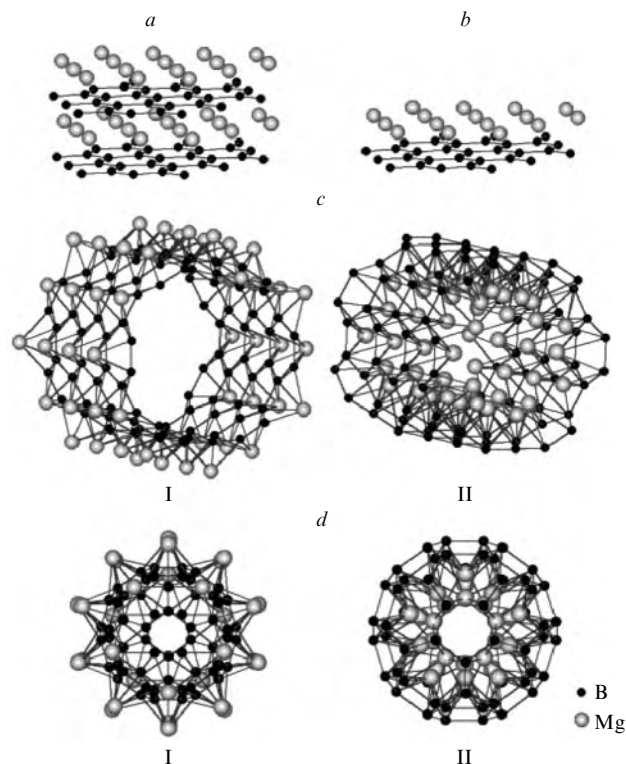


**Figure 16.** Fragments of a crystal (a), a bilayer (b) and atomic models of single-layer tubes (c) and fullerene-like molecules (d) based on metal diborides  $\text{AlB}_2$ .<sup>107</sup>

Two types are shown: a cylinder consisting of metal atoms (a polyhedral shell of the molecule) outside (I) or inside (II) the tube (shell) formed by boron atoms.

‘metallic’ cylinder is located outside (I) or inside (II) the cylinder composed of boron atoms (Fig. 16). This figure also shows models of polyhedral (fullerene-like)  $(\text{MB}_2)_n$  molecules.<sup>107</sup> The hemispheres of these molecules can serve as caps of closed diboride tubes. Like tubes, the  $(\text{MB}_2)_n$  molecules consisting of the concentric spherical  $\text{M}_n$  and  $\text{B}_{2n}$  shells can have two configurations with an  $\text{M}_n$  shell outside (I) or inside (II) the polyhedron composed of boron atoms.

Layered metal dichalcogenides  $\text{MX}_2$  ( $\text{X} = \text{S}, \text{Se}$  or  $\text{Te}$ ) contain the three-atom  $(\text{X}-\text{M}-\text{X})_\infty$  layers. These ‘molecular monolayers’ were wrapped to construct<sup>377–382</sup> models of  $\text{MX}_2$  NT consisting of three coaxial cylinders. The outer and inner cylinders are formed by chalcogen atoms and the central cylinder consists of the metal atoms. Theoretical electron diffraction patterns calculated from these structural models<sup>377</sup> agree well with the experimental patterns. Recently, models for more complex nanotubes of layered metal halide nitrides  $\beta\text{-MNX}$  ( $\text{M} = \text{Zr}$  or  $\text{Hf}$ ;  $\text{X} = \text{Cl}$  or  $\text{Br}$ ) have been proposed.<sup>113</sup> These hypothetical nanostructures (for examples, based on  $\beta\text{-ZrNCl}$ , in which the  $[\text{Cl}-\{\text{ZrN}\}-\{\text{ZrN}\}-\text{Cl}]$  ‘molecular layers’ include six atomic networks) consist of six concentric atomic cylinders ( $\text{Cl}-\text{Zr}-\text{N}-\text{Zr}-\text{N}-\text{Cl}$ , Fig. 17).

Models of single-layer nanotubes as ideal infinite cylinders, which are wrapped up from mono- or polyatomic basis molecular layers, are widely used to describe their electronic properties in terms of the band theory.<sup>6, 28, 31, 33–38</sup>

It is known that the ends of nanotubes can be open or closed. Various terminal structures can have hemispherical, conical or more complex structures. Multilayer nanotubes can consist of a set (up to several tens) of concentric cylinders or exhibit a roll-like, papier-mache or more complex (combined) morphology.<sup>2–38</sup> Nanotubes can be prepared in the isolated form or give various aggregates (bundles, intergrowths, etc.). Unique symbiosis nano-



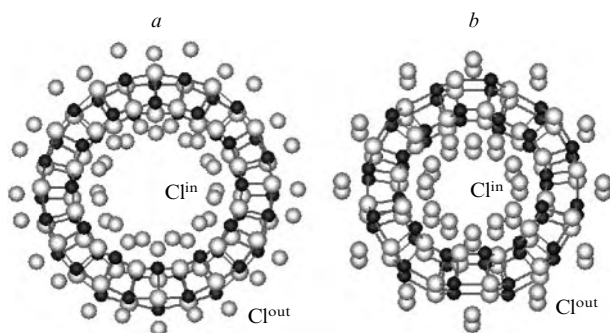


**Figure 17.** Structures of zigzag (12,0) (a) and armchair (12,12) (b) ZrNCl nanotubes.<sup>113</sup>

The positions of the chlorine atoms in the inner and outer cylinders are labelled by  $\text{Cl}^{\text{in}}$  and  $\text{Cl}^{\text{out}}$ , respectively.

structures, *viz.*, regular chains of fullerenes (including endohedral fullerenes) encapsulated into nanotubes, have been synthesised and extensively studied.<sup>383–401</sup> These nanostructures are called peapods.

Nowadays, studies on modelling of multilayer tubes and caps of closed NT are extended to nanotubular structures of boron nitride and d-metal disulfides.<sup>33–38, 377–382</sup> Attempts were made<sup>402, 403</sup> to design atomic models of more complex systems, *viz.*, nanotube composites. The structural model of composite silicon oxide nanotubes prepared with the use of a C-NT template is shown in Fig. 18.<sup>402</sup>

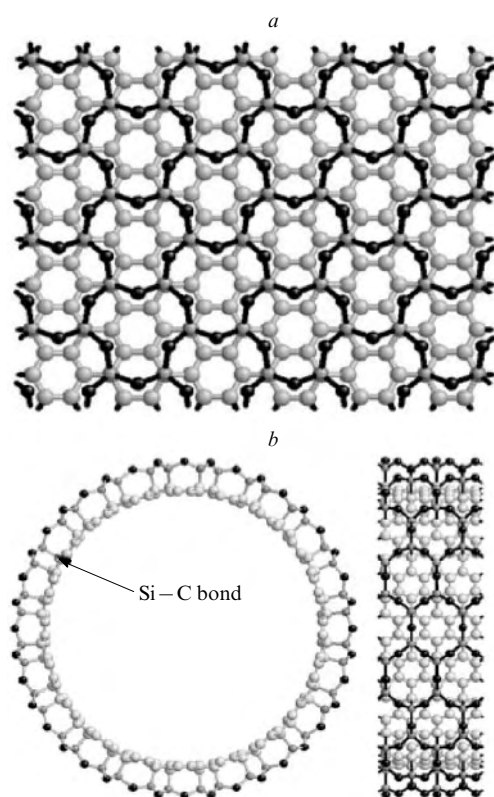


**Figure 18.** Model of the composite C/SiO<sub>x</sub> layer (a) and a nanotube constructed from this layer (b).<sup>403</sup>

## 2. Structural models and electronic structures of titanium, vanadium and molybdenum oxide nanotubes

Let us consider atomic models of Ti, V and M oxide nanotubes constructed by the above-described method and the results of theoretical studies of their electronic structures.

### a. Titanium oxide

Structural models of titanium dioxide nanotubes were constructed, their electronic structures and chemical bond parameters were studied, and these materials were compared with hypothetical VO<sub>2</sub> tubes.<sup>404, 405</sup> Models of TiO<sub>2</sub> NT were constructed using the anatase (101) layers, which, like graphene sheets, were wrapped into cylinders to form three-layer (O–Ti–O) tubes of armchair (*n,n*) and zigzag (*n,0*) types (Fig. 19). Models of tubes based on rutile-type VO<sub>2</sub> (space group  $P4_2/mnm$ ,  $a = b = 0.4555$ ,  $c = 0.2851$  nm) were constructed analogously.<sup>406</sup> The electron bands were calculated by the strong-bond method<sup>405</sup> for (*n,0*)- and (*n,n*)-like TiO<sub>2</sub> NT and for VO<sub>2</sub> in the (8,0)–(15,0) and (4,4)–(15,15) series, which corresponds to the  $\sim 0.6$ –2.3 nm range of the nanotube diameters.

The densities of states (DOS) of (*n,n*)- and (*n,0*)-like TiO<sub>2</sub> NT are similar for all nanotubes and show a general resemblance to DOS of crystalline titanium dioxide (anatase).<sup>407</sup> The valence band is formed by the Ti3d and O2p states, and the lower conduction band edge is formed predominantly by the Ti3d states. The forbidden band gap  $\Delta E$  depends most substantially on the type of the atomic configuration and the tube diameter. For nanotubes with the largest diameters,  $\Delta E$  are  $\sim 3.34$  and  $\sim 3.01$  eV for armchair (15,15)- and zigzag (15,0)-NT, respectively, which is comparable with the theoretical ( $\sim 2.0$  eV)<sup>407</sup> and experimental ( $\sim 3.4$  eV)<sup>408</sup> forbidden band gap for anatase. The

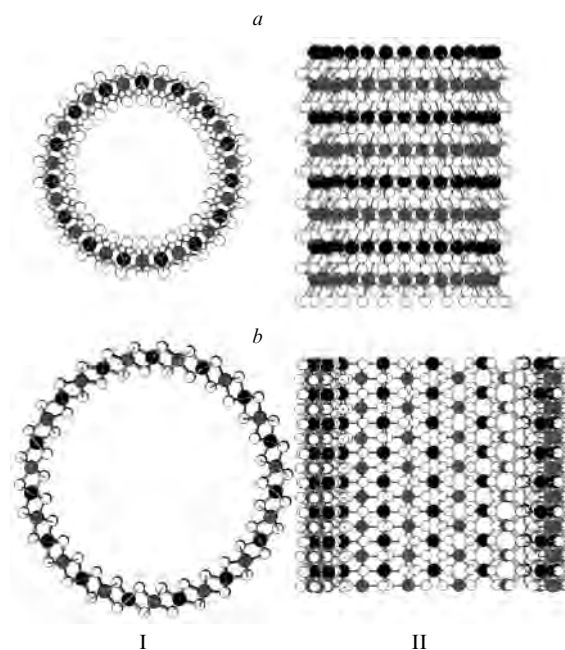


**Figure 19.** Structural models of zigzag (15,0) (a) and armchair (15,15) (b) titanium oxide nanotubes.<sup>410</sup>

Empty and solid circles represent O and Ti atoms, respectively. The model of the regular distribution of substitution elements to form rings of M atoms (model I, see the text) is illustrated by a zigzag (15,0) nanotube; the formation of bands of M atoms (model II) along the perimeter or the axis of the tubes alternating with the rings or bands composed of Ti atoms, respectively, is illustrated by an armchair (15,15) nanotube.

forbidden band gap decreases with decreasing diameters of NT, and  $\Delta E$  for armchair NT are larger than those for zigzag NT.

The calculated electronic spectra of VO<sub>2</sub> NT also correspond to the band structures of crystalline vanadium dioxides.<sup>409</sup> The V3d – O2p hybrid bands are completely filled, and the Fermi level ( $E_F$ ) is located in the V3d band. For armchair NT, the density of states near the Fermi level is rather low, whereas  $E_F$  for zigzag NT is in the region of a local DOS maximum. It should be noted that the analogous near-Fermi maximum of the density of states is responsible for phase instability of crystalline VO<sub>2</sub>.<sup>409</sup>

The dependence of the total electronic energy  $E_{\text{tot}}$  on the diameters of TiO<sub>2</sub> NT is shown in Fig. 20;  $E_{\text{tot}} \propto 1/D^2$ , which is indicative of a decrease in stability of nanotubes with decreasing  $D$ . Armchair nanotubes are more stable at small diameters ( $D < 1$  nm),<sup>404,405</sup> whereas zigzag tubes are more stable at large  $D$ . On the contrary, armchair nanotubes are more stable for all VO<sub>2</sub> NT. Analysis of the parameters of interatomic interactions demonstrated that the Ti–O (V–O) bonds play the major role in the nanotubes under consideration, whereas the Ti–Ti (V–V) bond populations are an order of magnitude smaller, and the O–O bonds are absent. The M=O bonds with the oxygen atoms belonging to the inner (O<sup>in</sup>) or outer (O<sup>out</sup>) oxygen cylinders are strongly polarised and differ in population (Table 4).<sup>405</sup>

Chemical modifications by introducing guest atoms or molecules into the inner cavities of NT, between the walls of multilayer NT or into intertubular regions between the adjacent nanotubes in their associates, as well as through adsorption of foreign atoms or

**Table 4.** Bond populations ( $e^-$ ) for cylindrical single-layer V<sub>2</sub>O<sub>5</sub> nanotubes.

| Nanotubes | Bonds                                   |                                          |                      |                       |
|-----------|-----------------------------------------|------------------------------------------|----------------------|-----------------------|
|           | V–O<br>[VO <sub>5</sub> ] <sup>in</sup> | V–O<br>[VO <sub>5</sub> ] <sup>out</sup> | V–O(1) <sup>in</sup> | V–O(1) <sup>out</sup> |
| (7,0)     | 1.673                                   | 0.856                                    | 0.921                | 0.856                 |
| (8,0)     | 1.630                                   | 0.856                                    | 0.883                | 0.856                 |
| (9,0)     | 1.614                                   | 0.856                                    | 0.867                | 0.856                 |
| (10,0)    | 1.608                                   | 0.855                                    | 0.861                | 0.855                 |
| (11,0)    | 1.602                                   | 0.855                                    | 0.859                | 0.855                 |
| (12,0)    | 1.601                                   | 0.855                                    | 0.858                | 0.855                 |
| (8,8)     | 1.239                                   | 1.035                                    | 0.855                | 0.847                 |
| (9,9)     | 1.239                                   | 1.035                                    | 0.854                | 0.846                 |
| (10,10)   | 1.239                                   | 1.035                                    | 0.854                | 0.845                 |
| (11,11)   | 1.239                                   | 1.035                                    | 0.853                | 0.845                 |
| (12,12)   | 1.239                                   | 1.035                                    | 0.853                | 0.845                 |
| (13,13)   | 1.239                                   | 1.035                                    | 0.852                | 0.844                 |

**Note.** The populations of the bond for the V<sup>in</sup> and V<sup>out</sup> atoms (in VO<sub>5</sub> pyramids) and the pair bonds between the vanadium atoms and the terminal O(1) atoms of the V=O vanadyl groups, which form the ‘outer’ and ‘inner’ oxygen cylinders of the nanotubes, are given.

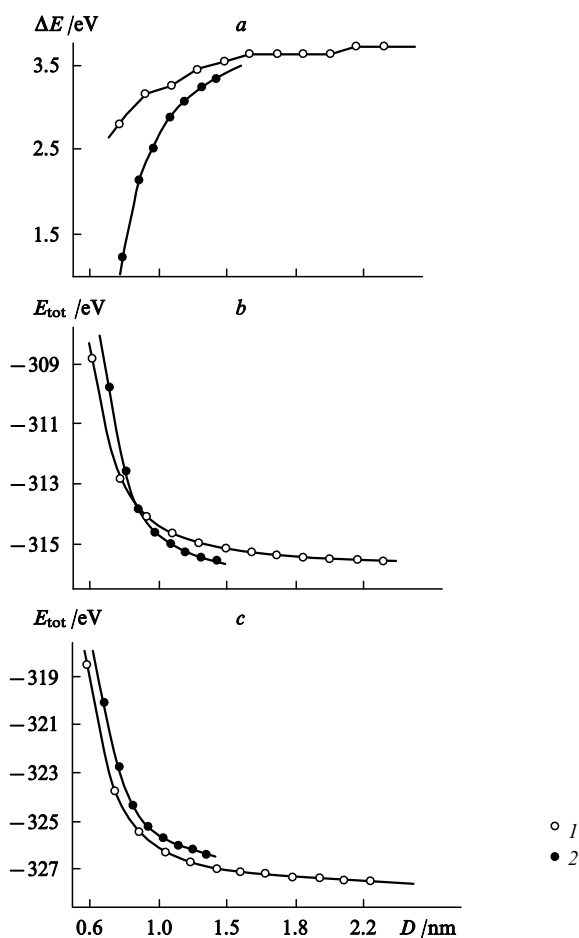


**Figure 20.** Plots of the forbidden band gap for TiO<sub>2</sub> NT (a) and the total band energy per (Ti,V)O<sub>2</sub> unit (b, c) vs. the diameters of TiO<sub>2</sub> (a, b) and VO<sub>2</sub> tubes (c).<sup>404</sup>

(1) An armchair configuration [( $n,n$ ) NT], (2) a zigzag configuration [( $n,0$ ) NT].

molecules on the surface or at the ends of NT or through the replacement of atoms in NT with atoms of other elements (doping of NT), provide efficient ways of controlling the properties of oxide NT. The latter approach was used *in situ* in a number of known procedures for the preparation of NT, in particular, in the template synthesis.

First results of quantum-chemical modelling of the electronic structures and chemical bond parameters of doped TiO<sub>2</sub> nanotubes were reported.<sup>410</sup> Silicon, germanium, vanadium and chromium were considered as elements replacing titanium, which allowed the authors<sup>410</sup> to discuss the results of both isoelectronic substitution ( $\text{Ti} \rightleftharpoons \text{Si, Ge}$ ) and electron doping ( $\text{Ti} \rightleftharpoons \text{V, Cr}$ ) of TiO<sub>2</sub> tubes. The structural models of the armchair (15,15) and zigzag (15,0) TiO<sub>2</sub> nanotubes were used as the starting models.<sup>404,405</sup>

The electronic properties of (15,0) and (15,15) tubes with composition Ti<sub>0.5</sub>M<sub>0.5</sub>O<sub>2</sub> were analysed depending on the mode of distribution of the substitution elements M (Si, Ge, V or Cr) in three Ti positions, which gives rise to rings (model I) or bands (model II) of M atoms along the perimeter or the axes of the tubes alternating with the rings or bands of Ti atoms, respectively (see Fig. 19). The electronic spectra of analogous TiO<sub>2</sub> and (Ti<sub>0.5</sub>M<sub>0.5</sub>)O<sub>2</sub> NT for both models of ordering of the substitution atoms remain unchanged upon isoelectronic substitution (doped tubes are semiconductors), and  $\Delta E$  changes by no more than 0.1 eV. The main differences concern the fine features of DOS distributions in the centre and near the lower valence band edge and are associated with the presence of (Si,Ge)p states. The electron doping ( $\text{Ti} \rightleftharpoons \text{V, Cr}$ ) has a radically different effect: the lower conduction band edge is partially filled and all (Ti<sub>0.5</sub>M<sub>0.5</sub>)O<sub>2</sub> tubes become metal-like.

The total electronic energy  $E_{\text{tot}}$  depends only slightly on the type of ordering of substitution atoms (models I or II), whereas doped armchair (15,15) (Ti<sub>0.5</sub>M<sub>0.5</sub>)O<sub>2</sub> tubes become more stable [for ‘pure’ TiO<sub>2</sub> NT, the zigzag (15,0) configuration is energetically more favourable].<sup>404</sup> It was hypothesised<sup>410</sup> that the substitution can provide a way of changing the type of the atomic configuration of dioxide tubes. It was also expected that doping of oxide nanotubes will be accompanied by the appearance of defects, which are responsible for the difference in the morphology of real NT and the ideal model of cylinders wrapped from polyatomic layers.

In addition to tubular nanostructures, cage nanoparticles [fullerene-like molecules (FM)] based on d-metal oxides (TiO<sub>2</sub>,

$\text{V}_2\text{O}_5$ ,  $\text{Co}_3\text{O}_4$ ,  $\text{MnO}_2$ , etc.) have been synthesised in recent years. In the context of the present review, these nanostructures are of interest as possible prototypes of the caps of the corresponding oxide nanotubes.

The structural models of  $\text{TiO}_2$ -based FM were proposed<sup>411,412</sup> and their electronic structures were calculated by quantum-chemical methods. These particles  $[(\text{TiO}_2)_n]$ , where  $n = 12, 16, 36, 48$  or  $64$  were built from fragments of the anatase (101) layer. They can be described as ‘three-shell’ cage molecules consisting of concentric polyhedral shells, the outer and inner shells being formed by oxygen atoms, whereas the medium shell being formed by titanium atoms (Fig. 21). The titanium and oxygen atoms have predominantly coordination numbers of 6 and 3, respectively. Each FM of stoichiometric composition includes also a group of four Ti and O atoms with coordination numbers of 5 and 2, respectively. The total energy of FM per atom ( $E_{\text{tot}}/N$ , where  $N$  is the number of atoms) decreases with increasing size of FM, i.e., stability of the molecules increases. The energy difference between HOMO and LUMO of the molecules is comparable with the forbidden band gap of the crystalline and tubular forms of  $\text{TiO}_2$ . The spectrum of  $\text{TiO}_2$  FM is characterised by molecular orbitals located between the main groups of occupied and free molecular orbitals.<sup>411</sup> Their appearance is associated with the change in the coordination number of the atoms occupying the vertices of polyhedral particles.

The dependence of the spectrum of  $(\text{TiO}_2)_n$  FM on the coordination numbers of the atoms was simulated<sup>412</sup> using the  $\text{Ti}_{64}\text{O}_{124}$  [i.e.,  $(\text{TiO}_2)_{64} - 4\text{O}$ ] and  $\text{Ti}_{64}\text{O}_{130}$  [i.e.,  $(\text{TiO}_2)_{64} + 2\text{O}$ ] molecules. In these molecules, four oxygen atoms with a coordination number of 2 are removed or two oxygen atoms are added to complete the environment of the Ti atoms with a coordination number of 5 to an octahedron. The forbidden band gap  $\Delta E$  is most substantially affected by the changes in the coordination number of the atoms (0.03 and 1.39 eV for the  $\text{Ti}_{64}\text{O}_{124}$  and  $\text{Ti}_{64}\text{O}_{130}$  molecules, respectively). Calculations of the orbital overlap populations (OOP) demonstrated that Ti–O interactions are the main covalent bonds in  $(\text{TiO}_2)_n$  FM. Some (non-equivalent) bonds are comparable in the orbital overlap population. The orbital overlap populations of the Ti– $\text{O}^{\text{out}}(2)$  bonds increase by more than 25% compared to those of the Ti– $\text{O}^{\text{out}}(3)$  bonds as the coordination numbers of the atoms decrease. However, the total

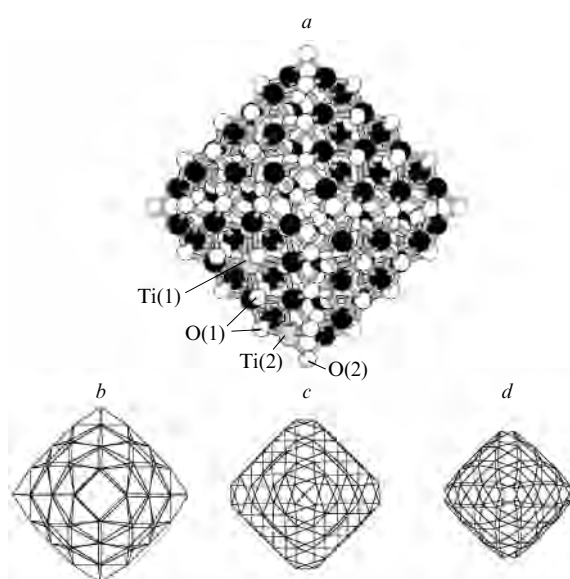


**Figure 21.** Structure of the fullerene-like  $(\text{TiO}_2)_{64}$  molecule (a); the structures of the outer (b), medium (c) and inner (d)  $(\text{TiO}_2)_{64}$  shells composed of O, Ti and O atoms, respectively.<sup>412</sup> Non-equivalent types of the Ti(1), Ti(2), O(1) and O(2) atoms with coordination numbers of 6, 5, 3 and 2, respectively are shown.

bond population of the oxygen atoms with a coordination number of 3 [ $\text{O}^{\text{out}}(3)$  type] is higher than that of the atoms with a coordination number of 2 [ $\text{O}^{\text{out}}(2)$ ] ( $\sim 0.399$ – $0.387$  and  $\sim 0.334$  e<sup>−</sup>, respectively).

## b. Vanadium oxides

Compared to classical carbon NT, the tubular structures of vanadium oxides have important distinguishing features. The available  $\text{VO}_x$  nanotubes are composed of many layers (the walls of the tubes contain from a few to tens of molecular layers) and are open. Ideal concentric cylinders are rare among such tubes. The morphology of these tubes is generally similar to a roll shape, and the constituent molecular layers contain different types of defects. It is also of importance that the elemental composition of  $\text{VO}_x$  NT is determined by the procedure used for the synthesis and the resulting ‘vanadium oxide’ tubes should be assigned to nanotube composites, in which the  $\text{VO}_x$  molecular layers are separated by organic template layers (amines, diamines, etc.). These structural and compositional features of vanadium oxide tubes make it difficult to construct their atomic models and study their electronic properties.

Simplified models of vanadium oxide tubes, viz., families of cylindrical structures, constructed by wrapping the  $\text{V}_2\text{O}_5$  (010) monolayer, were proposed.<sup>413</sup> Orthorhombic crystals of  $\text{V}_2\text{O}_5$  contain quasi-two-dimensional (010) layers formed by distorted  $\text{VO}_5$  pyramids. The  $\text{V}_2\text{O}_5$  units contain three structurally non-equivalent oxygen atoms: the terminal O(1) atoms of the vanadyl ions and the  $\mu_2$ -O(2) and  $\mu_3$ -O(3) atoms (Fig. 22). Wrapping of the (010) layer gives rise to tubes consisting of five coaxial cylinders ( $\text{O}^{\text{in}} - \text{V}^{\text{in}} - \text{O}^{\text{c}} - \text{V}^{\text{out}} - \text{O}^{\text{out}}$ ). In these tubes, the outer and inner cylinders ( $\text{O}^{\text{out}}$  and  $\text{O}^{\text{in}}$ , respectively) are formed by the O(1) atoms of the vanadyl groups, and the central cylinder ( $\text{O}^{\text{c}}$ ) is formed by the O(2) and O(3) atoms. These cylinders are separated by the outer and inner (with respect to  $\text{O}^{\text{c}}$ , respectively) cylinders consisting of vanadium atoms ( $\text{V}^{\text{in}}$  and  $\text{V}^{\text{out}}$ , respectively). By analogy with carbon NT, it is possible to construct three groups of quasi-one-dimensional  $\text{V}_2\text{O}_5$  structures: achiral armchair ( $n,n$ ), zigzag ( $n,0$ ) and chiral ( $n,m$ ) nanotubes.

The electronic structures of a series of ( $n,0$ )- and ( $n,n$ )-like  $\text{V}_2\text{O}_5$  nanotubes with indices in the ranges from (6,0) to (12,0) and from (2,2) to (13,13) (which correspond to the ranges of the outer diameters of the tubes ( $D^{\text{out}}$ ), 1.17–1.78 and 1.01–4.75 nm, respectively) were studied.<sup>413</sup> The valence band of the  $\text{V}_2\text{O}_5$  (010) molecular layer, like that in the  $\text{V}_2\text{O}_5$  crystal,<sup>414–424</sup> belongs to the hybrid V3d–O2p type and is completely occupied. The forbidden band gap of the  $\text{V}_2\text{O}_5$  (010) monolayer is  $\sim 2.5$  eV. The V–O covalent bonds are the strongest bonds in this layer, the V–V bonds are an order of magnitude weaker, and interactions

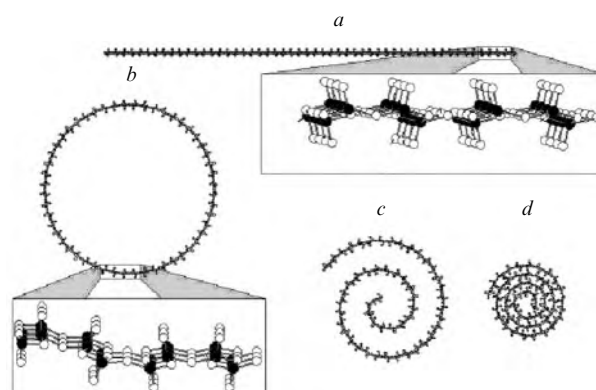


**Figure 22.** Atomic models of quasi-one-dimensional nanostructures of vanadium pentaoxide (cross-sections).<sup>425</sup> (a) A monolayer, (b) cylindrical (26,26) NT, (c, d) roll-like NT with distances between the adjacent walls of 1.5 and 0.45 nm, respectively.

between the oxygen atoms are antibonding. There is anisotropy in the V—O bond populations: the V—O(3) and V—O(1) bonds are the strongest and weakest bonds, respectively.

The dependence of  $E_{\text{tot}}$  on the diameters of  $\text{V}_2\text{O}_5$  NT takes the form  $E_{\text{tot}} \propto 1/D^2$  typical of nanotubular structures,<sup>2–7</sup> which is indicative of destabilisation of  $\text{V}_2\text{O}_5$  tubes as their diameter decreases. For vanadium oxide tubes with  $D > 1$  nm, the armchair-type atomic configurations are more stable. All cylindrical  $\text{V}_2\text{O}_5$  NT are semiconductors. For example,  $\Delta E$  for the tubes with the largest diameters (minimum wall curvature) considered in the study<sup>411</sup> are  $\sim 2.67$  and  $\sim 2.95$  eV for armchair (13,13) NT and zigzag (12,0) NT, respectively, which is comparable with  $\Delta E$  ( $\sim 2.5$  eV) of the  $\text{V}_2\text{O}_5$  (010) monolayer. The forbidden band gap decreases with decreasing tube diameter. It should be noted that this dependence of  $\Delta E$  on the diameter is also typical of semiconducting nanotubes of layered metal dichalcogenides.<sup>377–382</sup> The populations of the V—O bonds depend on their orientation relative to the tube axis and the coordination mode of the atoms belonging to the outer or inner atomic cylinders (see Table 4). The populations of the V—O<sup>in</sup> bonds are higher than those of the V—O<sup>out</sup> bonds. This is indicative of high reactivity of the outer oxygen atoms of the vanadyl groups and the probable distortion of the ideal structure of the outer oxygen shell due to relaxation processes and the formation of O atom vacancies.

The experimentally observed roll morphology is reflected in particular atomic models of  $\text{VO}_x$  NT.<sup>425</sup> To construct these models, the ideal cylindrical zigzag (26,0) and armchair (26,26)  $\text{V}_2\text{O}_5$  nanotubes with inner diameters of 2.958 and 8.712 nm, respectively, were cut along the axis and rolled up into helical forms shown in Fig. 22. The electronic structures of such tubes reflect the total densities of states presented in Fig. 23. It can be seen that the spectra of vanadium oxide nanorolls contain additional states near  $E_F$ , some of which, depending on the atomic configuration of the roll, can be filled. The latter fact should affect

substantially, in particular, the electrophysical properties of nanostructures. This modification of the spectrum of rolls (compared to cylindrical tubes) is associated with the presence of broken bonds in their inner and outer cross-sections, the differences in the curvature radius of individual layers of the  $\text{V}_2\text{O}_5$  molecular ribbons, which form the roll, and the interactions between the adjacent layers in the roll.

### c. Molybdenum oxides

Models of achiral NT were constructed<sup>426</sup> on the basis of the crystal structure of orthorhombic molybdenum trioxide (space group  $Pbnm$ , unit cell parameters  $a = 3.92$ ,  $b = 13.94$ ,  $c = 3.66$  Å), which is composed of layers of edge-sharing  $\text{MoO}_6$  octahedra. This monolayer was used to construct possible types of  $\text{MoO}_3$  tubes from coaxial  $(\text{O—Mo—O})_\infty$  atomic cylinders with different types of helicoid ordering of the chains of  $\text{MoO}_6$  octahedra (Fig. 24). Unlike the above-considered NT,  $\text{MoO}_3$  tubes are perforated. Their walls contain pores inside the rings formed by the  $[\text{MoO}_6]$  polyhedra, which provides an interesting possibility for intercalation with various atoms.

Calculations<sup>426</sup> of the electronic structures of  $(n,0)$ - and  $(n,n)$ -like  $\text{MoO}_3$  nanotubes ( $3 < n < 24$ ) showed that the forbidden band gap ( $\sim 3$ – $4$  eV) depends most substantially on the atomic configuration and the tube diameter and increases with increasing diameter. The dependence of  $E_{\text{tot}}$  on  $D$  is nearly linear, i.e., it

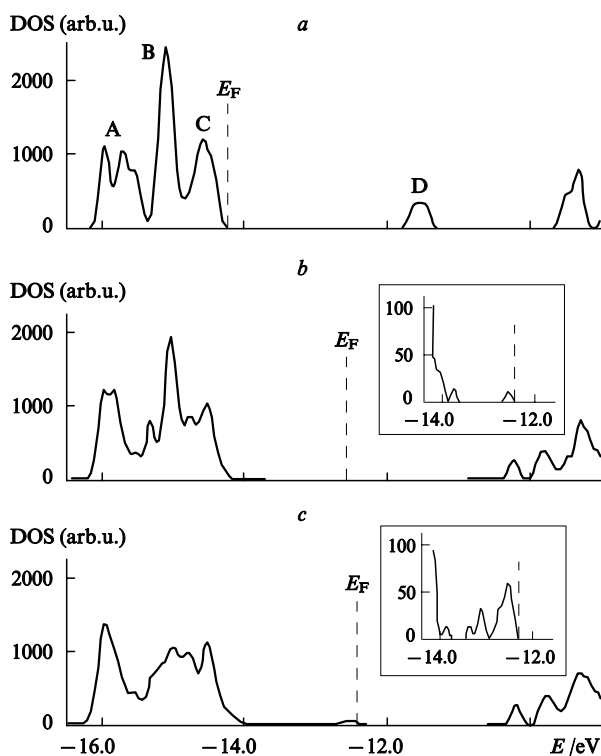


**Figure 23.** Total densities of states in  $\text{V}_2\text{O}_5$  NT;<sup>425</sup> (a) cylindrical (26,26) NT, (b and c) roll-like tubes with distances between the adjacent walls of 1.5 and 0.45 nm, respectively. The densities of states near  $E_F$  are shown in the insets.

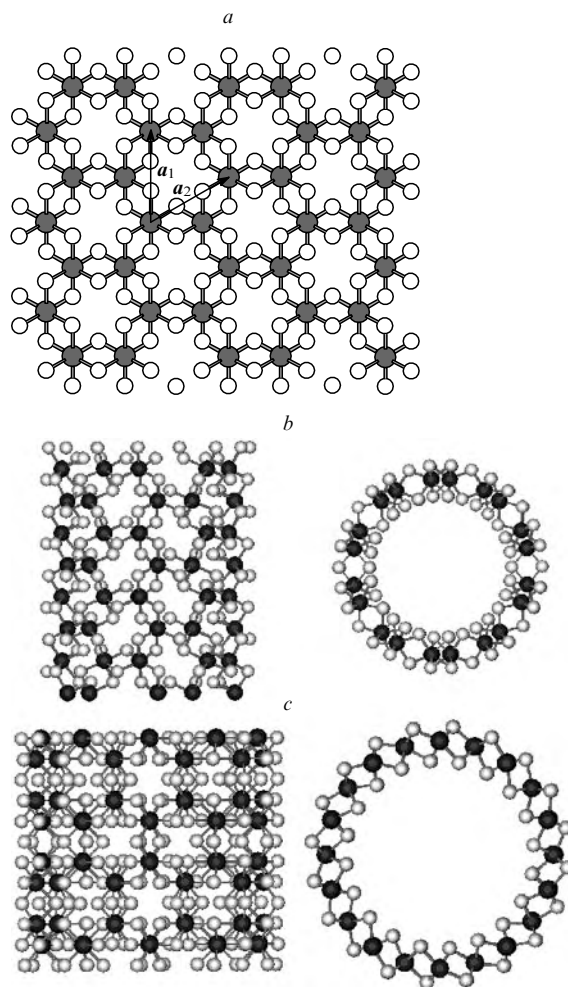


**Figure 24.** Structure of the molecular monolayer of molybdenum trioxide;<sup>426</sup>

$a_1$  and  $a_2$  are the basis vectors of the network of Mo atoms (a). The atomic models of armchair (5,5) (b) and zigzag (10,0) (c)  $\text{MoO}_3$  nanotubes viewed from the side and the top.

differs sharply from the analogous dependences ( $\propto 1/D^2$ ) known for carbon and non-carbon NT of other layered compounds (BN, MoS<sub>2</sub>, etc.). Evidently, this is associated mainly with the characteristic features of chemical bonding in MoO<sub>3</sub>, primarily, with the fact that there is no pronounced anisotropy in intra- and interlayer interactions. That is why MoO<sub>3</sub> were prepared experimentally<sup>358</sup> using MoO<sub>3</sub>/carbon NT nanotube composites as templates. Apparently, this characteristic feature is responsible for the observed<sup>358, 359</sup> polyhedral morphology of the Mo—O<sub>3</sub> tubes. In all MoO<sub>3</sub> NT, Mo—O interactions play the major role,<sup>426</sup> whereas Mo—Mo and O—O covalent bonds are virtually absent.

#### IV. Conclusion

Nowadays, studies of transition metal oxide nanostructures of transition metal oxides are aimed primarily at developing procedures for their synthesis and investigating the morphology of the products. Titanium, vanadium and zinc oxides have been studied most extensively. Titanium-dioxide-based nanostructures have promise as photocatalysts and materials for photoelements. The tubular forms of vanadium oxides allow enhancement of the activity of catalysts and an increase in the cathode capacity of chemical current sources. Zinc oxide nanostructures, which are used in electronics, optics, photocatalysis, solar batteries and sensors, have attracted considerable attention.

A great deal of experimental and theoretical data on metal oxide nanotubes and related nanostructures have been accumulated within a short period after the synthesis of the first materials of this class. Methods for the synthesis of these materials were developed, their morphology and properties were studied, the atomic models were constructed and characteristic features of the electronic structures and chemical bonding in oxide nanotubes were revealed. Various oxide nanostructures and nanocomposites as tubes, ribbons, rods and more complex geometric forms were synthesised, and ways of modifying these properties were proposed.

The results of investigations are of importance for the development of chemistry of metal oxides at nanoscale and for an understanding of the specific properties of nanotubular oxides compared to their crystalline forms and offer considerable possibilities for the technological use of such materials.

As opposed to classical carbon nanotubes and nanotubular structures of layered inorganic compounds, the most efficient procedures for the synthesis of metal oxide nanotubes are the template and chemical methods. In modern studies, considerable attention is being given to the template method, which allows the preparation of oxides and nanocomposites of a desired geometric shape. However, the structures of the tubes thus prepared are far from the ideal cylindrical shape, and they generally include template substances. Chemical methods for the synthesis of nanotubes are also being successfully developed. Intercalation compounds as sols or gels serve as main precursors.<sup>203</sup> The chemical methods allow one to perform syntheses in a wide temperature range and in various solvents and to use and remove templates. The drawback of the chemical hydrothermal method is that nanostructures contain components of the reaction medium. Nowadays, it is difficult to give preference to a particular method of synthesis, because materials science and technological studies of oxide nanotubes lag behind.

In the chemistry of nanotube forms of metal oxides, the immediate aims are to devise procedures for the synthesis of nanostructures with a desired morphology, including more complex geometric forms and their associates. Hence, new methods of synthesis, which will enable one to change the size and form of nanostructures as desired, are of great importance for studies in this field. Systematic investigations of the properties of oxide nanostructures and their dependence on the size and morphology are of equal importance.

The presence of non-compensated bonds of the surface atoms of oxide nanostructures open possibilities for preparing new

substances possessing unusual adsorption and chemical activity. The synthesis of complex oxide nanotubes would be expected<sup>427</sup> to provide new ingenious solutions of problems associated with the design of such materials.

A further development of structural and electronic models of oxide NT taking into consideration the specific features of their real morphology and composition is of great importance. This problem is directly related to elucidation of microscopic mechanisms of formation and growth of oxide NT and the processes of their association giving rise to compact materials (bundles, films or crystals).

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<sup>a</sup> — *Russ. J. Inorg. Chem. (Engl. Transl.)*<sup>b</sup> — *J. Exp. Theor. Phys. Lett. (Engl. Transl.)*<sup>c</sup> — *Dokl. Chem. (Engl. Transl.)*<sup>d</sup> — *Theor. Exp. Chem. (Engl. Transl.)*<sup>e</sup> — *Russ. J. Struct. Chem. (Engl. Transl.)*

# Pulsed EPR structural studies in the nanometre range of distances

S A Dzuba

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**Abstract.** The possibilities of investigations of the nanostructure of matter by pulsed EPR spectroscopy based on the measurement of the dipole–dipole coupling between the spins of unpaired electrons are considered. Using these methods, one can determine the conformations of long-chain organic biradicals and biomolecules (either doubly spin-labelled or containing paramagnetic metal ions) and study the supramolecular structure of matter, *i.e.*, peptide clustering, heterogeneity of polymer packing, structural details of photosynthetic reaction centres and other complex systems. Investigations of the photoinduced spin-correlated radical pairs also reveal the regularities of charge transfer in these systems. The methods are characterised by high accuracy of measurements (0.03 nm) and can be used for measuring distances in the 1.5–10 nm range. The bibliography includes 148 references.

## I. Introduction

Research on the structure of matter in the nanometre range of distances (1–10 nm or 10–100 Å) is necessary for the determination of biomolecule conformations, elucidation of the nanostructure of other complex molecular systems and solution to various problems of supramolecular chemistry. If a system under study is crystallisable, good results can be obtained using conventional X-ray crystallography.<sup>1</sup> Two-dimensional crystals are studied by electron crystallography<sup>2</sup> or scanning tunnelling microscopy.<sup>3</sup> Multidimensional NMR spectroscopy allows the structure of biomolecules of mass up to 100 kDa to be determined.<sup>4</sup> As for disordered media, objects with sizes ranging between 5 and 100 nm are studied by small-angle X-ray scattering (SAXS)<sup>5</sup> and small-angle neutron scattering (SANS).<sup>6</sup> Resonant fluorescence energy transfer is used to determine distances between chromophores in the range from 1 to 10 nm.<sup>7</sup>

If a system contains paramagnetic centres (*e.g.*, free radicals and ions), distances between them can be measured by EPR

spectroscopy. The use of this method is based on studies of the dipole–dipole (d–d) interaction between electron spins. Knowing the distances between paramagnetic centres in pairs or clusters (many biomolecules contain paramagnetic metal ions), it is possible to determine certain parameters of the supramolecular structure. Often, physicochemical and biophysical studies are carried out by the spin label and spin probe techniques, which involve introduction of paramagnetic centres into the system under study. Pairs of paramagnetic centres can also appear as a result of charge separation in photosynthesis, which involves formation of radical anion–radical cation pairs.

The dipole–dipole interaction between electron spins in a pair of paramagnetic centres is characterised by the parameter

$$\frac{\mu_0}{4\pi} \frac{g_e^2 \beta^2}{r^3},$$

where  $\mu_0$  is the magnetic permeability of vacuum,  $g_e$  is the  $g$ -factor of free electron,  $\beta$  is the Bohr magneton and  $r$  is the distance between the paramagnetic centres in the pair. Continuous-wave EPR spectroscopy is used for measuring distances in a pair of electron spins up to 1–1.5 nm range.<sup>8</sup> This limit is due to a masking effect of inhomogeneous broadening of the EPR lines owing to unresolved hyperfine coupling with the nuclei of the matrix, which can be as high as  $\sim 0.5$  mT for organic media.

Pulsed EPR methods based on electron spin echo (ESE) spectroscopy<sup>9,10</sup> are much more sensitive to the dipole–dipole interactions. When using such methods, the dipole–dipole interaction must be compared with the homogeneous broadening, which is much smaller ( $\sim 0.01$  mT) for organic media. From here the upper boundary of the measured distances is  $\sim 5$ –10 nm. The lower boundary (about 1.5 nm) is governed by the temporal resolution of the instrument ( $\sim 10^{-8}$  s). In this review we summarise the results obtained by ESE spectroscopy for long-chain organic biradicals and radical pairs in solids. The distances between paramagnetic centres in the systems under study lie between  $\sim 2$  to 8 nm.

An advantage of ESE spectroscopy is a high accuracy of measurements in this range of distances. For instance, for  $r \sim 3$  nm the error may be only  $\sim 0.03$  nm. High resolution of the method allows one to reveal some fine details in the nanostructure of matter, which cannot be detected by other methods. Besides, ESE studies do not require a specific sample preparation procedure (*e.g.*, crystallisation, high degree of purification, *etc.*).

**S A Dzuba** Institute of Chemical Kinetics and Combustion, Siberian Branch of the Russian Academy of Sciences, ul. Institutskaya 3, 630090 Novosibirsk, Russian Federation. Fax (7-3833) 30 73 50, tel. (7-3833) 33 12 76, e-mail: dzuba@ns.kinetics.nsc.ru

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The possibility of using ESE spectroscopy in studies of pairs of paramagnetic centres has long been established. A study of  $\text{SO}_4^- \cdots \text{SO}_4^-$  pairs stabilised in a UV irradiated  $\text{H}_2\text{S}_2\text{O}_8$  single crystal was reported in 1969.<sup>11</sup> Small width of the EPR spectrum (the possibility of excitation by MW pulses), the absence of magnetic nuclei and spatial orientation of pairs created prerequisites for successful determination of the distances in the pairs by conventional two-pulse ESE spectroscopy. However, the method appeared to be inappropriate for analysis of free radicals in polyoriented organic systems due to large linewidth in the EPR spectrum, masking effect of electron–nuclear interactions and the ‘dead’ time problem. Other experimental techniques were developed later, in particular, the Pulsed Electron–Electron Double Resonance (PELDOR),<sup>12,13</sup> the ‘2 + 1’ (see Ref. 14) and double-quantum coherence<sup>15,16</sup> methods as well as approaches based on solid-state NMR pulse sequences.<sup>17</sup> A conventional two-pulse method permits investigations of spin-correlated radical pairs in photosynthetic reaction centres.<sup>18</sup> Here, it is possible to eliminate the problems characteristic of polyoriented organic systems (see above).<sup>19</sup> The effects of partner spin relaxation in a radical–metal ion pair were first reported in Ref. 19. Later the procedure was essentially modified<sup>20</sup> (relaxation probe method). The relaxation effects were also used in the selective hole ‘burning’ technique<sup>21</sup> and dipolar relaxation-induced modulation enhancement.<sup>22</sup>

At present, ESE spectroscopy is widely used in studies of the nanostructure of complex molecular systems. Thermally equilibrated radical pairs and biradicals are most often studied by the PELDOR method while spin-correlated radical pairs are investigated by the two-pulse echo technique. A large number of reviews on current research are available (see, e.g., Refs 23–35), most of them being published recently. The aim of this review is to describe (i) all ESE spectroscopy-based methods of analysis of the nanometre range of distances and (ii) systems studied by these methods.

## II. The EPR spectrum of a radical pair

Biradicals and radical pairs differ from one another in the presence or absence of covalent bonds between paramagnetic fragments, respectively. For magnetic resonance, this difference is insignificant; therefore, in the text below we will use the term ‘a radical (or paramagnetic) pair’ (RP) except for the cases where we deal with particular chemical structures.

### 1. The spin Hamiltonian of a radical pair

The magnetic dipole–dipole interaction between the magnetic moments of electrons is the main interaction in long-chain biradicals and RPs. The classical expression for the energy of two interacting dipoles has the form

$$E_d = \frac{\mu_0}{4\pi} \frac{r^2 \boldsymbol{\mu}_1 \boldsymbol{\mu}_2 - (\boldsymbol{\mu}_1 \mathbf{r})(\boldsymbol{\mu}_2 \mathbf{r})}{r^5}, \quad (1)$$

where  $\mathbf{r}$  is the radius vector connecting two particles with the dipole moments  $\boldsymbol{\mu}_1$  and  $\boldsymbol{\mu}_2$ , respectively.

The energy of two dipoles with the same spatial orientation is given by

$$E_d = \frac{\mu_0}{4\pi} \frac{\mu_1 \mu_2}{r^3} (1 - 3 \cos^2 \theta), \quad (2)$$

where  $\theta$  is the angle between the direction of the dipole axis and the radius vector  $\mathbf{r}$ .

In quantum mechanics, expression (1) is replaced by the Hamiltonian

$$H_d = \frac{\mu_0}{4\pi} g_1 g_2 \beta^2 \frac{r^2 \mathbf{S}_1 \mathbf{S}_2 - (\mathbf{S}_1 \mathbf{r})(\mathbf{S}_2 \mathbf{r})}{r^5}, \quad (3)$$

where  $g_1$  and  $g_2$  are the  $g$ -factors of particles 1 and 2, respectively, and  $\mathbf{S}_1$  and  $\mathbf{S}_2$  are the spin operators of these particles.

The systems considered in this review are characterised by long spin–spin separations and weak exchange interaction, which can be ignored.

The wave functions of unpaired electrons are distributed in space; for some molecules, the distributions can be rather broad. Nevertheless, here on we will always use the point dipole approximation, which assumes that the whole spin density of unpaired electrons is localised at a point. This is a reasonable approximation in all practically valuable cases (see below).

In the framework of yet another approximation the electron–electron dipole–dipole interaction will be considered small compared to the Zeeman interaction between electron spins and the magnetic field, *i.e.*

$$\frac{\mu_0}{4\pi} \frac{g_e \beta}{r^3} \ll B_0,$$

where  $B_0$  is the magnetic field strength. This approximation *a priori* holds for the distances in RPs considered in this review; therefore, we can use the perturbation theory assuming that Hamiltonian (3) is small compared to the Hamiltonian of the Zeeman interaction. Expression (3) can be essentially simplified if we neglect the components with zero contributions in the first-order perturbation theory. Expression (3) written in spherical coordinates with the  $Z$  axis parallel to the magnetic field direction takes the form

$$H_d = \frac{\mu_0}{4\pi} \frac{g_1 g_2 \beta^2}{r^3} (1 - 3 \cos^2 \theta) \left[ S_{1z} S_{2z} - \frac{1}{4} (S_{1+} S_{2-} + S_{1-} S_{2+}) \right]. \quad (4)$$

Here we used the projections of the spin operators on the  $Z$  axis and the raising–lowering operators.

Relationship (4) is analogous to expression (2), but this analogy is incomplete, because the terms containing the raising–lowering operators have no classical analogues (they reflect the particle identity). The matrix elements involving these operators become significant only if the  $g$ -factors of two electrons are similar, so that the Zeeman energy difference  $|g_1 - g_2| \beta B_0$  becomes comparable with the energy of the dipole–dipole interaction. This is the case for strong spin–spin coupling (or the equivalent spin approximation). If

$$\frac{\mu_0}{4\pi} \frac{g_e^2 \beta^2}{r^3} \ll |g_1 - g_2| \beta B_0,$$

the coupling is weak (inequivalent spins). Note that this review concerns weakly coupled systems only.

The Hamiltonian (4) can be re-written using the total spin operator  $\mathbf{S} = \mathbf{S}_1 + \mathbf{S}_2$ ,

$$H_d = \frac{\mu_0}{4\pi} \frac{g_1 g_2 \beta^2}{4r^3} (1 - 3 \cos^2 \theta) (3S_z^2 - \mathbf{S}^2). \quad (5)$$

### 2. Energy levels and the EPR spectrum of a radical pair in magnetic field

Consider a radical pair comprising two radicals with different  $g$ -factors. The Hamiltonian of the RP in magnetic field, written in frequency units, has the form

$$\frac{H}{\hbar} = \omega_1 S_{1z} + \omega_2 S_{2z} + \frac{1}{4} \varepsilon_d (3S_z^2 - \mathbf{S}^2), \quad (6)$$

where  $\omega_1$  and  $\omega_2$  are the resonance frequencies of two radicals in the absence of the dipole–dipole interaction and  $\varepsilon_d$  is the magnitude of the dipole–dipole interaction

$$\varepsilon_d = \frac{\mu_0}{4\pi} \frac{g_1 g_2 \beta^2}{r^3 \hbar} (1 - 3 \cos^2 \theta).$$

We will write the solution to the Hamiltonian (6) using the wave functions of the triplet

$$|T_+\rangle = |\alpha\alpha\rangle,$$

$$|T_0\rangle = \frac{1}{\sqrt{2}}(|\alpha\beta\rangle + |\beta\alpha\rangle),$$

$$|T_-\rangle = |\beta\beta\rangle$$

and singlet

$$|S\rangle = \frac{1}{\sqrt{2}}(|\alpha\beta\rangle - |\beta\alpha\rangle),$$

states of the RP ( $\alpha$  and  $\beta$  are the electron spin projections)

$$|1\rangle = |T_+\rangle,$$

$$|2\rangle = \cos\phi|S\rangle + \sin\phi|T_0\rangle,$$

$$|3\rangle = -\sin\phi|S\rangle + \cos\phi|T_0\rangle,$$

$$|4\rangle = |T_-\rangle,$$

where

$$\tan 2\phi = \frac{2\Delta\omega}{\varepsilon_d}, \Delta\omega = \omega_1 - \omega_2.$$

Note that for weak coupling  $\phi \approx \pi/4$ , and the wave functions  $|2\rangle$  and  $|3\rangle$  are transformed into  $|\alpha\beta\rangle$  and  $|\beta\alpha\rangle$ , respectively. The energy levels are shown in Fig. 1 and the energies are given by

$$E_1 = \frac{1}{2}(\omega_1 + \omega_2) + \frac{1}{4}\varepsilon_d, \quad (8)$$

$$E_2 = -\frac{1}{4}\varepsilon_d + \frac{1}{4}\sqrt{\varepsilon_d^2 + 4(\Delta\omega)^2},$$

$$E_3 = -\frac{1}{4}\varepsilon_d - \frac{1}{4}\sqrt{\varepsilon_d^2 + 4(\Delta\omega)^2},$$

$$E_4 = -\frac{1}{2}(\omega_1 + \omega_2) + \frac{1}{4}\varepsilon_d.$$

The expressions for six possible energy differences are as follows

$$E_{12} = \frac{1}{2}(\omega_1 + \omega_2) + \frac{1}{2}\varepsilon_d - \frac{1}{4}\sqrt{\varepsilon_d^2 + 4(\Delta\omega)^2}, \quad (9)$$

$$E_{13} = \frac{1}{2}(\omega_1 + \omega_2) + \frac{1}{2}\varepsilon_d + \frac{1}{4}\sqrt{\varepsilon_d^2 + 4(\Delta\omega)^2},$$

$$E_{24} = \frac{1}{2}(\omega_1 + \omega_2) - \frac{1}{2}\varepsilon_d + \frac{1}{4}\sqrt{\varepsilon_d^2 + 4(\Delta\omega)^2},$$

$$E_{34} = \frac{1}{2}(\omega_1 + \omega_2) - \frac{1}{2}\varepsilon_d - \frac{1}{4}\sqrt{\varepsilon_d^2 + 4(\Delta\omega)^2},$$

$$E_{14} = \omega_1 + \omega_2,$$

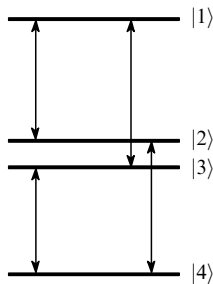


**Figure 1.** Schematic view of spin energy levels of a radical pair (biradical) in magnetic field. Shown are the resolved EPR transitions.

$$E_{23} = \frac{1}{2}\sqrt{\varepsilon_d^2 + 4(\Delta\omega)^2}.$$

The first four differences correspond to the allowed single-quantum transitions (see Fig. 1) and the last two differences correspond to the forbidden two-quantum and zero-quantum transitions.

According to relationships (7), for a thermally equilibrated system the allowed transition intensities are determined by the  $\sin^2\phi$  or  $\cos^2\phi$  factors because only the matrix elements between the triplet states differ from zero. Thus, the EPR spectrum of a radical pair consists of two doublets with a splitting of  $\varepsilon_d$  in each (Fig. 2a). In weakly coupled systems, all lines have the same intensities.

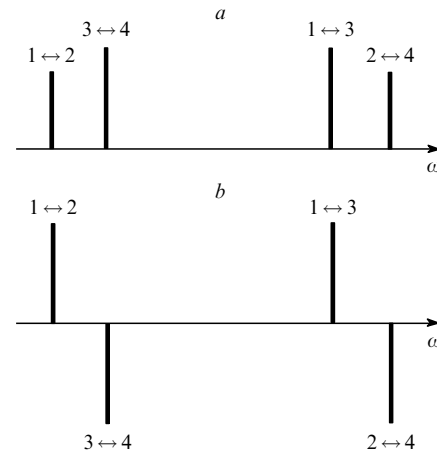


**Figure 2.** EPR spectrum of thermally equilibrated radical pair (a) and spin-correlated radical pair (b).

The EPR spectrum of a spin-correlated RP produced from an initial singlet state is shown in Fig. 2b. Such spin-correlated RPs are considered in more detail in Section III.

As will be shown below, all ESE methods are characterised by temporal dependences of the  $\cos \varepsilon_d t$  type for thermally equilibrated RPs and of the  $\sin \varepsilon_d t$  type for spin-correlated RPs. The Fourier transformation of such dependences creates a doublet at frequencies  $\pm \varepsilon_d$  in the EPR spectra. The doublet is symmetrical with respect to zero frequency for thermally equilibrated RPs and antisymmetrical for spin-correlated RPs. By analogy with solid-state NMR spectra this doublet is often called the Pake doublet. However, this is an incomplete analogy, because in NMR we always deal with strong coupling and the splitting in the doublet is  $(3/2)\varepsilon_d$ . In our case the total splitting in the doublet is  $2\varepsilon_d$ ,<sup>†</sup> and we will call this doublet the dipolar doublet.

### 3. Dipolar doublet in polyoriented system

For a polyoriented system the dependence of the line intensities of the dipolar doublet in the EPR spectra of an RP on the frequency  $\omega$  can be determined by averaging over all spatial orientations of the RP

$$f(\omega) = \frac{1}{4\pi} \int_0^\pi d\theta \sin\theta \int_0^{2\pi} d\varphi \left[ \delta(\omega - \varepsilon_d) \pm \delta(\omega + \varepsilon_d) \right] \propto \quad (10)$$

$$\propto \left( 1 - \frac{4\pi}{\mu_0} \frac{r^3 \hbar}{g_1 g_2 \beta^2} \omega \right)^{-1/2} \pm \left( 1 + \frac{4\pi}{\mu_0} \frac{r^3 \hbar}{g_1 g_2 \beta^2} \omega \right)^{-1/2}$$

<sup>†</sup> Historically, the transformation over  $\tau$  was accepted in ESE spectroscopy, although the transformation over  $2\tau$  is more correct (in this case, the splitting in the doublet is  $\varepsilon_d$ ).

(the ‘plus’ sign is used for thermally equilibrated pairs and the ‘minus’ sign is used for spin-correlated pairs). The frequency,  $\omega$ , of two resonance lines varies from

$$\omega_{\perp} = \pm \frac{\mu_0}{4\pi} \frac{g_1 g_2 \beta^2}{r^3 \hbar}$$

to

$$\omega_{\parallel} = \mp 2 \frac{\mu_0}{4\pi} \frac{g_1 g_2 \beta^2}{r^3 \hbar}$$

[here, the signs have another meaning, namely, the upper (lower) sign is used for the first (second) term in Eqn (10)]. The first limit corresponds to  $\theta = \pi/2$  (perpendicular orientation of RP). Here, a singularity appears in the spectrum. The second limit corresponds to  $\theta = 0$  or  $\theta = \pi$  (parallel orientation of RP) and determines the edges of the spectrum.

Almost always the spectrum is additionally broadened due to spin relaxation or distance distribution. A calculated spectrum for which the additional broadening was simulated by a Gaussian function with the half-width (between the points with maximum slopes) given by

$$0.05 \frac{\mu_0}{4\pi} \frac{g_1 g_2 \beta^2}{r^3 \hbar},$$

is shown in Fig. 3.

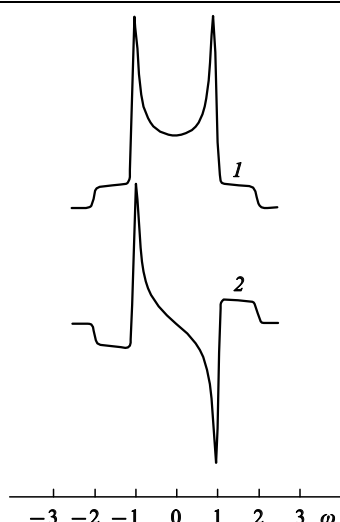


**Figure 3.** Dipolar doublet in polyoriented sample. Thermally equilibrated radical pair (1) and spin-correlated radical pair (2). The frequency axis is labelled in

$$\frac{\mu_0}{4\pi} \frac{g_1 g_2 \beta^2}{r^3 \hbar}$$

units.

Often, only the singularity can be observed in the experimental spectrum because of relatively low intensities of other lines; knowing its position, it is possible to immediately determine the distance  $r$ .

The expressions for  $\omega_{\perp}$  and  $\omega_{\parallel}$  with allowance for the dipole–dipole and exchange ( $J$ ) interactions in the pair take the form:<sup>18</sup>

$$\omega_{\perp} = \pm \left( \frac{\mu_0}{4\pi} \frac{g_1 g_2 \beta^2}{r^3 \hbar} - 2J \right), \quad (11)$$

$$\omega_{\parallel} = \pm \left( -2 \frac{\mu_0}{4\pi} \frac{g_1 g_2 \beta^2}{r^3 \hbar} - 2J \right).$$

Therefore, having established positions of the spectral singularity and the spectrum edges, one can determine the exchange interaction.

#### 4. On the accuracy of the point dipole approximation

The point dipole approximation assumes that the whole spin density is localised at a certain point. Let us estimate the error introduced by the spin density distribution over the molecule. The measured parameter is  $\varepsilon_d$ , which is proportional to  $1/r^3$  ( $r$  is the distance from a given spin to the partner spin). As the distance changes by  $\Delta r$  due to the spin density distribution, the variation,  $\Delta \varepsilon_d$ , is to a first approximation proportional to  $-3\Delta r/r^4$ . If the origin is at the ‘centre of gravity’ of the spin density (*i.e.*, the average value,  $\langle \Delta r \rangle$ , over the molecule is taken to be zero), the mean value  $\langle \Delta \varepsilon_d \rangle$  in this approximation will also be zero. In the second approximation,  $\langle \Delta \varepsilon_d \rangle$  is proportional to  $6\langle \Delta r^2 \rangle/r^5$ . As a result of this variation of  $\varepsilon_d$ , the distance measured in the point dipole approximation will have a systematic negative error

$$\delta r = -\frac{1}{3} \langle \Delta \varepsilon_d \rangle r^4 = -2 \frac{\langle \Delta r^2 \rangle}{r}.$$

Evaluation of the  $\delta r$  parameter for the radicals with an RMS spin density distribution width of  $\langle \Delta r^2 \rangle = (1.5 \text{ \AA})^2$  and a spin–spin separation of 30 Å using this expression gives a value of  $-0.15 \text{ \AA}$ . If the spin density distribution is known and can be taken into account in calculations of the dipole–dipole interaction, this small error can be made even smaller.

### III. Experimental methods based on electron spin echo envelope modulation

If a MW pulse is applied to a spin system in the magnetic field at a frequency equal to the spin resonance frequency, the free induction signal is produced. The signal is maximum at a magnetisation flip angle of  $90^\circ$  and decreases with time owing to two reasons, (i) irreversible relaxation due to stochastic processes and (ii) phase defocusing due to static inhomogeneity of the resonance frequencies in the sample. Defocusing is reversible; application of a  $180^\circ$  pulse again produces the free induction signal at some delay after the second pulse. The delay time ( $\tau$ ) equals the time interval between two pulses. This signal is called the spin echo (Fig. 4 a).

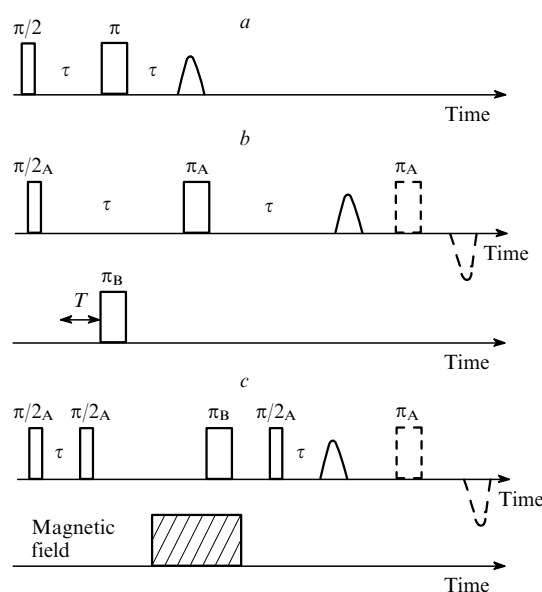


**Figure 4.** ESE pulse sequences used in studies of the dipole–dipole interaction between electron spins in radical pair. Conventional two-pulse sequence (a), two-frequency double resonance (PELDOR) (b) and magnetic-field-jump PELDOR (c).

The origination of the echo signal is readily understandable from the following simple considerations. After application of the first pulse each spin precesses in its own local magnetic field as a result of static inhomogeneity of the resonance frequencies. Let us denote the deviation of the resonance frequency of a certain spin from the carrier frequency of the spectrometer as  $\Delta\omega_0$ . At the instant of application of the second pulse the phase change becomes equal to  $\Delta\omega_0\tau$  (see Fig. 4a). If  $\Delta\omega_0\tau \gg 1$ , the free induction signal decreases to zero because of averaging over all spins. Application of the second  $180^\circ$  pulse leads to phase reversal and the phase becomes equal to  $\pi - \Delta\omega_0\tau$ . Then, the phase changes again, namely, it changes with time as  $\pi - \Delta\omega_0\tau + \Delta\omega_0(t - \tau)$ , where  $t$  is the time passed from the first pulse. At  $t = 2\tau$ , all spins have the same phases equal to  $\pi$  and independent of  $\Delta\omega_0$ . This means the refocusing and the appearance of the echo signal.

The situation described above corresponds to a two-level spin system, for which the distribution over the energy difference between the levels ( $\Delta\omega_0$  distribution) owing to various additional interactions is only possible. The situation becomes more complicated [as in the case of, e.g., a radical pair (see Fig. 1)], if there are a number of energy levels and the MW pulses excite different transitions. This is accompanied by additional effects due to pulse-assisted alternation of magnetic interactions in the pair. In the text below we will show that such effects cause modulation of the echo signal decay on change in  $\tau$ .

In this Section both spins in the pair are assumed to have rather long relaxation times ( $> 10^{-6}$  s).

### 1. Modulation in two-pulse electron spin echo technique

The simplest experimental method suitable for studying the dipole–dipole interaction between spins in a pair is a conventional two-pulse echo technique. Application of the second pulse causes not only the precession phase reversal but also changes the orientation of the partner spin in the pair. As a result, the precession frequency is shifted by a value of  $\varepsilon_d$  and the spin-precession phase at  $t = 2\tau$  is  $\pi \pm \varepsilon_d\tau$  rather than  $\pi$ . The measured signal is proportional to  $\cos \varepsilon_d\tau$ , which means oscillation of the spin echo signal decay with  $\tau$ . This phenomenon is termed an Electron Spin Echo Envelope Modulation (ESEEM).

Detailed calculations of ESEEM were carried out for spins in a thermally equilibrated pair<sup>11</sup> and for a more general case of arbitrary populations of the energy levels.<sup>36</sup> The effect of the flip angle of the first pulse was not considered in detail;<sup>11</sup> it was postulated to be the same as in the case of a single spin. In a more recent study<sup>36</sup> it was shown that this effect is more complex in character. However, the study<sup>36</sup> did not consider the effect of the flip angle of the second pulse, although earlier<sup>11</sup> mention was made of such an effect. Probably, both results obtained for arbitrary flip angles are inexact. For a conventional pulse sequence ( $90^\circ - \tau - 180^\circ - \tau$  - echo) both calculations lead to the same results. The echo signal of a thermally equilibrated radical pair is given by

$$E(2\tau) = \sin^2 2\phi \cos \varepsilon_d\tau + \cos^2 2\phi \cos \left( \frac{1}{2} \sqrt{\varepsilon_d^2 + 4(\Delta\omega)^2} \tau \right) \cos \varepsilon_d\tau - \cos 2\phi \sin \left( \frac{1}{2} \sqrt{\varepsilon_d^2 + 4(\Delta\omega)^2} \tau \right) \sin \varepsilon_d\tau. \quad (12)$$

Note that the second and third terms on the right side of Eqn (12) at  $\tau \neq 0$  are efficiently averaged owing to large inhomogeneous broadening ( $\Delta\omega\tau \gg 1$ ). Only the first term is retained, which is proportional to  $\cos \varepsilon_d\tau$ . This is consistent with the simple qualitative consideration given above and, apparently, must be valid for all flip angles of the magnetisation vector. In the case of weak coupling ( $\phi \approx \pi/4$ ) the role of the second and third terms is even less significant. In strongly coupled systems (this case is left out of consideration in this review) the signal is proportional to  $\cos(3/2)\varepsilon_d\tau$ , as mentioned above.

However, practical implementation of this two-pulse approach to studies of the dipole–dipole interaction in RPs faces some difficulties. First, MW pulses have a limited amplitude (usually, less than 1 mT) while the signal of, e.g., nitroxyl biradicals has a total width of about 7 mT. Therefore, the probability of excitation of the partner spin in a pair (this is the necessary condition for applicability of this approach) is low. As a result, the effect of the signal decay modulation as compared to the large portion of non-modulated decays of single spins becomes weak. Second, not only the electron–electron but also the electron–nuclear interactions contribute to modulation. For nitroxyl biradicals, this contribution predominates.<sup>22</sup> Third, there is the ‘dead’ time problem, namely, the system’s response cannot be measured immediately after the pulse is applied owing to transient processes in the cavity (usually, at  $\tau < 100$  ns). It should be noted that reliability of the results of mathematical extrapolation to the ‘dead’ time region always casts some doubt.

There are a few studies on the observation of the modulation induced by electron–electron dipole–dipole interaction in two-pulse ESE spectra. Among them is a pioneering study<sup>11</sup> of RPs in single crystals containing no magnetic nuclei. A peak observed after Fourier transformation of the signal decay for nitroxyl biradicals dissolved in liquid crystals was attributed to the dipole–dipole interaction in the pair.<sup>26</sup> This peak was also recorded for polyoriented nitroxyl biradicals.<sup>22</sup> The contribution of this type of modulation was very small<sup>22,26</sup> compared to the contribution of the electron–nuclear interaction.

Note that in the case of two-pulse ESE of photochemically generated spin-correlated RPs the difficulties mentioned above can be almost completely eliminated (see below).

The search for solutions to the problems posed in studies of radical pairs by the conventional two-pulse ESE method stimulated development of modified experimental techniques.

### 2. Pulsed electron–electron double resonance

PELDOR<sup>12,13</sup> was the first modification of the ESE technique elaborated for the study of the ESEEM induced by the electron–electron dipole interaction. In this case the echo signal is excited using a conventional two-pulse sequence and an additional 180 pump pulse is applied at some other resonance frequency (see Fig. 4b). The spins producing the echo signal are called A-spins and the partner spins in the pair (to which in this case the additional pulse is applied) are called B-spins.

The results of this experiment can be represented with ease using the phase ratios assuming weak spin–spin coupling. At time  $t$ , the phase of the A-spin after the first pulse is  $[\Delta\omega_0 \pm (1/2)\varepsilon_d]t$  (the ‘plus’ or ‘minus’ sign depends on the projection of the B-spin). After the action of the  $180^\circ$  pulse applied at the B-spin frequency at time  $T$  the shift of the precession frequency due to the dipole–dipole interaction changes its sign and the phase at time  $\tau$  (before application of the second pulse at the A-frequency) is given by

$$\varphi_A = \Delta\omega_0\tau \pm \frac{1}{2}\varepsilon_d T \mp \frac{1}{2}\varepsilon_d(\tau - T).$$

After the second pulse applied at the A-frequency one has

$$\varphi_A = \pi - \Delta\omega_0\tau \pm \frac{1}{2}\varepsilon_d T \pm \frac{1}{2}\varepsilon_d(\tau - T) + \Delta\omega_0(t - \tau) \mp \frac{1}{2}\varepsilon_d(t - \tau).$$

From here it follows that at  $t = 2\tau$

$$\varphi_A = \pi \mp \varepsilon_d T.$$

The echo signal is proportional to  $\cos \varepsilon_d T$ , which means a modulation of the signal on change in time  $T$  at a frequency  $\varepsilon_d$ .

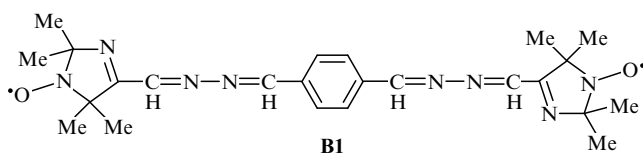
In the experiment, the pump pulse excites only a portion of the partner spins of a given A-spin. We will denote it  $P_B$ . Then, the probability of non-modulated signal decay is  $(1 - P_B)$  and the probability of modulated signal decay is  $P_B$ ; the total signal is given by

$$V(T) = 1 - P_B + P_B \cos \varepsilon_d T. \quad (13)$$

The advantage of the PELDOR technique is the absence of electron–nuclear modulation. Indeed, application of a pulse at the B-spin resonance frequency does not change the electron–nuclear interactions of the A-spin. It is also important that in this case the ‘dead’ time problem is almost eliminated because the pulse at the B-frequency can be applied immediately after the first pulse at the A-frequency. The remaining uncertainty is due to the finite pulse duration. It can also be decreased by using an additional refocusing pulse at the A-spin frequency (see dashed lines in Fig. 4*b*) and by positioning the pump pulse between the second pulse at the A-frequency and the additional pulse.<sup>37</sup> The position of the pump pulse can coincide with that of the echo signal excited by the first and second pulses at the A-frequency, which must correspond to zero time. Yet another advantage of the technique is that the signal modulation is not superimposed with the spin relaxation induced signal decay (as in the two-pulse method considered above).

At present, the PELDOR method is most widely used in studies of thermally nonequibrated systems.

Except for the action on the B-spins at some other resonance frequency, the magnetic field can be changed in a stepwise fashion, as in the X- (see Ref. 38) and W-band EPR studies.<sup>39</sup> The pulse sequence is shown in Fig. 4*c*. The A-spins were excited using the three-pulse stimulated echo sequence. The magnetic field jump synchronised with the 180° pump pulse was positioned between the second and third pulses. Due to the shift of the resonance field the 180° pump pulse affected only the B-spins. The three-pulse (instead of the two-pulse scheme, as in two-frequency PELDOR) scheme for excitation of the A-spins is used because the magnetic field jump in the two-pulse modification of the technique causes significant phase distortions for the A-spins. According to the three-pulse scheme, the magnetisation between the second and third pulses is retained along the Z axis of the rotating frame and the phase does not increase. The time  $\tau$  between the first and the second pulses can be varied. Modulation is due to both the electron–electron and electron–nuclear interactions. The two mechanisms can be discriminated by switching the pump pulse off. Since both mechanisms are independent, their effect on the observed echo decay modulation must be multiplicative. This approach was employed in a magnetic-field-jump PELDOR study of rigid biradical **B1**.<sup>38</sup>



The ESE signal decays of **B1** in protonated and deuterated solvents are shown in Fig. 5. The initial decays (see curves 1 and 2) exhibit only the modulation at the frequencies of electron–nuclear interactions, while the result of division (curve 3) is independent of the type of isotopes. Therefore, the observed ESEEM can be treated as electron–electron modulation. The results of Fourier transformation are shown in Fig. 6 (spectra I and II). Sharp lines seen in the spectrum correspond to singularities of the dipolar doublet (see Fig. 3*a*). The distance between paramagnetic fragments —  $r = 19.0 \pm 1.6$  Å was determined from positions of these singularities.

The dipolar doublets in spectra I and II exhibit no shoulders, which must appear according to theory (see Fig. 3). The absence of shoulders seems to be due to low intensities, which can be increased by orienting biradicals in the sample in such a manner that the line connecting both spins is parallel to the magnetic field direction. This can be done by placing the radical into a liquid crystal oriented in such a way that the axis of its director is parallel to the direction of the external magnetic field. The results of investigation of biradical **B1** are also shown in Fig. 6 (spectrum

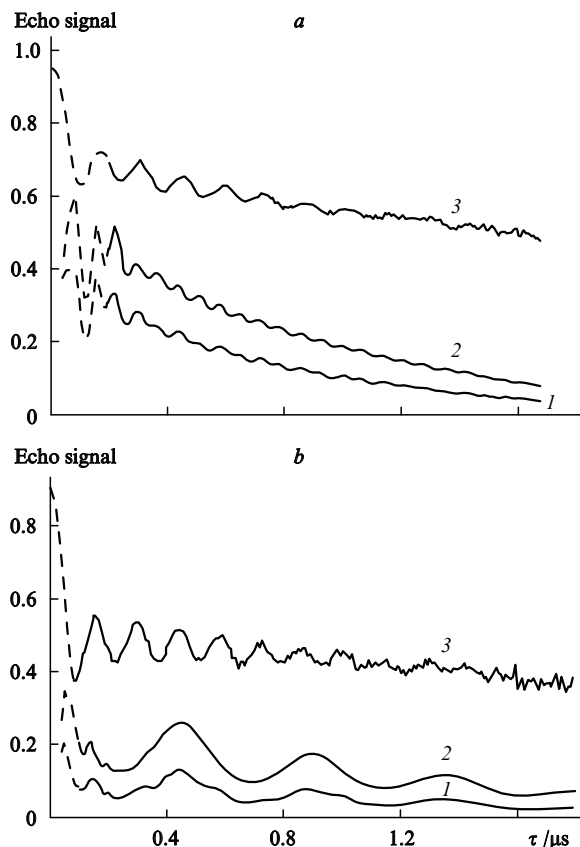


**Figure 5.** Magnetic-field-jump PELDOR signal decays obtained for biradical **B1** in toluene (*a*) and deuterated (*b*) toluene at 77 K.<sup>38</sup> Signal decays obtained by  $\tau$  scanning (see Fig. 4*c*) (1); the same, but the pump pulse  $\pi_B$  is switched off (2); and curve 1 divided by curve 2 (3). The vertical axes are given in relative units for curves 1 and 2 and in absolute units for curves 3. Dashed lines denote the results of signal recovery during the ‘dead’ time.

III).<sup>38</sup> As can be seen, the shoulders became much more intense. Exchange interaction was found to be zero from the shoulder positions using expressions (11).

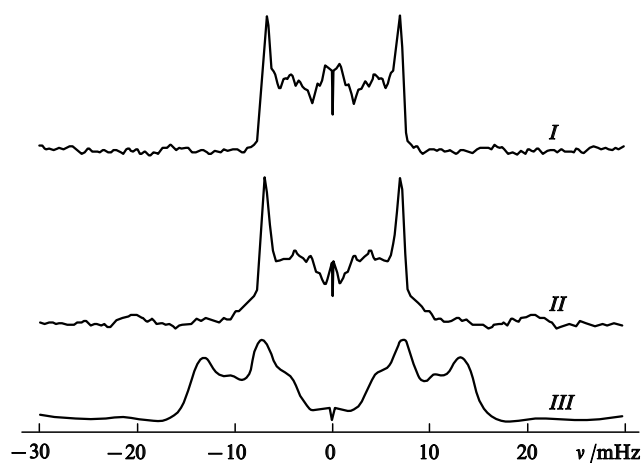


**Figure 6.** Results of cosine Fourier transformation of experimental data in the time domain.<sup>38</sup> Experimental data: curve 3 in Fig. 5*a* (I), curve 3 in Fig. 5*b* (II); and data for biradical **B1** in oriented liquid crystal (the biradical axis is nearly parallel to the magnetic field direction) (III).



The advantage of the magnetic-field-jump PELDOR over the two-frequency PELDOR technique consists in the possibility of using a scanning pump<sup>38</sup> owing to an increase in the portion of spins (radical pairs) to be excited. Here, the 'dead' time can also be eliminated using an additional refocusing pulse. A drawback of the technique is the effect of relaxation processes on the echo decay.

A comparative PELDOR study of biradicals in two (X and S) EPR bands was carried out.<sup>40</sup> Since the electron–nuclear modulation depends on the MW band while the electron–electron modulation is independent of it, this approach can be employed to determine the contribution of electron–electron modulation.

The PELDOR technique cannot be used in studies of RPs with a relatively narrow EPR spectrum (less than 2 mT), where the excitation pump pulses and the reading pulses are superimposed and the effects observed are hard to interpret. Such spectra are typical of free radicals in photosynthetic reaction centres. It is more appropriate to study these systems by 'single-frequency' methods involving identical excitation of both A- and B-spins (see below).

### 3. The '2 + 1' method

The '2 + 1' method<sup>14,27</sup> is much like the PELDOR technique considered above. It employs the same pulse sequences (see Fig. 4b), but the pulses are applied at the one resonance frequency; *i.e.*, the basis pulse sequence is as follows: pulse 1 –  $T$  – pulse (+1) –  $(\tau - T)$  – pulse 2 –  $\tau$  – echo. The echo signal appears after application of two pulses (pulse 1 and pulse 2); the additional pulse (pulse +1) is necessary to achieve alternation of the dipole–dipole interaction. Experiments involve variation of the time  $T$  at constant  $\tau$ . The ESEEM occurs by the same mechanisms as in the PELDOR experiments; however, here both partner spins are excited identically.

In addition to the possibility of studying narrow spectra, the '2 + 1' method (compared to PELDOR) does not require an additional generator and special cavity. However, it also has significant drawbacks. First, the '2 + 1' technique is not free from electron–nuclear ESEEM. Elimination of this type of modulation requires special procedures, *e.g.*, comparison with a reference sample in which no dipole–dipole interaction occurs. Second, the dipole–dipole interaction alternates under the action of not only pulse +1 but also the second pulse (see above). Correct allowance for interference between these two effects is not always possible. For instance, if in polyoriented medium there are two types of pairs, with long and short distances, the major contribution to the echo signal will come from the pairs with the long distance, because the signal from the pairs with the short distance is rapidly damped due to alternation (see above). Therefore, in the presence of a distance distribution the distribution function will be significantly distorted. The PELDOR method is free from this drawback, because it usually involves observation at the edge of the spectrum, where only a small portion of A spins is excited.

### 4. Double-quantum coherence method

Using an appropriately designed pulse sequence, it is possible to excite a coherence between the highest and lowest levels in the scheme shown in Fig. 1.<sup>15,16,26</sup> A commonly used pulse sequence for this experiment (see Fig. 7a) includes four pulses. Three of them ( $\pi/2$  pulses) create a stimulated echo signal. The additional  $\pi$ -pulse is applied at the midpoint of the time interval between the second and third pulses.

The first two pulses create the double-quantum and zero-quantum coherences. They are refocused after applying the  $\pi$ -pulse and create a single-quantum coherence after application of the  $\pi/2$  pulse observed as an echo signal. The contribution of the double-quantum coherence is selected using the pulse phase cycling from one series to another. Experiments involve variation of the time  $\tau$ ; the signal is modulated at the  $\varepsilon_d$  frequency.

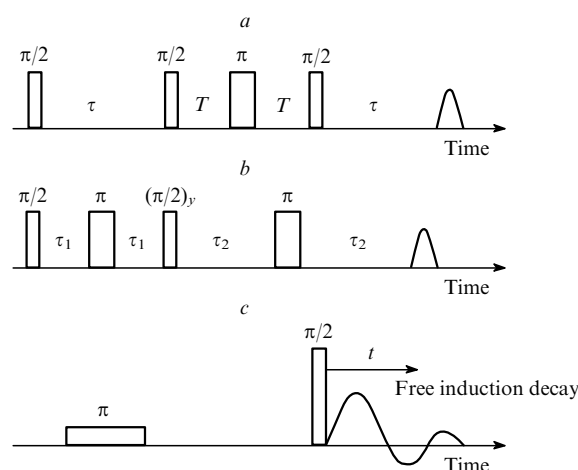


**Figure 7.** ESE pulse sequence used in studies of dipole–dipole interaction between electron spins in a radical pair.

Double-quantum coherence method (a), solid echo technique (b) and selective hole 'burning' (c).

In order to avoid the loss of signal during the 'dead' time, an additional refocusing (fifth) pulse or a six-pulse sequence is used, in which the double-quantum coherence is created by three  $(\pi/2 - \tau/2 - \pi - \tau/2 - \pi/2)$  rather than two pulses.<sup>26</sup> The advantage of the double-quantum coherence method is the absence of the interference effects described in the preceding chapter. However, in this case the electron–nuclear ESEEM occurs too. A drawback of the technique consists in a large number of phase change cycles (a total of sixty-four cycles), which can introduce an additional error. Besides, the phenomenon is characterised by a rather complicated theoretical description and the lack of a clear insight.

### 5. Solid-state NMR pulse sequences method

A Single-Frequency Technique for Refocusing (SIFTER) the dipole–dipole interactions was proposed.<sup>17</sup> It is based on the 'solid echo' and Jeener–Broekaert solid-state NMR pulse sequences. Consider the effects produced taking solid echo as an example.

The pulse sequence used in NMR is  $(\pi/2)_x - \tau - (\pi/2)_y - \tau - \text{echo}$ . It permits refocusing of the dipole–dipole interaction between two nuclear spins (*e.g.*, protons in a bound water molecule in a crystal hydrate). The echo signal on the left and on the right of its maximum is modulated at the frequency of the dipole–dipole interaction. No 'dead' time problem is posed when observing this modulation. This gave an impetus to use of this pulse sequence in EPR as well.<sup>17</sup> However, this approach is only applicable to a pair of equivalent spins, when  $\Delta\omega \ll \varepsilon_d$  (as in solid-state NMR). The reverse holds for EPR, which deals with inequivalent spins in the pair. This problem can be solved by adding two more refocusing  $(\pi)_x$  pulses (see Fig. 7b). At  $\tau_2 = \tau_1$ , the solid echo appears. This signal is created in such a fashion that static scatter of the resonance frequencies over the sample (except for their shift induced by the dipole–dipole interaction in the RP) has no effect on its shape. By varying the difference between two delays

$$t = \tau_2 - \tau_1$$

the observed signal can be modulated by the dipole–dipole interaction. This is performed at a constant total delay  $\tau_2 + \tau_1$ , which allows the relaxation effect to be excluded.

Selection of an informative signal is achieved by phase cycling (a total of three cycles). In order to suppress the electron–nuclear modulation of the decay, measurements are carried out at different total delays  $\tau_2 + \tau_1$ . Electron–nuclear ESEEM depends on this parameter, while the electron–electron ESEEM is independ-

ent of it. Therefore, averaging of the results obtained must lead to selection of the desired effect. For instance, the results of averaging over twenty-five values of this parameter were reported.<sup>17</sup>

This method is characterised by much simpler experimental design compared to the double-quantum coherence technique, because the number of phase change cycles decreases. However, theoretical description remains complicated and no clear representation of the phenomenon is available (the results can hardly be obtained without the density matrix formalism).

Thus, analysis of different methods of investigation of thermally equilibrated systems showed that PELDOR is the most convenient method. It provides a clear picture of the phenomenon and essentially simplified theoretical description. Besides, the electron–nuclear modulation effects are nearly completely eliminated. The only limitation of this approach is inapplicability to systems with narrow EPR spectra of RPs (biradicals).

## 6. Modulation of two-pulse out-of-phase electron spin echo for spin-correlated radical pairs

A chemical or photochemical reaction can produce spin-correlated radical pairs. An example is provided by photosynthesis in plants and bacteria. The process involves absorption of a light quantum followed by formation of a primary electron-donor radical cation and an electron, which is then consecutively trapped by different acceptor molecules to give corresponding radical anions. Initially, the pair is generated in the singlet spin state.

In this case only two inner energy levels are populated (see scheme in Fig. 1). In accord with the portion of the singlet state [see Eqns (7)] the populations of four levels are as follows:  $p_1 = 0$ ,  $p_2 = \cos^2\phi$ ,  $p_3 = \sin^2\phi$  and  $p_4 = 0$ . These populations are not thermally equilibrated; as a consequence, this gives rise to the spin polarisation effect. In weakly coupled systems this population distribution means that if one spin is in the  $\alpha$  state, the second spin is in the  $\beta$  state, and *vice versa*. Therefore, such pairs are called spin-correlated pairs. In addition to the nonequilibrated populations, quantum-mechanical coherence of energy levels also occurs. However, these effects are rapidly damped (it takes less than 100 ns) and consideration of these phenomena goes beyond the scope of this review. The EPR spectrum of a spin-correlated radical pair exhibits two absorption and two emission lines (see Fig. 2b), all line intensities being equal.

Calculations of the echo signals of spin-correlated states for a conventional two-pulse sequence (see Fig. 4a) were carried out.<sup>36,41–43</sup> We cite below the results<sup>36</sup> where coherence effects were averaged. Let us denote arbitrary initial populations as  $p_1$ ,  $p_2$ ,  $p_3$  and  $p_4$ . Application of two pulses ( $\theta_1$  and  $180^\circ$ ) along the  $X$  axis of the rotating frame creates an echo signal at  $t = 2\tau$  with projections on the  $Y$  (in-phase echo) and  $X$  (out-of-phase echo) axes. The intensities of these signals are proportional to the corresponding magnetisations

$$\begin{aligned} M_x &= P \sin 2\theta_1 [S_0 \sin^2 2\phi + \cos 2\phi (S_{-1} \cos^2 \phi - S_{+1} \sin^2 \phi)] + \\ &+ \sin \theta_1 (p_2 - p_3) \sin^2 2\phi \cos 2\phi \left( S_0 - \frac{1}{2} S_{+1} - \frac{1}{2} S_{-1} \right), \quad (14) \\ M_y &= (p_4 - p_1) \sin \theta_1 \times \\ &\times [C_0 \sin^2 2\phi + \cos 2\phi (C_{-1} \cos^2 \phi - C_{+1} \sin^2 \phi)], \end{aligned}$$

where

$$P = -\frac{1}{2}p_1 + p_2 \sin^2 \phi + p_3 \cos^2 \phi - \frac{1}{2}p_4,$$

$$S_q = \sin \left( -\varepsilon_d \tau + q \frac{1}{2} \sqrt{\varepsilon_D^2 + 4(\Delta\omega)^2} \tau \right),$$

$$C_q = \cos \left( -\varepsilon_d \tau + q \frac{1}{2} \sqrt{\varepsilon_D^2 + 4(\Delta\omega)^2} \tau \right).$$

In thermodynamic equilibrium one has  $p_2 = p_3$ ,  $P = 0$  and the out-of-phase echo is absent; the expression for  $M_y$  coincides

with Eqn (12). In contrast to this, only the out-of-phase echo is present for a spin-correlated radical pair born in the singlet state.

For inequivalent spins (weak coupling case), expressions (14) are significantly simplified:

$$M_x = -\frac{1}{2}(-p_1 + p_2 + p_3 - p_4) \sin 2\theta_1 \sin \varepsilon_d \tau, \quad (15)$$

$$M_y = (p_4 - p_1) \sin \theta_1 \cos \varepsilon_d \tau.$$

An example of experimentally observed modulation is shown in Fig. 8 (an RP in Photosystem I). Figure 9 presents the results of Fourier transformation of these experimental data.

An amazing feature of the ESE in spin-polarised RPs is the absence of electron–nuclear modulation effects. First of all, this follows from good correspondence between the experimental and calculated spectra in the frequency domain (see Fig. 9 and curve 2 in Fig. 3); Fig. 9 exhibits no peaks that could be attributed to electron–nuclear interaction. A comparison of isotopically substituted samples ( $^{14}\text{N}/^{15}\text{N}$ , see Ref. 18 and  $^1\text{H}/^2\text{H}$ , see Ref. 44) led to identical results. Computer simulation<sup>45</sup> revealed that the absence of electron–nuclear modulation effects is due to polarisation of corresponding electron–nuclear transitions and mutual cancellation of corresponding peaks in the frequency spectrum of a polyoriented sample.

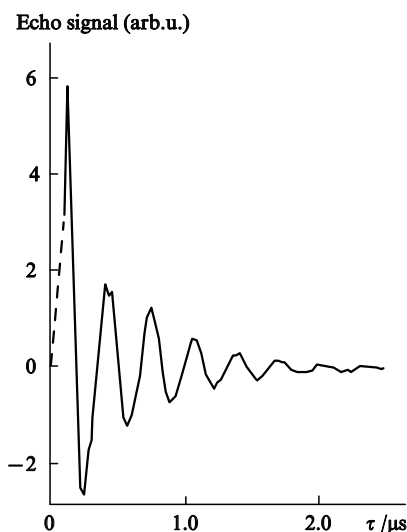


**Figure 8.** Out-of-phase echo signal modulation for  $\text{P}_{700}\text{A}_1^-$  spin-correlated radical pair in Photosystem I.

Dashed line denotes the signal interpolated to the 'dead' time region.

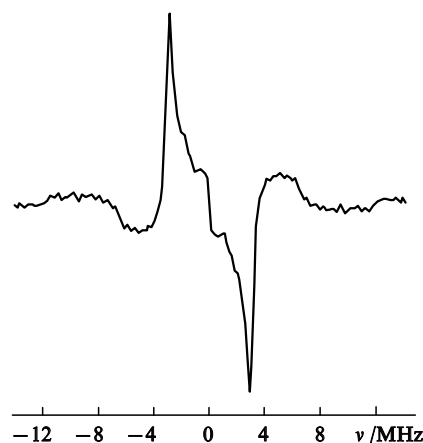


**Figure 9.** Results of sine Fourier transformation of the data shown in Fig. 8.

Yet another feature of the method is a sine-type dependence of the ESE signal amplitude on time  $\tau$ . This allows the signal amplitude at  $\tau = 0$  to be determined immediately (it with necessity equals zero). Thus, signal extrapolation to the 'dead' time region is reduced to a simpler case of interpolation (see Fig. 8).

Eventually, the linewidth in the spectrum of free radicals in photosynthetic reaction centres is of the order of 1–2 mT, which corresponds to the amplitudes of experimentally used MW pulses (excitation band). This means good conditions for excitation of both radicals in RP.

All these features of ESE experiments with spin-polarised RPs make the technique a rather efficient tool for investigation of structural features of the reaction centres.

## 7. Free induction decay modulation under selective excitation

This method employs the pulse sequence shown in Fig. 7c.<sup>46</sup> The first small-amplitude  $180^\circ$  pulse selectively excites only one transition of a radical pair (see Figs 1 and 2). The action of this pulse is similar to 'burning' of a narrow hole in the spectrum. The second large-amplitude pulse excites all four transitions of the RP (non-selective pulse). It plays a dual role, *viz.*, creates a free induction signal and changes the dipole–dipole interaction in the RP. Frequency interference between different transitions leads to modulation of the free induction decay at the frequency  $\varepsilon_d$ .<sup>46</sup> The technique provides a better signal-to-noise ratio for spin-correlated RPs compared to two-pulse ESE<sup>46</sup> and permits studies of zero-quantum and two-quantum relaxation times of RPs.

## IV. Experimental methods based on spin relaxation

Methods employing the partner spin relaxation effects can be divided into two groups, namely, with fast and slow relaxation of B-spins. In the latter case both the A- and B-spins can be of the same type. The fast-relaxation case corresponds to the exchange narrowing of the splitting due to the dipole–dipole interaction, when  $\varepsilon_d^2 T_{1B} \ll 1$ . Slow relaxation means that the reverse inequality holds. Rapidly relaxing spins are characteristic of metal ions. Slowly relaxing spins are typical of free radicals and also metal ions. Methods employed in the case of fast relaxation are based on the A-spin longitudinal ( $T_1$ -effects) and transverse ( $T_2$ -effects) relaxation rate measurements. In the case of slow relaxation, two methods are used, *viz.*, selective hole 'burning' and dipolar modulation enhancement in stimulated ESE.

### 1. A-Spin longitudinal relaxation rate measurements.

#### $T_1$ -Effects

In the case of fast B-spin relaxation ( $\varepsilon_d T_{1B} \ll 1$ ) the A-spin longitudinal relaxation rate ( $T_{1A}^{-1}$ ) is related to the B-spin longitudinal ( $T_{1B}$ ) and transverse ( $T_{2B}$ ) relaxation times as follows:<sup>47</sup>

$$\frac{1}{T_{1A}} = \frac{1}{T_{1A}^0} + S_{rmB}(S_B + 1) \frac{\mu_0^2}{16\pi^2} \times \left[ \frac{b^2 T_{2B}}{1 + (\omega_B - \omega_A)^2 T_{2B}^2} + \frac{c^2 T_{1B}}{1 + \omega_A^2 T_{1B}^2} + \frac{e^2 T_{2B}}{1 + (\omega_B + \omega_A)^2 T_{2B}^2} \right], \quad (16)$$

where  $T_{1A}^0$  is the time  $T_{1A}$  in the absence of B-spin,  $S_B$  is the B-spin and  $\omega_A$  and  $\omega_B$  are the A-spin and B-spin resonance frequencies, respectively

$$b^2 = \frac{1}{6} g_A^2 g_B^2 \beta^4 \frac{(1 - 3 \cos^2 \theta)^2}{\hbar^2 r^6},$$

$$c^2 = 3 g_A^2 g_B^2 \beta^4 \frac{\sin^2 \theta \cos^2 \theta}{\hbar^2 r^6},$$

$$e^2 = \frac{3}{2} g_A^2 g_B^2 \beta^4 \frac{\sin^4 \theta}{\hbar^2 r^6}.$$

The  $T_{1A}$  time is measured in the signal recovery experiments after pulse saturation (or inversion). There are two types of experiments, (i) using an ESE spectrometer with pulsed signal detection (usually, by the spin echo technique) and (ii) using a pulsed EPR spectrometer with signal detection using a small-amplitude continuous-wave MW field. Various types of EPR spectrometers have been described.<sup>48</sup>

Determination of the distance  $r$  from expression (16) requires knowledge of the parameters  $T_{2B}$ ,  $T_{1B}$ ,  $\omega_A$  and  $\omega_B$ . Extended (in the frequency domain) spectra must be averaged over  $\omega_A$  and  $\omega_B$ . A severe problem consists in that not all B-spin transitions are observed experimentally. For instance, large zero-field splitting allows only one transition between the sublevels  $m_S = \pm 1/2$  to be observed in the EPR X-band even for the Kramers ions, such as  $\text{Fe}^{3+}$ . Other non-observable transitions can also contribute to B-spin relaxation. Yet another important problem is complexity of the measurements with allowance for spectral diffusion, which is due to the excitation of a certain portion only of an inhomogeneously broadened EPR spectrum.

For these reasons, the results obtained using this approach are not always reliable and some of them were found to be erroneous. Therefore, in the present review the results obtained by this method are cited only in the case of some comparative experiments.

### 2. A-spin transverse relaxation rate measurements.

#### $T_2$ -Effects, relaxation probe method

If  $T_{1B}|\omega_A - \omega_B| \gg 1$  (recall that  $\varepsilon_d^2 T_{1B}^2 \ll 1$ ), the transverse relaxation rate is given by<sup>47</sup>

$$\frac{1}{T_{2A}} = \frac{1}{T_{2A}^0} + \frac{1}{2T_{1A}} + S_B(S_B + 1) \times \frac{\mu_0^2}{16\pi^2} g_B^2 g_A^2 \beta^4 T_{1B} \frac{(1 - 3 \cos^2 \theta)^2}{3\hbar^2 r^6}, \quad (17)$$

where  $T_{2A}^0$  is the  $T_{2A}$  time in the absence of B-spin.

The transverse relaxation is measured from the ESE signal decay. This approach requires only knowledge of  $T_{1B}$ .

A measuring technique<sup>49</sup> involves determination of  $T_{1B}$  from the transverse relaxation of A-spins in the sample with uniform random spatial distribution of both types of spins. For such samples, the expression for the echo signal decay has the form<sup>9</sup>

$$v_{\text{random}}(2\tau) = \exp \left[ -\frac{16\pi\sqrt{\pi}}{27} \sqrt{S_B(S_B + 1)} \times \frac{\mu_0}{4\pi} \frac{g_B g_A \beta^2}{\hbar} C_B \sqrt{2\tau T_{1B}} \right], \quad (18)$$

where  $C_B$  is the concentration of B-spins.

From here  $T_{1B}$  can be found with ease. The technique has the advantage of self-consistency. In the case of pair and uniform spatial distribution, only one parameter (A-spin transverse relaxation rate) is to be measured and the same relaxation mechanism occurs. Here, the problem of inobservability of some B-spin transitions (see above) is by default completely eliminated. A limitation of the method consists in the necessity of preparing samples with uniformly distributed B-spins.

Often, radical and radical ion pairs produced in radiation-induced and photochemical reactions in solids are characterised by a large scatter of distances. The dependence of  $(T_{2A})^{-1}$  on the separation in the RP [see Eqn (17)] allows one to set the problem of determination of the distance distribution function for RPs. This can be done by varying the temperature and thus the  $T_{1B}$  time, provided the physical properties of the sample do not change. The A-spins in the vicinity of B-spins do not contribute to the ESE signal. Thus, B-spins will be surrounded by a region of 'invisibility' for A-spins, the size of the region being varied with temperature. This approach can be called the relaxation probe method. Usually, the  $T_{1A}$  and  $T_{2A}^0$  times depend on temperature much more weakly than  $T_{1B}$  (recall that usually the A-spins are the

organic radical spins and the B-spins are metal-ion spins). The distance distribution function for RPs can to a good accuracy be estimated by comparing the data of two experiments<sup>49</sup> as

$$n(r) = \frac{dv_{\text{pair}}(2\tau)}{d[\ln(v_{\text{random}}(2\tau))/C_B]}, \quad (19)$$

where  $v_{\text{pair}}(2\tau)$  is the ESE decay for the sample with the pair distribution under study.

### 3. Selective hole ‘burning’

Selective hole burning is used in the case of slow B-spin relaxation ( $\varepsilon_d^2 T_{1B}^2 \gg 1$ ). Here, from Eqn (17) it follows that  $T_{1B} \gg T_{2A}$ , *i.e.*, the spin–lattice relaxation of B-spins is slow on the ESE time scale. Since the B-spins are usually the metal-ion spins with broad EPR spectra, in this chapter the possibility of their excitation by applying MW pulses will be ignored. This is the main difference of the technique in question from the selective excitation method considered above.

The pulse sequence employed in the selective hole ‘burning’ technique<sup>21</sup> is shown in Fig. 7c. The first small-amplitude pulse ‘burns’ a narrow hole in the EPR spectrum, the hole width being of the same order of magnitude as the pulse amplitude. After time  $T$  the hole is broadened due to a change in the dipole–dipole interaction owing to spin–lattice relaxation induced fluctuations of the B-spin orientation.

Consider the A-spin whose resonance line is shifted by  $\pm(1/2)\varepsilon_d$  owing to the interaction with the B-spin (in our case the spin B is  $1/2$ ). After time  $T$ , the B-spin will change its value to the opposite with the probability  $(1/2)[1 - \exp(-T/T_{1B})]$  and will retain it with the probability  $(1/2)[1 + \exp(-T/T_{1B})]$ . Thus, if initially the hole was described in the frequency domain by the function  $h_0(\omega)$ , after time  $T$  it will be given by

$$h_T(\omega) = \frac{1}{2} \left[ 1 + \exp\left(-\frac{T}{T_{1B}}\right) \right] h_0(\omega) + \frac{1}{2} \left[ 1 - \exp\left(-\frac{T}{T_{1B}}\right) \right] \left[ \frac{1}{2} h_0(\omega - \varepsilon_d) + \frac{1}{2} h_0(\omega + \varepsilon_d) \right].$$

Application of the second pulse causes the free induction decay (without changing the interactions in the system, because the excitation of B-spins is ignored), which corresponds to the Fourier image of the EPR spectrum. If we consider the difference between the signals in the presence and in the absence of the first selective pulse, the free induction decay can be described by the expression

$$H_T(t) = \int_{-\infty}^{\infty} d\omega [1 - h_T(\omega)] \cos \omega t = \frac{1}{2} \left[ 1 + \exp\left(-\frac{T}{T_{1B}}\right) \right] + \frac{1}{2} \left[ 1 - \exp\left(-\frac{T}{T_{1B}}\right) \right] \cos \varepsilon_d t. \quad (20)$$

Thus, the free induction decay is modulated at the frequency  $\varepsilon_d$  and the larger the  $T/T_{1B}$  ratio, the larger the modulation depth.

Usually, substantial inhomogeneous broadening in EPR causes the free induction decay to be very short and to damp during the ‘dead’ time. But in the case in point the decay signal is observed due to the fact that it is created only by those spins whose resonance frequencies lie in a narrow spectral interval determined by the width of the hole.

### 4. Relaxation induced dipolar modulation enhancement and stimulated echo experiment

Consider a three-pulse sequence for stimulated ESE,  $\pi/2 - \tau - \pi/2 - T - \pi/2$ -echo. In the interval between the second and third pulses the B-spin changes its orientation with the probability  $(1/2)[1 - \exp(-T/T_{1B})]$  and retains it with the probability  $(1/2)[1 + \exp(-T/T_{1B})]$ . Analysis of the spin precession

phases between the first and second pulses, on the one hand, and after the third pulse on the other hand leads to the following expression for the echo signal decay

$$E(2\tau + T) = \frac{1}{2} \left[ 1 + \exp\left(-\frac{T}{T_{1B}}\right) \right] + \frac{1}{2} \left[ 1 - \exp\left(-\frac{T}{T_{1B}}\right) \right] \cos \varepsilon_d \tau, \quad (21)$$

which means modulation at the  $\varepsilon_d$  frequency with scanning  $\tau$ .<sup>22</sup> This permits determination of  $\varepsilon_d$ . The larger the  $T/T_{1B}$  ratio, the more pronounced the effect observed; therefore, this approach can be called Relaxation Induced Dipolar Modulation Enhancement (RIDME).

Expressions (20) and (21) are similar. This is not surprising because both methods, selective hole ‘burning’ and RIDME, are based on the same physical principle, being different in detection technique. Modulation is due to stochastic spin relaxation between pulses rather than the coherence effects upon excitation of different transitions in the spin system (see above).

There is an analogy with the PELDOR method, which involves an artificial change in the dipole–dipole interaction caused by application of the MW pulse. In the RIDME case the dipole–dipole interaction is changed by a natural process, spin–lattice relaxation. The advantage of the RIDME method is a much larger portion of the B-spins involved in modulation ( $P_B$ ). From Eqns (20) and (21) it follows that this portion can be as high as 50%. (*cf.*  $P_B = 10\% - 20\%$  for X-band PELDOR).

Due to inhomogeneous line broadening in high-field EPR the  $P_B$  parameter in the PELDOR becomes small and the modulation effect cannot be observed. For both relaxation methods described above (selective hole ‘burning’ and RIDME) this parameter is independent of the EPR frequency band. In particular, a high-field (4.5 T) RIDME EPR study was reported.<sup>50</sup>

A drawback of the relaxation methods is that other mechanisms, *e.g.*, intramolecular motions can also contribute to the relaxation observed.<sup>51</sup> Separation of these undesired contributions requires elaboration of additional experimental procedures. For instance, separation of the contributions of B-spin relaxation and methyl group rotation in a RIDME study<sup>50</sup> involved measurements of the temperature dependences of these contributions. The temperature behaviour of intramolecular motions obeys the Arrhenius relation while the  $T_1$  time of free radicals is usually proportional to  $T^2$ . In the latter case the temperature dependence is much weaker and by lowering temperature one can eliminate the contribution of intramolecular motions. A selective hole ‘burning’ study was reported, in which the contributions of other mechanisms were separated using a reference sample depleted of the particles bearing B-spins.<sup>52</sup>

### 5. Out-of-phase stimulated electron spin echo for triplet spin-correlated radical pairs

If a photoinduced spin-correlated pair comprises a radical and a short-lived triplet molecule, only the in-phase echo signal is initially observed.<sup>53</sup> Then, the out-of-phase stimulated echo signal appears, which proceeds in parallel with the decay of the triplet state. Variation of the time  $\tau$  leads to modulation of both the in-phase and the out-of-phase echo signals at the frequency of the dipole–dipole interaction.

The modulation mechanism of the in-phase echo signal is similar to the RIDME mechanism (see above). The difference consists in that the RIDME modulation is due to a spontaneous shift of the spin resonance frequency caused by the spin–lattice relaxation induced change in the dipole–dipole interaction while in this case modulation is due to the change in the dipole–dipole interaction caused by the decay of the paramagnetic triplet state. The out-of-phase echo signal and its modulation are due to not only this reason but also the spin polarisation of the initial state of

the triplet–triplet RP. The in-phase and out-of-phase signals are described by the following equations:<sup>53</sup>

$$M_y = n_0 + (n_1 + n_{-1}) \exp(-KT) + (n_1 + n_{-1})[1 - \exp(-KT)] \cos \varepsilon_d \tau, \\ M_x = (n_1 - n_{-1})[1 - \exp(-KT)] \sin \varepsilon_d \tau,$$

where  $n_1$ ,  $n_0$  and  $n_{-1}$  are the initial populations of the corresponding triplet states of the RP and  $K$  is the decay constant of the triplet state.

Note that the out-of-phase signal appears only in the presence of the dipole–dipole interaction and only as a result of the decay of the triplet state. Besides, spin polarisation in the system is required.

Selective hole ‘burning’ experiments similar to those described above for spin-correlated RPs can be carried out with triplet RPs.<sup>54</sup> In this case the free induction decay signal becomes modulated.

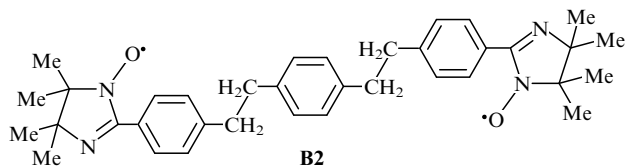
## V. Conformations of long-chain biradicals and doubly spin-labelled and metal-containing biomolecules

### 1. Long-chain nitroxyl biradicals

Long-chain biradicals with single bonds in their structures can adopt a variety of conformations characterised by different biradical length. The distance between the terminal paramagnetic fragments can be used for characterisation of the conformational structure. The results of measurements of these distances in the shape-persistent biradicals, which are assumed to adopt only one conformation, are usually in good agreement with the results of structure simulations.<sup>17, 22, 55, 56</sup>

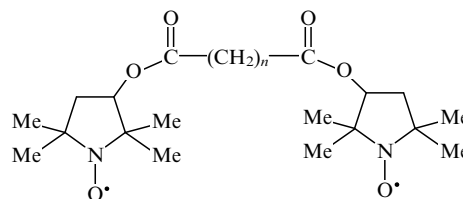
Flexible long-chain biradicals can adopt a larger number of conformations. In this case one must introduce a distance distribution function between paramagnetic fragments. Mathematically, this is an inverse problem of solving the Fredholm integral equation of the first kind. To this end, different methods were proposed, in particular, a truncated expansion of the kernel of the integral equation,<sup>57</sup> a discrete integral transformation of the equation with appropriately chosen transformation kernel (analogous to Fourier transformation)<sup>33, 58</sup> and the Tikhonov regularisation.<sup>33</sup>

All these methods involve rather complicated computational procedures. If a narrow distance distribution is assumed, its width can be estimated immediately from the modulation decay.<sup>38</sup> This approach was employed in a magnetic-field-jump PELDOR study<sup>38</sup> of a shape-persistent biradical **B1** (see above) and a flexible radical **B2**.



The ESE signal decays for **B1** are shown in Fig. 5 and the results of Fourier transformation are presented in Fig. 6. For the **B2** radical the modulation damped much faster than for **B1**. This can be associated with the presence of a distance distribution. The spin–spin separation estimated from the peak position in the frequency domain for **B2** was 20.5 Å. Damping of modulation for the shape-persistent biradical is due to scatter of the dipole frequencies caused by polyorientation of the sample. Any additional damping can be associated with the distance distribution. A comparison of the signal decays for **B2** and **B1** gave the distribution width  $\Delta r = 3$  Å.<sup>38</sup>

### Conformations of biradical



were studied by PELDOR.<sup>58, 59</sup> This biradical contains  $n$  methylene groups ( $n = 8–20$ ). The average distances between the radical fragments were calculated from the frequency spectra obtained after the Fourier transformation of the decay traces. These data were compared with the results of calculations for the limiting case of completely stretched *trans*-conformation and with the results of the calculations of conformational statistics at the glass transition temperature of the polystyrene matrix. The results of distance measurements were found to be similar (within the limits of experimental error) to the calculated conformational statistics.

The distance distribution function for  $n = 10$  was determined by the integral transformation and using the Tikhonov regularisation.<sup>33, 58</sup> Both methods gave similar results, namely, at  $n = 10$ , the width of the distribution function at half-height was  $\sim 5$  Å at the average spin–spin separation  $r = 21$  Å.

Determination of the distance distribution function in a sample with a complex mutual spatial distribution of RPs faces an additional problem of separation of the intrapair and pair–pair interactions. This is a complicated problem because of complex correlations between the radial and angular variables. However, angular spin–spin correlations of RPs can be neglected if the modulation depth of the echo signal decay is low.<sup>58</sup>

The PELDOR method is appropriate for measuring the dipole–dipole interaction not only in nitroxyl biradicals but also in biradicals containing paramagnetic metal ions as partner spins. As mentioned above, it is required that spin relaxation of the ion during the period of action of the pulse sequence be slow and the EPR spectrum be relatively narrow. A pulsed EPR study of a terpyridine-based Cu(II) complex containing phenylene- and ethynylene-based shape-persistent groups attached on two sides and two terminal nitroxyl labels was reported.<sup>60</sup> The observed decay modulation was interpreted as a result of dipole–dipole interactions in the copper–nitroxyl (distance 24.3 Å) and nitroxyl–nitroxyl (distance 48.6 Å) pairs.

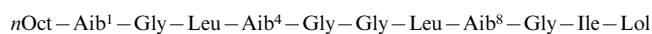
The PELDOR method also allows the conformational structure of spin-labelled polymers (in essence, they are polyradicals) to be investigated. This can be done by monitoring the signal decay kinetics, which become non-exponential in the case of linear polymers (the cubic root of the time under the exponent). It is this decay law that was established in studies of spin-labelled poly(4-vinylpyridine) in a glassy solution.<sup>61</sup>

### 2. Doubly spin-labelled peptides and RNA

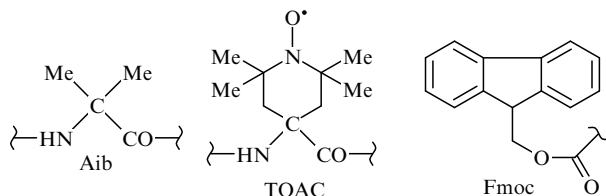
Recent development of biochemical methods of selective spin label attachment to specified fragments of biomolecules led to the wide use of this approach.<sup>62, 63</sup> The secondary structure of a doubly spin-labelled peptide can be established by studying the dipole–dipole interaction between the spin labels. If the distance between spin labels is shorter than 15 Å, continuous-wave EPR studies are carried out; for some results, see Ref. 64. If this distance exceeds 15 Å, the dipole–dipole interaction remains unresolved in continuous-wave EPR and one must use pulsed EPR spectroscopy.

A number of studies of doubly spin-labelled peptide trichogin GA IV have been reported.<sup>65–70</sup> This compound is a peptide antibiotic of fungal origin, rich in aminoisobutyric (Aib) acid, and possesses antibacterial and antifungal properties. Such peptides can produce ionic channels in membranes, which make them permeable and cause cell death.

A distinctive feature of trichogin GA IV is relatively small chain length. The length of the peptide is small compared to the membrane thickness; therefore, the mechanism of membrane permeability is still unclear. The peptide structure comprises three aminoisobutyric acid residues.



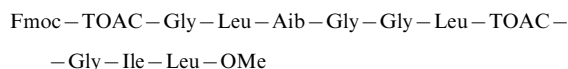
In the chemical synthesis these residues are replaced by structurally similar nitroxyl spin labels TOAC.<sup>68</sup>



Two types of trichogin were used, namely, substituted trichogin (F-trichogin with *n*-octanoyl group replaced by Fmoc) and unsubstituted compound. Besides, the 1,2-aminoleucinol (Lol) residue was replaced by the L-leucine methyl ether (Leu-OMe) residue. These substitutions did not change the bioactivity of the peptides.<sup>71</sup>

Studies of doubly labelled (at positions 1 and 4, 4 and 8 and 1 and 8) peptides were performed. The first two types of biradicals were investigated by continuous-wave EPR<sup>64</sup> and the last type was studied by pulsed EPR spectroscopy owing to large spin-spin separation.

The conformation of spin-labelled F-trichogin-1,8



was studied by three-pulse PELDOR in various glassy solvents at 77 K. As a rule, no Fourier transformation was performed and the analysis was carried out in the time domain. The ESEEM observed in chloroform-DMSO solution was ascribed to the dipole-dipole interaction with the interspin separation of  $\sim 20$  Å.<sup>65</sup> The modulation damping was associated with the distance distribution of width  $\sim 2$  Å. It should be noted that only 25% of the labelled molecules are characterised by these parameters of the distribution function, while the remaining 75% of molecules are characterised by a broader distribution.

Doubly labelled trichogin-1,8 and F-trichogin-1,8 were also studied in other polar glassy solvents, *viz.*, methanol, ethanol, trifluoroethanol and in chloroform/DMSO mixtures with different component ratios.<sup>66</sup> It was found that modulation significantly differs depending on the type of the molecule and the matrix. For F-trichogin-1,8, modulation is observed only in the chloroform/DMSO mixture, whereas for trichogin-1,8 it is observed in all matrices, but with different oscillation frequencies. The distances between paramagnetic fragments vary from 15.3 Å in trifluoroethanol to 21.8 Å in ethanol.

These distances can be compared with the structural parameters of peptides, established by X-ray scattering.<sup>69,70</sup> Using commonly accepted values for the peptide backbone torsion angles in the secondary structures ( $\alpha$ - $3_{10}$ -,  $2_7$ - and  $2_5$ -helices), one can calculate the interspin distances.<sup>65,69,70</sup> Based on the results of calculations, it was concluded that trichogin-1,8 and F-trichogin-1,8 adopt the  $2_7$ -helix conformation in all matrices except for trifluoroethanol, where the peptides adopt the  $3_{10}$  conformation.

The conformation of the same doubly labelled peptide in a tetrameric cluster formed in a matrix of low polarity (chloroform/toluene mixture) was studied.<sup>67</sup> The distance  $r = 15.7$  Å is similar to the value 14 Å calculated for the  $3_{10}$ -helix.

The structures of doubly spin-labelled proteins (lysozyme T4 mutants) were studied using the double-quantum coherence technique<sup>72</sup> in the 9 and 17 GHz bands. The distances found lie

in the range from 20 Å (mutant 65/76) to 47 Å (mutant 61/135). High-quality spectra obtained made it possible to determine the distance distribution function. Analysis of this function revealed a variety of conformations of these molecules. The experimental results were compared with the results of molecular modelling.

The pioneering study<sup>73</sup> of spin-labelled RNA was carried out by the PELDOR method and involved two types of RNA with known molecular structures, labelled with nitroxyl labels in two positions of the uridine residue. According to structural data, the distance between paramagnetic fragments must be 35 Å for one type of RNA while the other type is characterised by a broad distance distribution. The results obtained coincided with the expectations, namely, the signal modulation observed in the former case corresponded to a distance of  $35 \pm 2$  Å, whereas in the latter case no modulation was observed.

The PELDOR method was employed in determining the distance between two tyrosyl radicals in ribonucleic reductase *E. coli*.<sup>74</sup> The distance between two radicals found from the peak position in the frequency domain was  $33.5 \pm 0.4$  Å. The modulation depth showed that at least 25% of radicals were in dimeric form (monomeric radicals can also be present in this system).

### 3. Metal-containing biomolecules

Many proteins and enzymes contain paramagnetic metal ions. If such ions form pairs and clusters, the mutual arrangement of these objects in space can be studied by EPR. In metal-containing biomolecules, the second spin can be delivered by incorporating a nitroxyl spin label. In some cases diamagnetic ions in proteins can be replaced by paramagnetic ions, *e.g.*, Zn(II) by Co(II) and Mg(II) by Mn(II).

The spin relaxation of spin labels was studied over a wide temperature range in order to realise both fast and slow ion relaxation.<sup>75–78</sup> Transverse relaxation was studied by two-pulse sequence and longitudinal relaxation was studied by the saturation-recovery technique. Low-spin iron(III) porphyrins were investigated.<sup>75</sup> Raising the temperature from 8 to 120 K led to a decrease and then to an increase in  $T_2$ . Experimental data were analysed using the measured Fe(III) relaxation times. The distance in the metal-ion pair was estimated at 10.5–15 Å. High-spin iron(III) porphyrins were also studied.<sup>76</sup> Axial ligands were fluorine, chlorine and bromine. The temperature dependence of  $T_2$  exhibited a minimum near 6 K. The experimental data were analysed using independently determined iron relaxation rates. The interspin distances were between 11.6 and 15.0 Å, which is in agreement with the values obtained for low-spin iron (see above). A study<sup>77</sup> of low-spin methemoglobins spin-labelled at the cysteine  $\beta$ -93 position revealed a decrease and then an increase in  $T_2$  value with an increase in temperature from 6 to 120 K. The distance in the spin label-ion pair (15–15.5 Å) was determined analogously. These distances in high-spin fluoro- and aquamethemoglobins increased to 15.8–17.5 Å.<sup>78</sup>

The PELDOR method was employed to study the dipole-dipole interaction between two paramagnetic centres (PCs) in [3Fe–4S](+) and [NiF] clusters in *Desulfovibrio vulgaris* Miazaki *F. hydrogenase*.<sup>79</sup> The distance between PCs, known from X-ray data, differs from the PELDOR measured value. Probably this is due to specific exchange binding in the iron/sulfur cluster. Nevertheless, such studies make it possible to collect information on the internal structure of multinuclear metal clusters.

The Mo(V)/Fe(III) state of sulfite oxidase was studied by the PELDOR method in different (X- and C-) MW bands at 4.2 K.<sup>80</sup> A-Spins were the Fe(III) ion spins. Analysis of the decay curves suggested multiple conformations of the flexible loop connecting the Mo and Fe.

## VI. Cluster nanostructures

### 1. Peptide clustering in non-polar media

Peptides can form clusters or aggregates; this property can play the determining role for their physiological functions. ESE

spectroscopy provides a unique possibility of studying the clustering of spin-labelled peptides. All known experimental techniques employed in such studies are based on the same principle. We will consider it taking the PELDOR method as an example.

The echo signal from radicals in an RP is given by expression (13). Assume that a cluster comprises  $N$  particles and that the probability of simultaneous excitation of more than one B-spin is low, *i.e.*,  $P_B N \ll 1$ . Then, for the  $n$ th particle ( $n = 1, 2, \dots, N$ ) one has

$$V_n(T) = \prod_{k \neq n} \left[ 1 - P_B + P_B \cos(\varepsilon_d^{nk} T) \right],$$

where  $\varepsilon_d^{nk}$  is the parameter of the dipole–dipole interaction with the  $k$ th spin.

This expression should be averaged over all possible pairs. At low  $P_B$ , the averaging can be performed independently for each pair

$$V(T) = \left[ 1 - P_B (1 - \cos(\varepsilon_d T)) \right]^{N-1}.$$

From this it follows that at  $t \rightarrow \infty$  the quantity  $V(T)$  tends to the limit

$$(1 - P_B)^{N-1} \approx 1 - (N-1) P_B. \quad (23)$$

The number,  $N$ , of particles in the cluster can be estimated from the asymptotic (long-time) ESE kinetics.

This approach was used in PELDOR and continuous-wave EPR studies of the aggregation of spin-labelled peptide trichogin GA IV (see Section V) in glassy polar and low-polar solutions at 77 K.<sup>81</sup> It was hypothesised that the peptide forms channels in membranes by forming a bundle comprising a number of molecules with polar groups directed to the interior and hydrophobic groups pointing to the exterior. However, numerous previous studies revealed no aggregation. Two types of solvents were a chloroform/toluene (7:3) and a chloroform/toluene/ethanol (3.5:1.5:5) mixture. The choice of the mixture compositions was determined by two factors, the peptide solubility and the formation of glassy state on freezing. The first mixture was a medium of low polarity while the second mixture was a polar liquid. Peptides were spin labelled at positions 1 and 4.

Continuous-wave EPR studies of various media at 77 K revealed the absence of spectral differences. The PELDOR data are shown in Fig. 10. A smooth signal decay observed in the polar matrix is characteristic of uniform intermolecular distribution. In the non-polar matrix, a dramatic signal decay occurs at times 100–150 ns, which is much more pronounced than that of F-trichogin-1,8 biradical shown for comparison.

This behaviour can be explained by aggregation of molecules in the non-polar matrix. Using expression (23) and the data for a model biradical system, one can immediately estimate the number

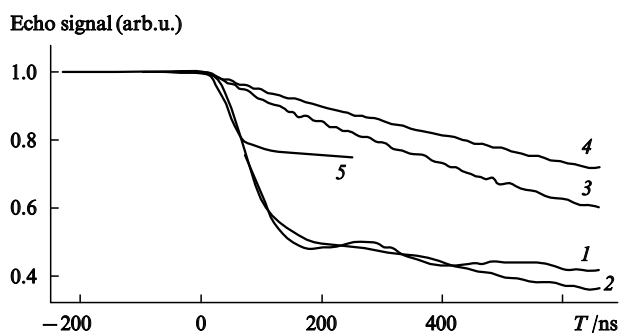


**Figure 10.** Two-frequency PELDOR signal decays obtained for peptide glassy solutions with scanning time  $T$  (see Fig. 4b) at 77 K.<sup>81</sup> F-trichogin-4 (1) and trichogin-4 (2) in chloroform/toluene mixture; F-trichogin-4 (3) and trichogin-4 (4) in chloroform/toluene/ethanol mixture and doubly labelled peptide F-trichogin-1,8 in methanol (5).

of molecules in the aggregate. Indeed, in both cases the portion,  $P_B$ , of excited spins (in this case,  $N = 2$ ) can be found from the asymptotic data for the biradical given identical experimental conditions with allowance for similar EPR spectral pattern. Knowing  $P_B$  from the asymptotic data (see Fig. 10), one can immediately determine  $N \approx 4$  in the solution of low polarity. Thus, this peptide forms tetrameric clusters in the glassy solution of low polarity.

The signal modulation observed in the experiments (see Fig. 10, curves 1 and 2) can be explained by narrow distribution of the distances between spin labels in the cluster structure. The cluster size estimated from the initial decay rate (at times shorter than 150 ns) is 30–36 Å. The distances determined from the decay modulation for F-trichogin-4 and trichogin-4 are 23.5 and 26.0 Å, respectively.<sup>81</sup>

It is noteworthy that these solvents exhibit significantly different room-temperature continuous-wave EPR spectra.<sup>81</sup> The EPR lines in the spectrum of the solvent of low polarity are much broader; this is similar to line broadening due to slowing down of the orientation motion, which is known in the EPR of spin labels and probes. This should be expected in the case of clustering, because the orientation relaxation time is proportional to the particle size according to the Stokes–Einstein–Debye relation. The cluster size was estimated from the broadening of the continuous-wave EPR spectra.<sup>82</sup> The results of measurements coincided with the estimate of the number of molecules in the cluster ( $N \approx 4$ ). Therefore, the results obtained by both continuous-wave EPR of liquids at room temperature and by PELDOR of glassy frozen solutions substantiate the peptide clustering.

Analogous measurements were carried out for mixtures of other solvents of low polarity, namely, chloroform/toluene, carbon tetrachloride/toluene and dichloroethane/toluene.<sup>83</sup> In all cases, aggregation was revealed, with  $N \approx 3.1–4.3$  depending on the system. The modulation observed corresponded to inter-spin distances of 23, 26 and 33 Å, respectively (one distance or a set of distances depending on the system).

Aggregation of spin-labelled zervamicin IIA (a hexadecapeptide of fungal origin) was investigated.<sup>84</sup> This compound is known to form hollow channels in phospholipid double layers. The PELDOR study of frozen glassy mixtures in the toluene/methanol system at 77 K revealed aggregation. The average distance between spin labels was 25–35 Å (depending on the mixture composition). It was concluded that peptide molecules have an antiparallel orientation and that the increase in the methanol concentration in the mixture led to loosening in the cluster structure.

No aggregation of spin-labelled trichogin dimers (covalent compounds comprising two molecules linked ‘head-to-tail’) in methanol was observed, but it did occur in a chloroform/toluene mixture (2 to 3 molecules).<sup>85</sup> The distances between spin labels in clusters were found to be in the range from 30 to 45 Å. An increase in the peptide concentration in non-polar solvents led to formation of tetrameric clusters.<sup>86</sup>

A double-quantum coherence ESE study<sup>16</sup> revealed clustering of peptides MTSL–CPPPPC–MTSL in a glycerol/water/trifluoroethanol mixture at  $-82^\circ\text{C}$ . An increase in the peptide concentration from 0.75 to 3 mmol g<sup>-1</sup> was followed by the appearance of the double-quantum coherence signals from both intramolecular and intermolecular pairs. In the latter case the parameters of the signal indicated a high local spin concentration. Clustering was observed in a polar matrix. A structurally similar peptide MTSL–CPPPPC–MTSL showed no aggregation.<sup>16</sup>

## 2. Nanostructure of ionomers

Ionomers are polymers with terminal ion groups.<sup>87,88</sup> Their structures contain clusters of ion groups of the size of a few nanometres separated by distances of the same order. Both these parameters of the nanostructure can be evaluated using ionic spin probes.<sup>33,89,90</sup> A study of ionomers based on a polyisoprene/polystyrene copolymer showed that ion groups can cap one or

both chain ends or be situated at the polyisoprene/polystyrene interface. It was shown that the surface of ion clusters is accessible to ionic probes.<sup>91</sup>

Experiments<sup>33,89,90</sup> were carried out using the PELDOR method. The concentration of spin probes was chosen to provide on the average two probes per cluster. The temporal evolution of the PELDOR signal was treated as a result of manifestation of the pair distribution function represented by a superposition of two Gaussian curves and a uniform distribution. The Gaussian curves corresponded to the distances  $r_1 \approx 2$  nm and  $r_2 \approx 5-7$  nm, where  $r_1$  is the characteristic interparticle distance in the cluster and  $r_2$  is the characteristic intercluster distance.

A comparative experiment with a non-polar spin probe revealed only a uniform distribution. The results obtained for three ionic spin probes characterised by increasing distance between the nitroxyl and ionic groups substantiated the interpretation mentioned above. A shift of the first distribution peak towards longer distances<sup>89</sup> was interpreted as additional evidence for the fact that the probe is situated on the surface (with the nitroxyl group directed inside the polymer chains) and that this peak should be attributed to the cluster size. SAXS data<sup>91</sup> are consistent with the PELDOR data<sup>33</sup> given some assumptions concerned with specific features of the interpretation of the results obtained by both methods.

Studies of polymers with different molecular masses and, hence, different chain lengths revealed that the cluster size is independent of the molecular mass except for the cases where the size of the ionic group is much shorter than the chain length. The cluster-cluster distance must be a linear function of the chain length. Such a correlation established for polymers with ionic caps at one end<sup>33</sup> has the form

$$r_2 \sim M^{0.334},$$

where  $M$  is the molecular mass of the cluster. Polymers ion-capped at both chain ends (an anion at one end and a cation at the other end of the polyisoprene/polystyrene copolymer) exhibited no correlation between  $r_2$  and  $M$ . This is due to specific features of the polymer packing, which is characterised by the formation of the polyisoprene/polystyrene interface containing surface ionic groups. In this case an increase in  $M$  can have no effect on the mutual arrangement of clusters on the surface.

## VII. Stable paramagnetic pairs in photosynthetic reaction centres of plants and bacteria

### 1. Radicals and ions in photosynthetic reaction centres

Photosynthesis in higher plants, algae and some bacteria occurs in the photosynthetic reaction centres. These are protein complexes containing a number of cofactors that absorb the energy of a light quantum and participate in subsequent charge separation, producing radical pairs comprised of paramagnetic radical cations and radical anions. Besides, the RC structure *a priori* contains paramagnetic ions. Therefore, EPR spectroscopy can be an efficient tool of research on the structure and operation of RC.<sup>92-95</sup>

The RC structure was the subject of a number of X-ray studies (see, *e.g.*, Refs 96-102 and references cited therein). These methods require crystallisation of samples. The spatial resolution varies from 2 to 4 Å depending on the complexity of the system and the quality of the crystals. Molecular modelling<sup>103</sup> is also a useful tool in structure analysis; here, conclusions about the structure of more complex systems are drawn based on the known data of relatively simple systems (purple bacteria RC).

Pulsed EPR studies of RC offer the following advantages. First, preparation and modification of samples (by *e.g.*, artificial replacement of cofactors) are much less labour-consuming processes compared to their crystallisation (corresponding artifacts are also ruled out). Second, higher spatial resolution permits refinement of the supramolecular structure established by other methods and in some cases facilitates the interpretation of data. Third,

the observation of photo- and thermally induced structural rearrangements becomes possible. Finally, it is possible to investigate the interrelations between the structure and the functioning of the RC, because EPR studies are directly related to the cofactors responsible for electron transfer.

The bacterial RC has the simplest structure. Corresponding data were obtained with the highest resolution, 2.3-3 Å.<sup>96-99</sup> The RC contains a primary electron donor, namely, a bacteriochlorophyll dimer, which is usually denoted as  $P_{870}$  (the subscript denotes the maximum wavelength of the optical absorption band, expressed in nanometres). Absorption of a light quantum produces a radical cation  $P_{870}^+$  and an electron, which migrates along the chain of other cofactors. The migrating electron consecutively forms corresponding radical anions. First, it arrives at the bacteriochlorophyll molecule adjacent to the dimer, then at the bacteriopheophytine molecule, at the primary quinone acceptor,  $Q_A$ , and at the secondary quinone acceptor,  $Q_B$ . Each charge separation step involves two particles (a radical pair). The dimer cation is reduced owing to electron transfer from the nearest cytochrome molecule. After absorption of two light quanta the doubly reduced  $Q_B$  is protonated to quinone and leaves the reaction centre. Its position is then occupied by another quinone from the so-called quinone pool, and the process can proceed again. The bacterial RC also contains a paramagnetic non-heme Fe(II) ion. All cofactors have their 'twins' arranged symmetrically with respect to the line connecting the centre of  $P_{870}$  and the iron ion (symmetry group  $C_2$ , the  $P_{870}$  dimer also has a symmetrical structure). Thus, there are two pathways, A and B, the charge separation process following only the former. The reason why pathway B is not involved is still unclear.

Photosynthesis in higher plants is a much more complicated process and involves consecutive operation of two RC, photosystem II (PS II) and photosystem I (PS I). It is known that operation of these RCs results, in particular, in the evolution of oxygen from water molecules. This occurs in the so-called oxygen-evolving complex (tetranuclear manganese cluster).

The structure of PS I was established by X-ray analysis with a 4 Å resolution.<sup>100</sup> In PS I, an electron is initially transferred from the primary chlorophyll donor  $P_{700}$  to the chlorophyll molecule ( $A_0$ ) and then to the phyloquinone molecule ( $A_1$ ). This results in a  $P_{700}^+A_1^-$  pair.

The structure of PS II was also established by X-ray analysis with a 3.7-3.8 Å resolution.<sup>101,102</sup> The protein backbone of PS II contains a number of cofactors analogous to the bacterial RC, *i.e.*, the chlorophyll electron donor  $P_{680}$ , pheophytine, plastoquinone and non-heme iron(II). It is believed that these cofactors also form a structure with a  $C_2$  symmetry, which is similar to the bacterial RC. Plastoquinone  $Q_B$  is transformed into plastoquinol, which becomes an electron donor for PS I *via* cytochrome  $b_6f$ ;  $P_{680}^+$  is reduced by tyrosine  $Y_Z$ . There is yet another symmetrically arranged tyrosine molecule  $Y_D$  whose function is unclear as yet.

The oxidation of the manganese cluster occurs in a stepwise manner on consecutive absorption of light quanta. As a result, absorption of four light quanta leads to splitting of two water molecules into four protons and four electrons *via* five intermediate states, namely,  $S_0$ ,  $S_1$ ,  $S_2$ ,  $S_3$ ,  $S_4$  (transition from the  $S_4$  state to the  $S_0$  state is a dark transition) and eventually gives an oxygen molecule.<sup>104</sup> A number of models for the operation of this cluster are available (see, *e.g.*, Ref. 105).

Under laboratory conditions, different states of the  $S_0-S_4$  cycle can be achieved by specific biochemical treatment, irradiation and freezing. A broad multicomponent EPR signal of tetranuclear manganese cluster with spin 1/2 is observed in the  $S_2$  state.

### 2. Stable paramagnetic pairs

$P_{870}^+-Q_A^-Fe^{2+}$  pairs in the RC of purple bacteria *Rhodobacter sphaeroides* R26 were studied<sup>106</sup> using the selective hole 'burning' technique. A distance of  $26 \pm 2$  Å determined in the experiments is in good agreement with the data of X-ray analysis. This was



treated as a substantiation of correctness of the method employed; later, this technique was used in studies of other systems.

The  $Y_Z$ – $Mn_4$  pair in PS II was investigated by saturation–recovery ESE<sup>107</sup> and a 15 Å distance was determined. Possible sources of errors in the technique were reported in another study.<sup>108</sup> It should be noted that the dipole–dipole interaction in this pair is well observed by continuous-wave EPR; analysis of the lineshape by different authors gave a distance of  $\sim 8$  Å.<sup>109–112</sup>

Measurements for the  $Y_D$ – $Mn_4$  pair in PS II were carried out by different ESE spectroscopy methods, in particular, the selective hole ‘burning’ technique.<sup>52</sup> In this approach, it is of crucial importance to exclude all sources of hole broadening except for those associated with the dipole–dipole interaction. This was achieved by comparing the spectra obtained with the spectra of a sample containing no manganese complex. To attain a better agreement with the experiments, it was assumed that the manganese complex is characterised by non-exponential spin-lattice relaxation with a small contribution (12%) of a ‘long-tail’ component. In addition, a distance distribution in the range 4–6 Å was assumed. Measurements for the  $S_2$  state gave a distance of 28 Å. A similar value of  $27 \pm 0.2$  Å was obtained by the PELDOR method.<sup>113</sup>

The results of these investigations revealed an essentially unsymmetrical arrangement of  $Y_D$  and  $Y_Z$  with respect to the manganese complex. A rather long distance from the complex to  $Y_D$  suggests that the latter is not involved in primary electron transfer.

The dipole–dipole interaction in the  $Y_D$  and  $Y_Z$  pairs in PS II was studied by the ‘2 + 1’ method<sup>114</sup> using samples depleted of manganese complex. A distance of  $\sim 30$  Å was determined. This approach was employed also to study oriented membranes.<sup>115</sup> The angle between the radius vector of the pair and the normal to the membrane surface was found to be  $100 \pm 2^\circ$ .

Oriented membranes depleted of manganese complex were studied by the ‘2 + 1’ technique.<sup>116</sup> The angle between the vector connecting  $Y_D$  and  $Chl_Z$  and the normal to the membrane was found to be  $50 \pm 5^\circ$ . The separation in the pair, obtained for a polyoriented sample, was  $29.4 \pm 0.5$  Å.<sup>116, 117</sup> The distance in the  $Y_D$ – $Q_A^-$  radical pair studied by the same method was  $38.8 \pm 1.1$  Å.<sup>117</sup>

The  $Y_D$ – $Fe(II)$  pairs in PS II were investigated by the selective hole ‘burning’ technique.<sup>106</sup> The distance was  $42 \pm 2$  Å. Calculations carried out with allowance for zero-field splitting gave a value of 0.81 for the effective spin of the ion.

Data for the  $Y_Z$ – $Fe(II)$  and  $Y_D$ – $Fe(II)$  pairs were obtained using the saturation–recovery method.<sup>118</sup> As mentioned above, the technique is inappropriate for obtaining reliable quantitative data, but qualitative information can appear to be useful. Samples depleted of manganese complex were studied. In the mutants containing no  $Y_D$  it is possible to characterise the  $Y_Z$ – $Fe(II)$  pair. It was found that  $Y_Z$  and  $Y_D$  obey identical saturation–recovery kinetics. This suggests that both tyrosines are at equal distances from  $Fe(II)$ , being arranged symmetrically with respect to  $Fe(II)$ .

## VIII. Photoinduced spin-correlated pairs in photosynthetic reaction centres of plants and bacteria

Isolated RC make it possible to investigate short-lived RPs produced after absorption of a light quantum in the course of electron transfer. For instance, no electron transfer beyond  $Q_A$  occurs in bacterial RC at low temperatures; the  $P_{870}^+Q_A^-$  pair has a lifetime of 30 ms and disappears *via* reverse recombination. The distance in the pair ( $\sim 25$  Å) makes it a convenient subject for ESE spectroscopy studies. Since the pair was born in the singlet spin state, the spins are not thermally equilibrated and we deal with a spin-correlated pair. Therefore, the use of ESE spectroscopy is of additional interest for studying spin correlation effects.

The ESE signal of a radical pair in photosynthetic RC was first detected by Thurnauer and Norris.<sup>119</sup> It was found that the signal phase is shifted by  $90^\circ$  compared to the signals of thermally equilibrated systems (the out-of-phase signal). The nature of the signal and of the phase shift remained unclear at that time. The theory of ESE in spin-correlated radical pairs was developed much later<sup>41, 42</sup> and it does predict the out-of-phase signal for spin-correlated RPs (see Section III).

This theory also predicts that an increase in the interval between pulses will cause modulation of the two-pulse ESE signal (ESEEM) at the frequency of the dipole–dipole interaction in the pair. However, first experimentally observed ESEEM<sup>120</sup> was attributed to the electron–nuclear interaction and not analysed. A long time after it was established that the electron–nuclear interaction in spin-correlated RPs does not manifest itself and the observed modulation is completely governed by the electron–electron interaction in the pair.<sup>18, 44</sup> This was substantiated not only by good agreement between the experimental and theoretical dipolar doublet but also by the results of the  $^{14}N/^{15}N$  and H/D isotope substitution experiments.<sup>18, 44</sup>

The reason for the absence of the electron–nuclear contribution in ESEEM (which strongly complicates measurements of the dipole–dipole interaction in thermally equilibrated pairs) seems to be polarisation of electron–nuclear transitions, whose lines are mutually cancelled in the frequency domain of a polyoriented sample.<sup>45</sup>

Numerous studies of RPs in photosynthetic RC by the out-of-phase ESE decay modulation have been carried out since publication.<sup>18</sup> Because of the absence of an electron–nuclear contribution, correspondence between the width of the EPR spectrum and the excitation bandwidth of an ESE spectrometer and ease of signal interpolation to the ‘dead’ time (see Section IV) the dipolar doublet appears to be similar to the theoretical one (see Figs 3 and 9). Not only the perpendicular but also the parallel orientation is well resolved. This permits determination of the distance in the pair with a very high accuracy (up to a few fractions of an Ångström) and analysis of subtle effects due to structural changes under the action of external factors.

Three types of RC, namely, bacterial, PS I and PS II ones are characterised by production of structurally similar RPs in the initial steps of electron transfer. Pairs comprised of a primary electron donor and a primary quinone acceptor are convenient for ESE studies.

### 1. Bacterial reaction centres

At low temperatures, no electron transfer from  $Q_A$  to  $Q_B$  occurs in the reaction centres of purple bacteria *Rhodobacter sphaeroides* R26, and a radical pair  $P_{870}^+Q_A^-$  with a lifetime of 30 ms is produced; then, it disappears *via* reverse recombination. This pair was studied in Zn-substituted samples.<sup>18, 44, 121, 122</sup> The out-of-phase echo signal was detected, which was strongly modulated with  $\tau$ . The distances in the pair were determined by analysing the dipolar doublet in the frequency domain. The structures of these RC were established by X-ray diffraction; therefore, one of the goals was to evaluate the new experimental technique.

It was found that the distances in the pair, obtained in different studies, are also different. According to X-ray scattering data, the distance in the pair must be 28.1 (see Ref. 98) or 29.2 Å,<sup>99</sup> but the dipole–dipole interaction in the pair corresponded to a shorter distance.<sup>18</sup> The distance in freshly prepared samples was 28.9 Å,<sup>122</sup> being in good agreement with the X-ray structural data. These discrepancies were attributed to ‘ageing’ of the sample, *i.e.*, a change in its structure in the course of long-term storage (the authors of study<sup>18</sup> used the samples kept at a liquid nitrogen temperature for months). The distance 28.4 Å<sup>44, 121</sup> is similar, within the limits of error, to the results obtained in Ref. 122.

Good correspondence with the X-ray structural data suggests that the method based on the out-of-phase echo signal decay modulation provides correct information on the distances in the

pair. It should be noted that these methods are used to study different systems. X-Ray analysis deals with a crystalline sample, does not involve exposure to light and no charges are produced in the system. ESE investigations are usually carried out with amorphous samples (although it can also be crystalline, see below), being aimed at studying a pair comprising two oppositely charged particles. Therefore, the results obtained also mean that these differences cause no pronounced structural changes. In particular, the electrostriction effects in the course of charge separation must be insignificant.

A study of the RC of *Rhodospseudomonas viridis* bacteria in Zn-substituted samples treated with *o*-phenanthroline in order to block electron transfer to  $Q_B$  was reported.<sup>123</sup> The distance in the  $P_{680}^+Q_A^-$  pair also appeared to be similar to that determined by X-ray scattering.<sup>124</sup>

The temperature dependence of the shape of the dipolar doublets found for the bacterial RC at cryogenic temperatures<sup>122</sup> was interpreted as a result of rearrangement of the RC protein backbone on changes in the temperature.

## 2. Reaction centre of PS I

Spin-correlated pairs  $P_{700}^+A_1^-$  in PS I have been the subject of considerable research.<sup>44, 121, 125–130</sup> It was found that the shape of the dipolar doublets in the Fourier transformed ESEEMs of these systems (see Fig. 9) is similar to the theoretical shape, *i.e.*, these doublets are nearly unbroadened due to other interactions (see Fig. 3). Here, spectral lines are much narrower than in the spectra of similar pairs in bacterial RC or in the reaction centre of PS II (see below). Temperature dependence was also not observed for this spectrum. Small linewidths allowed the distance in the pair to be determined with record (for this range) accuracy, namely,  $25.4 \pm 0.3$  Å.<sup>44, 121</sup> Nearly the same results were obtained in another study.<sup>125</sup> A decrease in  $r$  compared to the bacterial RC must be pointed out.

This accuracy also nearly corresponds to the width of the distance distribution in the pair. So narrow distribution for rather long distances seems to be non-trivial. It should be emphasised that the case in point is an amorphous system ( $\sim 60\%$  of the total volume is occupied by glycerol, a cryoprotector, which facilitates a low-temperature glass transition). This means that large biomolecules in an amorphous environment can exhibit a high level of structural organisation in the nanometre range of distances.

Studies of reaction centres in which phyloquinone was replaced by various synthetic quinones showed<sup>125, 128, 129</sup> that the distances in RPs in these systems remained constant within the limits of experimental error. This means that synthetic quinones are incorporated at the same binding site as the native quinones. From the EPR spin polarisation data<sup>93</sup> it follows that native and synthetic quinones are oriented in different way. The same distances in these two cases mean that the operation of  $A_1$  as electron acceptor is independent of the binding direction of quinone.<sup>128</sup>

Single crystals of the reaction centre of PS I (symmetry group  $P6_3$ , two PS I trimers in the unit cell) were studied.<sup>127</sup> Rotation of the crystal revealed a strong orientation dependence of the dipolar doublet, which allowed determination of the orientation of the axis connecting both particles in the pair. The angle was  $27 \pm 5^\circ$  relative to the  $c$  crystallographic axis and its projection on the  $ab$  plane is parallel to the  $a$  axis.

The results obtained permitted a quite correct determination of two possible positions of phyloquinone  $A_1$  in the electron transfer chain, which appeared to be related by pseudo- $C_2$  symmetry of chlorophyll cofactors. This was used in the interpretation of X-ray scattering data.<sup>131</sup>

A study of oriented membranes<sup>130</sup> showed that the angle between the direction of the  $P_{700}A_1$  pair and the normal to the membrane is  $24 \pm 4^\circ$ . Based on these results and X-ray scattering data, the direction of electron transfer in RC was suggested.

## 3. The reaction centre of PS II

Absorption of a light quantum in PS II produces a  $P_{680}^+Q_A^-$  radical pair (see Refs 130, 132–134). The width and shape of rather broad lines observed in experiments depend on the sample preparation procedure.<sup>132</sup> If the linewidths were markedly different from the theoretical values, the presence of two different types of pairs with the distances between paramagnetic centres ranging from 26 to 29 Å was assumed.<sup>132</sup> The distances in the pair obtained in other cases were  $r = 27.4 \pm 0.3$  Å,<sup>130, 133</sup>  $27.2 \pm 1$  Å,<sup>132</sup>  $27.7 \pm 0.7$  Å.<sup>134</sup> As can be seen, these results are in good agreement with one another, although one study<sup>132</sup> was carried out at 80 K and other studies near room temperature.<sup>133, 134</sup> In respect of a large linewidth the accuracy of measurements reported in Refs 130 and 133 seems to be overestimated.

The angle between the normal to the membrane and the axis of the  $P_{680}^+Q_A^-$  pair in oriented membranes was found to be  $21 \pm 5^\circ$ .<sup>130</sup>

Transformation of the dipolar doublet with an increase in the delay after application of a laser pulse with the characteristic time of the order of 1 ms was reported.<sup>133, 134</sup> This can be explained by the reduction of  $P_{680}$  tyrosine  $Y_Z$  with the formation of the  $Y_Z^{ox}O_A^-$  pair. Analysis of the dipolar doublet for this pair revealed a distance of  $34 \pm 1$  Å.<sup>134</sup>

## 4. The Kleinfeld effect

The kinetics of back recombination of the  $P_{870}^+Q_A^-$  and  $P_{870}^+Q_B^-$  pairs in the reaction centres of purple bacteria differ significantly depending on whether the sample was frozen in the light or in the dark.<sup>135</sup> It is believed that this is due to photo-induced structural changes. X-Ray studies of samples frozen in the light or in the dark were reported.<sup>136</sup> In the latter case, the  $P_{870}^+Q_B^-$  pairs were produced.  $Q_B^-$  was found to be shifted by 5 Å from the fixed position of the neutral molecule  $Q_A$ .

Comparative out-of-phase ESE investigations of the  $P_{870}^+Q_A^-$  pairs in the samples frozen in the light or in the dark were reported. No changes in the distance were detected in study<sup>137</sup> while a possible increase in the distance by  $0.4 \pm 0.2$  Å was pointed out in another study.<sup>138</sup> In this case the higher accuracy of measurements was due to the fact that two spectra with practically identical shapes were compared. However, the value determined was found to be too small to explain the Kleinfeld effect by changes in the distance between the  $P_{870}$  and  $Q_A$  cofactors. Probably, the reason consists in the motion of some polar groups of the molecules involved in charge transfer.

## 5. Temperature dependence of the supramolecular structure of bacterial reaction centres

The dipolar doublets in bacterial RC exhibit marked temperature dependences.<sup>18, 122</sup> Below 100 K the doublets are considerably broadened. This can be attributed to the appearance of a distance distribution. Comparison with the results of model calculations showed that the width of the distribution function increases from  $\sim 1$  to  $\sim 4$  Å as the temperature decreases to 15 K. At  $T < 100$  K, the distribution shape is temperature dependent; a hysteresis was observed on temperature variation.

These data point to the low-temperature dynamics of proteins constituting the RC backbone and containing (in this case) the  $P_{870}$  and  $Q_A$  cofactors under study. Certain indications of the low-temperature protein dynamics were obtained by different methods, *e.g.*, spectral hole 'burning' in optical spectra and photon echo,<sup>139–141</sup> IR echo,<sup>142, 143</sup> single-molecule spectroscopy,<sup>144</sup> Mössbauer spectroscopy,<sup>145</sup> *etc.* However, in all these cases the dynamics were studied in the atomic scale of distances. But the distances in the  $P_{870}^+Q_A^-$  pair show that these effects can be co-operative, being governed by the motion of a certain molecular cluster of nanometre size.

A study<sup>146</sup> similar to that reported in Ref. 122 was carried out at temperatures  $\sim 15$  K and below. It was found that lowering the temperature in the range 13–20 K causes a pronounced line narrowing of the dipolar doublet. This is an indication of a more

ordered state on lowering the temperature. A transition from one state to the other becomes fully reversible. Visually, it is similar to transformation of a crystal into a highly viscous liquid (this is also substantiated by the temperature hysteresis mentioned above). Such low-temperature structural transitions were not reported earlier.

This means that the energy landscape of the protein RC involves very low barriers. A photon echo study<sup>139</sup> of myoglobin revealed low barriers (about several tens of Kelvin).

An observable transition must be characterised by some possibility of structural rearrangements in the nearest environment of protein (in the nanometre range of distances). Dynamic heterogeneity in disordered molecular media, which can arise in this range of distances, has been the subject of intensive discussions.<sup>147, 148</sup>

## IX. Conclusion

Pulsed EPR spectroscopy methods based on the electron spin echo technique permit investigations of biomolecule conformations, nanostructure of polymers and the supramolecular structure of such complex objects as photosynthetic reaction centres in plants and bacteria. These methods make it possible to determine the distances between paramagnetic fragments ranging from 15 to ~100 Å with a high accuracy (e.g., 0.3 Å at  $r \approx 25$  Å in studies of spin-correlated radical pairs in PS I). High resolution allows one to obtain information on fine changes in the nanostructure of matter, occurring under the action of external factors. A marked example is provided by the dynamics of the nanostructure of a bacterial photosynthetic reaction centre at cryogenic temperatures.

Basic to the use of these methods is the presence in the system of free radicals or ions that form pairs or clusters. This situation can be realised naturally (in, e.g., photosynthetic reaction centres or in metal-containing biomolecules) or created artificially by introducing spin probes and labels (usually, based on nitroxyl radicals). At present, a wide use of spin labels is due to the development of biochemical methods of site-directed spin labelling.

Many different methods of investigation of the dipole–dipole interaction between paramagnetic centres have been proposed. The choice of a particular method for studying a given system is governed by the width of the signal in the EPR spectrum and by the relaxation times. Other properties of the system, e.g., the possibility of carrying out comparative experiments in the absence of the dipole–dipole interaction can also play a significant role. When choosing a method of investigation, simplicity of theoretical description and the absence of the masking effects produced by other interactions (in particular, electron–nuclear interaction) are of great importance. The best results in studies of nitroxyl biradicals (most widely used systems) are obtained by the PELDOR technique. Conventional two-pulse ESE spectroscopy is more convenient in studies of photoinduced spin-correlated radical pairs.

Recent advances made by researchers from different laboratories point to great prospects for structural studies of complex molecular systems by pulsed EPR spectroscopy.

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<sup>a</sup> — *Theor. Exp. Chem. (Engl. Transl.)*<sup>b</sup> — *Phys. Solid State (Engl. Transl.)*<sup>c</sup> — *Russ. J. Struct. Chem. (Engl. Transl.)*<sup>d</sup> — *Opt. Spectroscop. (Engl. Transl.)*<sup>e</sup> — *Dokl. Chem. (Engl. Transl.)*

# Thermal and catalytic intramolecular [4 + 2]-cycloaddition in 2-alkenylfurans

F I Zubkov, E V Nikitina, A V Varlamov

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**Abstract.** The published data on the intramolecular Diels–Alder reaction in compounds of the 2-alkenylfuran series are generalised. The methods and conditions for the preparation of tricyclic systems are considered. The effects of the substituents in the furan and the unsaturated fragments on the cycloaddition are discussed. The application of this reaction to the synthesis of alkaloids and terpenoids is exemplified. The bibliography includes 168 references.

## I. Introduction

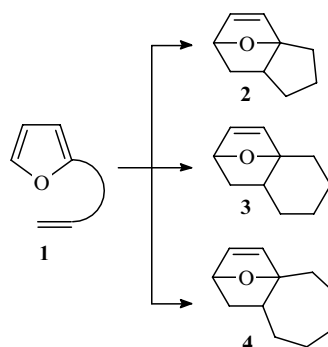
In 1928, O Diels and K Alder<sup>1</sup> discovered the [4 + 2]-cycloaddition reaction, one of the most interesting and important, from a practical standpoint, transformations in classical organic chemistry. A quarter of a century later, Alder reported<sup>2</sup> on accomplishing, for the first time, an intramolecular version of this reaction. The same year, Dunlop published an 800-page treatise on the chemistry of furan.<sup>3</sup> This monograph provided numerous examples of intermolecular condensations where the furan ring acted as a diene. However, it was not until 1961 that the first reports on the successful involvement of furan derivatives in the intramolecular Diels–Alder reaction appeared.<sup>4</sup>

Subsequent years were marked by an increasing number of publications devoted to the intramolecular [4 + 2]-cycloaddition of furan derivatives containing unsaturated fragments. Here we shall list only the most important of them. The comprehensive reviews by Dean<sup>5,6</sup> generalise the data on the synthesis and reactivities of furan systems published between 1968 and 1979. A special chapter in the review by Kappe *et al.*<sup>7</sup> summarises the data on intramolecular cycloaddition of various unsaturated fragments (alkene, alkyne, allene) to the furan ring. The reviews<sup>8,9</sup> are devoted to the use of five-membered rings (including furan) in organic synthesis and in the synthesis of natural compounds. Some features of the [4 + 2]-cycloaddition are considered by Dell.<sup>10,11</sup> The published data on the intramolecular Diels–Alder

reaction are generalised in the reviews,<sup>12–15</sup> much attention is paid to the cyclisation of alkenylfurans. The review published in 1986 (in Japanese)<sup>16</sup> is an overview of the published data on intramolecular cyclisation of furan derivatives only. The stereochemical aspects of intramolecular [4 + 2]-cycloaddition are highlighted in the review by Craig.<sup>17</sup> And, finally, we mention the recently published papers,<sup>18,19</sup> one of which is devoted to the synthesis and reactivities of 7-oxabicyclo[2.2.1]hept-2-enes (including annelated heptenes), while the other deals with the transannular Diels–Alder reaction, and a brief survey<sup>20</sup> of studies by Padwa *et al.* on the cyclisation of *N*-alkenyl-2-aminofurans.

The aim of this review is to generalise the experimental results of the intramolecular cycloaddition in compounds of the alkenylfuran series. The thermal and catalytic cycloaddition reactions in 2-alkenylfurans **1** will be considered where the furan ring plays the role of a diene (Scheme 1).

Scheme 1



This conversion results in the tricyclic compounds **2–4** containing a five-, a six- or a seven-membered ring, respectively, annelated to the 7-oxabicyclo[2.2.1]hept-2-ene fragment. The annelated ring may contain heteroatoms (as a rule, oxygen, sulfur or nitrogen).

It is noteworthy that all the attempts to use this method for the preparation of this type of derivative with a four-membered third ring were unsuccessful, while the synthesis of furan derivatives with a more than seven-membered annelated ring has not been documented so far. This review encompasses the data, most of which were published mainly between 1988 and 2003.

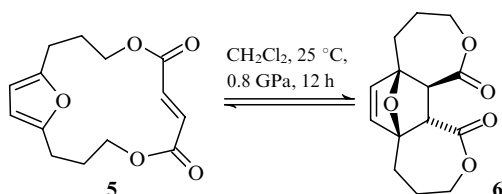
**F I Zubkov, E V Nikitina, A V Varlamov** Department of Physical, Mathematical and Natural Sciences, Peoples' Friendship University of Russia, ul. Miklukho-Maklaya 6, 117198 Moscow, Russian Federation. Fax (7-095) 955 07 79, tel. (7-095) 955 09 72, e-mail: fzubkov@sci.pfu.edu.ru (F I Zubkov), enikitina@sci.pfu.edu.ru (E V Nikitina), avarlamov@sci.pfu.edu.ru (A V Varlamov)

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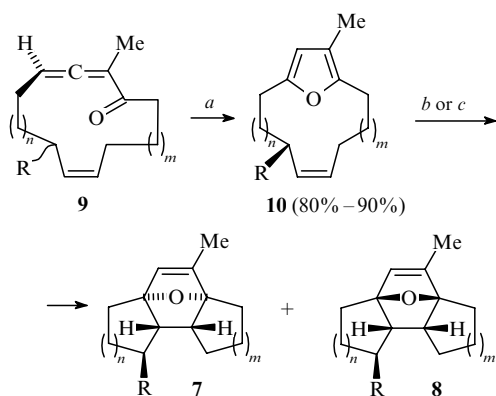
## II. The transannular Diels–Alder reactions in alkenylfurans

It was not until 1996 that a new report on the transannular cycloaddition in the furan series came out following the pioneering works dating back to the 1960's.<sup>21</sup> Using <sup>1</sup>H NMR spectroscopy, it was demonstrated that the macrocyclic ester **5** containing a furan fragment and the transannular cycloadduct **6** are in equilibrium at elevated pressure. Presumably, the formation of compound **6**, which is unstable at atmospheric pressure and contains two seven-membered lactone rings fused to the oxabicycloheptene ring, is unfavourable.



The tetracycles **7** contained two five- and/or six-membered annelated rings (in one case together with a diastereomer **8**).<sup>22</sup> The macrocyclic allenic ketones **9** were used as the starting compounds, they underwent cyclocondensation into the corresponding furans **10** catalysed by silver salts in the presence of CaCO<sub>3</sub> in aqueous acetone (Scheme 2).

Scheme 2



(a) AgNO<sub>3</sub>, CaCO<sub>3</sub>, Me<sub>2</sub>CO, H<sub>2</sub>O; (b) CHCl<sub>3</sub>, 25 °C, 52 h; (c) PhMe, 80 °C, 3 h; MOM is methoxymethyl.

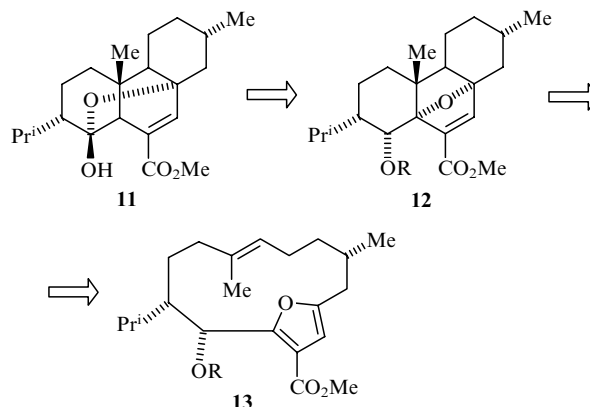
| R    | n | m | Conditions of cycloaddition | Yield (%) |                 |
|------|---|---|-----------------------------|-----------|-----------------|
|      |   |   |                             | <b>10</b> | <b>7</b>        |
| H    | 1 | 1 | b                           | 80–90     | 100             |
| MOMO | 1 | 1 | b                           | 80–90     | 100             |
| MOMO | 2 | 1 | c                           | 95        | 93 <sup>a</sup> |
| MOMO | 2 | 2 | c                           | 95        | 96              |

<sup>a</sup> Compound **8** was also obtained in 5% yield.

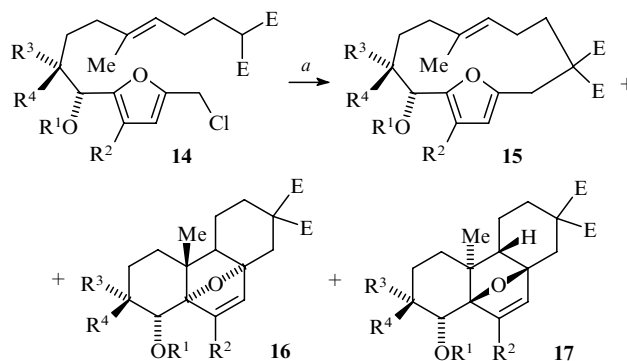
Like the original allenes **9**, the furans **10** contained a *cis*-CH=CH bond. At room temperature or upon brief heating, these compounds cyclise into the tetracyclic derivatives **7**. It is of note that the mixture of the diastereomers **7** and **8** (95 : 5) is formed only from the furan with *n* = 1, *m* = 2; in all other cases, this reaction occurs stereoselectively and yields only one diastereomer. The isomers of the macrocycles **10** having a *trans*-configuration of the endocyclic double bond do not undergo the Diels–Alder condensation.<sup>22</sup>

Toró *et al.* suggested<sup>23,24</sup> that the transannular Diels–Alder reaction was used in the synthesis of the diterpene (+)-chatancin **11** isolated from the corals *Sarcophyton sp.* The reaction sequence relied on the retrosynthetic analysis of the natural diterpene and

included the intramolecular transesterification of compound **12**, which is the intermediate cyclisation product of the alkenylfuran **13**.



A large series of model furans **14** containing alkenyl substituents have been synthesised.

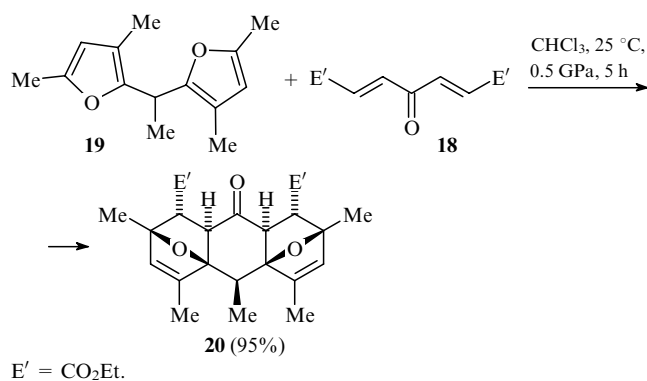


(a) Cs<sub>2</sub>CO<sub>3</sub> (10 equiv.), MeCN, Δ; R<sup>1</sup> = H, Bn, Bz; R<sup>2</sup> = H, E; R<sup>3</sup> = Pr<sup>i</sup>, R<sup>4</sup> = H; R<sup>3</sup>–R<sup>4</sup> = S(CH<sub>2</sub>)<sub>3</sub>S; E = CO<sub>2</sub>Me.

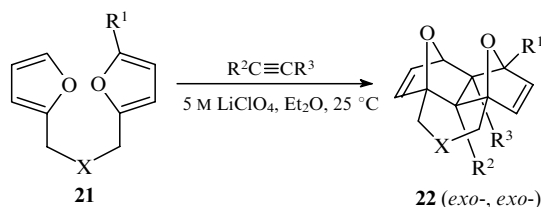
The intramolecular nucleophilic substitution of chlorine in the substituted furans **14** gives the macrocycles **15** (yields 15%–46%). Depending on the nature of the substituents in the alkenyl fragment [e.g., for R<sup>1</sup> = Bn, R<sup>2</sup> = H, R<sup>3</sup>–R<sup>4</sup> = S(CH<sub>2</sub>)<sub>3</sub>S] and the reaction conditions (e.g., under high dilution, 2 mmol litre<sup>–1</sup>), the latter can be isolated from the reaction mixture. However, compounds **15** are prone to further spontaneous intramolecular cyclisation. This affords mixtures in which the geometrical isomers **16** and **17** (total yield 80%–93%) predominate. It has been found that the conversions **15** ⇌ **16** ⇌ **17** were reversible, and that the isomer ratio depended on the polarity of the solvent used. However, the attempts to apply the retrosynthetic scheme to the synthesis of the target diterpene have been unsuccessful so far.<sup>24</sup>

## III. Tandem intramolecular cycloaddition in bisfurans

A series of transformations given below represents a two-step one-pot synthesis of bisfuran systems. Formally, the definition 'intramolecular cycloaddition of unsaturated compounds to bisfurans' can only be applied to the second step of this reaction, since the first step represents an intermolecular process. Examples of these elegant domino syntheses are scarce due to the low availability of difuryl derivatives. For the first time, the tandem intramolecular cycloaddition in bisfurans was described<sup>25</sup> for the reaction of (*E,E*)-4-oxohepta-2,5-diene (**18**) with 1,1-difurylthane **19** at elevated pressure. Diepoxyanthracene **20** is formed in a nearly quantitative yield.



A detailed study of this type of intramolecular cycloaddition was carried out by the Canadian chemists Lautens and Fillion,<sup>26, 27</sup> who developed efficient procedures for the synthesis of difuryls **21** including those containing heteroatoms in the bridging alkanediyl chains.

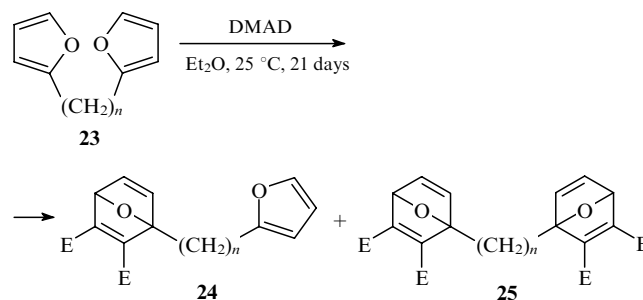


$\text{X} = \text{CH}_2, \text{O}, \text{S}, \text{NBn}, \text{NC}_6\text{H}_4\text{OMe-4}$ ;  $\text{R}^1 = \text{H}, (\text{CH}_2)_3\text{Cl}$ ;  
 $\text{R}^2 = \text{H}, \text{Me}, \text{Ac}, \text{CO}_2\text{H}, \text{CO}_2\text{Me}, \text{SO}_2\text{Ph}$ ;  
 $\text{R}^3 = \text{Ac}, \text{CO}_2\text{H}, \text{CO}_2\text{Me}, \text{SO}_2\text{Ph}, \text{Ts}$ .

Alkynes containing electron-withdrawing substituents add to difuryls **21** in a regio- and stereospecific manner to give the *exo,exo*-adducts **22** (yields 63%–83%). The adduct of methyl 4-oxopent-2-ynoate ( $\text{R}^2 = \text{CO}_2\text{Me}$ ,  $\text{R}^3 = \text{Ac}$ ) with 1,3-bis(2-furyl)propane ( $\text{X} = \text{CH}_2$ ), which represents a mixture of two stereoisomers (4:1), is an exception. The introduction of even one electron-donor substituent into the alkyne component results in complete inhibition of the cycloaddition reaction.

No sequential pincer-type [4 + 2]-cycloaddition occurs with 1,2-bis(2-furyl)ethane and 1,4-bis(2-furyl)butane (**23**).<sup>26, 27</sup> The reaction with an equimolar amount of dimethyl acetylenedicar-

boxylate (DMAD) yields linear adducts to one or two alkyne molecules (compounds **24** and **25**, respectively).



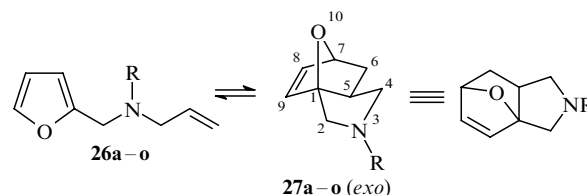
| <i>n</i> | Yield (%) |           |
|----------|-----------|-----------|
|          | <b>24</b> | <b>25</b> |
| 2        | 38        | 16        |
| 4        | 38        | 22        |

## IV. Oxabicycloheptenes fused to various rings

### 1. Five-membered rings

#### a. Synthesis of 3-aza-10-oxatricyclo[5.2.1.0<sup>1,5</sup>]dec-8-enes

The intramolecular cyclisation of substituted *N*-allylfurfuryl-amines **26**, which yields 5,7*a*-epoxyisoindoles (3-aza-10-oxatricyclo[5.2.1.0<sup>1,5</sup>]dec-8-enes) **27**, is the most studied intramolecular [4 + 2]-cycloaddition reaction in the 2-alkenylfuran series by virtue of high availability of the starting compounds (unsaturated fufurylamines) and smooth reaction (Table 1).



It has been found that the thermal intramolecular Diels–Alder cycloaddition of the non-substituted allylfurfurylamine and its *n*-alkyl derivatives cannot be realised even under drastic conditions.<sup>28, 29</sup> A prerequisite for the cyclisation is the presence

**Table 1.** Cyclisation of substituted allylfuran-2-ylmethylamines **26**.

| Compound <b>26</b><br>(see <sup>a</sup> ) | R                                                                   | Reaction conditions           |               |              | <b>26</b> : <b>27</b> ratio | Yield of<br><b>27</b> (%) | Ref.   |
|-------------------------------------------|---------------------------------------------------------------------|-------------------------------|---------------|--------------|-----------------------------|---------------------------|--------|
|                                           |                                                                     | solvent                       | <i>T</i> / °C | <i>t</i> / h |                             |                           |        |
| <b>a</b>                                  | H                                                                   | PhMe                          | 110           | > 50         | —                           | 0                         | 28, 29 |
| <b>b</b>                                  | Bn                                                                  | xylene                        | 135           | 60           | 49:1                        | < 2                       | 28, 29 |
| <b>c</b>                                  | Bn                                                                  | xylene                        | 135           | 34           | 1:1                         | 35                        | 28, 29 |
| <b>d</b>                                  | Ph <sub>2</sub> CH                                                  | PhMe                          | 110           | 40           | 1:32                        | 85                        | 28, 29 |
| <b>e</b>                                  | 2,4,6-Me <sub>3</sub> C <sub>6</sub> H <sub>2</sub> CH <sub>2</sub> | xylene                        | 135           | 60           | 9:1                         | < 10                      | 28, 29 |
| <b>f</b>                                  | PhCO                                                                | PhMe                          | 110           | 21           | 1:4                         | 60                        | 28     |
| <b>g</b>                                  | MeCH <sub>2</sub> CCO                                               | MeCN                          | 60            | 20           | see <sup>b</sup>            | 83                        | 30     |
| <b>h</b>                                  | Ts                                                                  | PhMe                          | 110           | 21           | 1:4                         | 60                        | 28     |
| <b>i</b>                                  | SO <sub>2</sub> Me                                                  | C <sub>6</sub> D <sub>6</sub> | 80            | —            | —                           | 77                        | 31     |
| <b>j</b>                                  | SO <sub>2</sub> Et                                                  | C <sub>6</sub> D <sub>6</sub> | 80            | —            | —                           | 78                        | 31     |
| <b>k</b>                                  | SO <sub>2</sub> Pr <sup>n</sup>                                     | C <sub>6</sub> D <sub>6</sub> | 80            | —            | —                           | 82                        | 31     |
| <b>l</b>                                  | SO <sub>2</sub> Pr <sup>i</sup>                                     | C <sub>6</sub> D <sub>6</sub> | 80            | —            | —                           | 80                        | 31     |
| <b>m</b>                                  | SO <sub>2</sub> Ph                                                  | C <sub>6</sub> D <sub>6</sub> | 80            | —            | —                           | 90                        | 31     |
| <b>n</b>                                  | 2,4,6-Me <sub>3</sub> C <sub>6</sub> H <sub>2</sub> SO <sub>2</sub> | C <sub>6</sub> D <sub>6</sub> | 80            | —            | —                           | 86                        | 31     |
| <b>o</b>                                  | 2,4,6-Pr <sub>3</sub> C <sub>6</sub> H <sub>2</sub> SO <sub>2</sub> | C <sub>6</sub> D <sub>6</sub> | 80            | —            | —                           | 92                        | 31     |

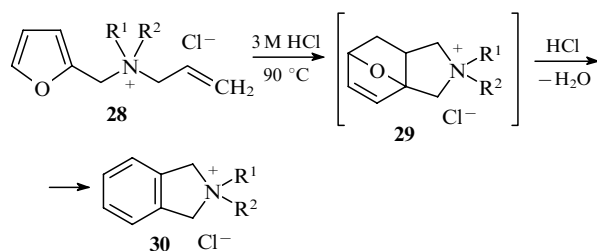
<sup>a</sup> In the case of compounds **26i–o**, the reaction was carried out in an NMR tube until equilibrium was reached. The reaction time is not indicated; the calculated yields are given; <sup>b</sup> the formation of the reaction product takes place even at 20 °C.



of a bulky group R (compounds **26b–e**) or a substituent able to induce the transition of the nitrogen atom into the planar state (compounds **26f–o**)<sup>28–31</sup> (see Table 1).

In contrast to *N*-aralkyl derivatives, the cyclisation of amides and sulfonamides **26f–o** occurs more smoothly: the reaction is usually complete within several hours at 70–110 °C.<sup>28,31</sup> This cycloaddition is reversible, but, as can be evidenced from the data listed in Table 1, the reaction equilibrium is always shifted towards the cycloadduct (the yields of the isoindoles **27f–o** are no less than 60%).

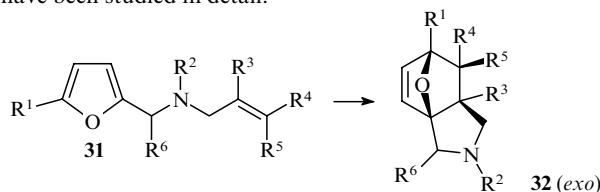
Thermal cyclisation of *N*-allyl-*N*-furfurylamine hydrochlorides **28** in 3 M HCl is accompanied by aromatisation of the tricycles **29** resulting in the isoindolium salts **30** in good yields.<sup>32,33</sup>



$R^1, R^2 = \text{H, Me, Et, Allyl, Pr}^i, \text{Bu}^n, \text{Bu}^i, \text{Ph};$   
 $R^1-R^2 = (\text{CH}_2)_5, (\text{CH}_2)_2\text{O}(\text{CH}_2)_2.$

UV spectroscopic studies have shown<sup>34,35</sup> that the rate of formation of epoxides **29** ( $\text{H}_2\text{O}$ , 83 °C) depends on the nature of the substituents ( $R^1, R^2$ ) at the nitrogen atom and decreases in the order:  $(\text{CH}_2)_5 > \text{O}[(\text{CH}_2)_2]_2 > \text{Et}$ ,  $\text{Et} > \text{Me}$ ,  $\text{All} > \text{Me}$ ,  $\text{Me} > \text{Me, Ph}$ .

The regularities of the cyclisation of the substituted *N*-allyl-furfurylamines **31** into 3-aza-10-oxabicyclo[5.2.1.0<sup>1,5</sup>]dec-8-enes **32** have been studied in detail.<sup>36–40</sup>

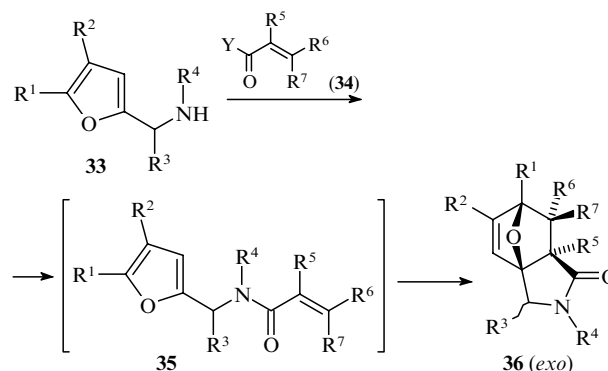


$R^1 = \text{H, Me, OMe, I, NO}_2; R^2 = \text{Ac, Cl}_3\text{CCO, 4-MeC}_6\text{H}_4;$   
 $R^3 = \text{H, PhSO}_2; R^4, R^5 = \text{H, Me}; R^6 = \text{H, CH}=\text{CH}_2.$

It has been established<sup>36</sup> that electron-withdrawing groups at position 5 of the furan ring ( $R^1$ ) increase, while electron-donor groups, contrariwise, decrease the activity of the diene fragment in the [4+2]-cycloaddition reaction. Thus the reaction rates and the yields of the cycloaddition products of 5-nitro- and 5-iodofurfurylamines **31** are higher than those of the 5-methyl- or 5-methoxy derivatives. Studies of the substituent effect in the dienophilic fragment of furans **31** on the cyclisation have shown<sup>36,39</sup> that the yields of the adducts **32** decrease drastically (from 75% to 0%) for a compound with  $R^1 = R^3 = R^6 = \text{H}$ ,  $R^2 = 4\text{-MeC}_6\text{H}_4$  with an increase in the number of the methyl groups at the double bond, *i.e.*, on going from the *N*-allyl- to the but-2-enyl- and then to the isopentenyl substituent. This fact is attributed<sup>36</sup> to greater steric hindrance created by the alkyl substituents in the transition state. In the case of the *N*-acyl derivatives **31**, the yields of the products **32** are rather high (62%–83%) irrespective of the sizes and electronic effects of the substituents  $R^3$  and  $R^6$ . Interestingly, epoxyisoindoline **32** ( $R^1 = \text{OMe}$ ,  $R^2 = 4\text{-MeC}_6\text{H}_4$ ,  $R^3 = R^5 = R^6 = \text{H}$ ,  $R^4 = \text{Me}$ ) is unstable and undergoes quantitative dehydration into the corresponding isoindole in the course of chromatographic isolation.<sup>36,38</sup> The aromatisation of some other 3-aza-10-oxatricyclo[5.2.1.0<sup>1,5</sup>]dec-8-enes **32** demands acidic conditions (*e.g.*,  $\text{HBr} - \text{AcOH}$ ).<sup>37,38</sup>

A one-pot procedure for the synthesis of epoxyisoindolines **32**, which involves alkylation of *N*-aryl-*N*-furfurylamines with allyl bromide in boiling benzene, has been developed.<sup>41</sup> The intermediate *N*-allyl derivatives **31** ( $R^3 = R^4 = R^5 = \text{H}$ ) are converted into the corresponding oxabicycloheptenes **32** as a result of intramolecular [4+2]-cycloaddition.

Acylation of furfurylamines **33** by  $\alpha,\beta$ -unsaturated carboxylic acid anhydrides or chlorides **34** (usually, by maleic, fumaric, acrylic and cinnamic acid derivatives) affords the unsaturated amides **35**. As the double bonds of the latter are activated by the electron-withdrawing carbonyl group, the unsaturated fragment becomes an active dienophile. As a rule, the amides of the type **35** cannot be isolated, since they are immediately cyclised into azaoxatricyclo[5.2.1.0<sup>1,5</sup>]decenones **36** (Table 2).



The effect of the substituents in the dienophilic fragment of *N*-furfurylamides **35** on the yield of epoxyisoindolones **36** has been studied in detail.<sup>42–51</sup> The data presented in Table 2 prompt the following conclusions.

1. The presence of a substituent  $R^4$  at the nitrogen atom is a prerequisite for the formation of epoxyisoindolones **36**. If  $R^4 = \text{H}$ , the reaction is stopped in the step of formation of the amide **35**.

2. Electron-withdrawing substituents in the dienophilic fragment favour the cycloaddition. If two such substituents are present at the double bond of the acylating reagent **34**, no heating is required for the cycloaddition, which occurs spontaneously at room temperature.<sup>42,45,48–50</sup> Thus the presence of an electron-withdrawing  $\text{CF}_3$ -group in the alkenyl fragment increases significantly the yield of the Diels–Alder adduct in comparison with its analogue possessing a donor Me-group (see Table 2).<sup>43</sup> Even weak donor substituents in the alkenyl fragment, *e.g.*, methyl groups, decelerate the cycloaddition reaction (long-term heating at 80–110 °C is required), however, without any appreciable effect on the product yield. No examples of successful cycloaddition in alkenylfurans containing two donor substituents in the dienophilic fragment are documented in the literature.

3. The data on the effects of substituents in the furan ring on the [4+2]-cycloaddition in compounds **35** are ambiguous. The published data<sup>44,47,52</sup> suggest that the donor substituents at positions 4 (see Ref. 47) and 5 (see Refs 44 and 52) of furan favour intramolecular cycloaddition. With the exception of 2-alkenyl-5-nitrofurans,<sup>53</sup> only one example of a successful synthesis of 3a,6-epoxyisoindolones **36** starting from *N*-alkenylfurfurylamines containing an electron-withdrawing substituent in the furan ring has been described in the literature.<sup>52</sup>

4. The sizes of substituents at the double bond are less critical for the reaction than their electronic effects.

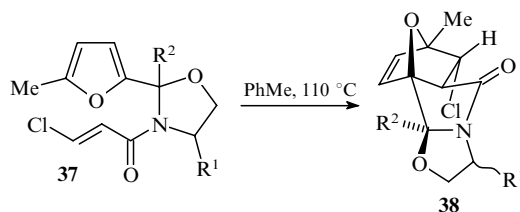
Special mention should be made of the efficient one-step synthesis of substituted 4-oxo-3-aza-10-oxatricyclo[5.2.1.0<sup>1,5</sup>]dec-8-enes **36**, by the reaction of *N*-benzyl-*N*-furfurylamines with  $\alpha,\beta$ -unsaturated acids in the presence of a catalytic system DIC–DIEA–DMAP (see Table 2).<sup>44</sup> This reaction proceeds under mild conditions in good yields.

**Table 2.** Preparation of substituted azaoxatricyclo[5.2.1.0<sup>1,5</sup>]decenones **36**.

| Y                | R <sup>1</sup> | R <sup>2</sup> | R <sup>3</sup>  | R <sup>4</sup>                                     | R <sup>5</sup>  | R <sup>6</sup>                       | R <sup>7</sup>                         | Reaction conditions                                       | Yield of <b>36</b> (%) | Ref. |
|------------------|----------------|----------------|-----------------|----------------------------------------------------|-----------------|--------------------------------------|----------------------------------------|-----------------------------------------------------------|------------------------|------|
| See <sup>a</sup> | H              | H              | H               | Ph                                                 | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 86                     | 42   |
| See <sup>a</sup> | H              | H              | H               | Bn                                                 | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 90                     | 42   |
| See <sup>a</sup> | H              | H              | H               | C*HMePh                                            | H               | H                                    | CO <sub>2</sub> H                      | Et <sub>2</sub> O, 0 °C, 18 h                             | 100 <sup>c</sup>       | 43   |
|                  |                |                |                 |                                                    |                 |                                      |                                        | PhH, 25 °C, 96 h                                          | 81 <sup>c</sup>        |      |
|                  |                |                |                 |                                                    |                 |                                      |                                        | CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 96 h             | 76 <sup>c</sup>        |      |
| See <sup>a</sup> | H              | H              | H               | 3-ClC <sub>6</sub> H <sub>4</sub>                  | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 89                     | 42   |
| See <sup>a</sup> | H              | H              | H               | 3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>    | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 80                     | 42   |
| See <sup>a</sup> | H              | H              | H               | 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>    | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 74                     | 42   |
| See <sup>a</sup> | H              | H              | H               | tetrahydrofurfuryl                                 | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 37                     | 42   |
| See <sup>a</sup> | H              | H              | H               | cyclo-C <sub>3</sub> H <sub>7</sub>                | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 35                     | 42   |
| See <sup>a</sup> | H              | H              | H               | Cy                                                 | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 90                     | 42   |
| See <sup>a</sup> | H              | H              | H               | MeO(CH <sub>2</sub> ) <sub>2</sub>                 | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 92                     | 42   |
| See <sup>a</sup> | H              | H              | H               | furfuryl                                           | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 95                     | 42   |
| OH               | H              | H              | H               | Bn                                                 | H               | Ac                                   | H                                      | CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 1 h <sup>d</sup> | 83                     | 44   |
| Cl               | H              | H              | H               | 4-ClC <sub>6</sub> H <sub>4</sub>                  | H               | CO <sub>2</sub> (–)-Menth            | H                                      | CHCl <sub>3</sub> , 65 °C, 20 min                         | 65 <sup>c</sup>        | 45   |
| Cl               | H              | H              | H               | 4-MeOC <sub>6</sub> H <sub>4</sub>                 | H               | CO <sub>2</sub> (–)-Menth            | H                                      | CHCl <sub>3</sub> , 65 °C, 20 min                         | 68 <sup>c</sup>        | 45   |
| Cl               | H              | H              | H               | 4-EtOC <sub>6</sub> H <sub>4</sub>                 | H               | CO <sub>2</sub> (–)-Menth            | H                                      | CHCl <sub>3</sub> , 65 °C, 20 min                         | 62 <sup>c</sup>        | 45   |
| OH               | H              | H              | H               | Bn                                                 | H               | CO <sub>2</sub> Et                   | H                                      | CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 1 h <sup>d</sup> | 89                     | 44   |
| OH               | H              | H              | H               | Bn                                                 | H               | 4-ClC <sub>6</sub> H <sub>4</sub> CO | H                                      | CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 1 h <sup>d</sup> | 80                     | 44   |
| OH               | H              | H              | H               | Bn                                                 | H               | 4-CyC <sub>6</sub> H <sub>4</sub> CO | H                                      | CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 1 h <sup>d</sup> | 78                     | 44   |
| OH               | H              | H              | H               | Bn                                                 | H               | H                                    | CO <sub>2</sub> Et                     | CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 1 h <sup>d</sup> | 75                     | 44   |
| OH               | H              | H              | H               | Bn                                                 | H               | H                                    | Pr <sup>n</sup> NHCO                   | CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 1 h <sup>d</sup> | 70                     | 44   |
| OH               | H              | H              | H               | Bn                                                 | H               | H                                    | 3-ClC <sub>6</sub> H <sub>4</sub> NHCO | CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 1 h <sup>d</sup> | 74                     | 44   |
| Cl               | H              | H              | H               | Me                                                 | Me              | H                                    | H                                      | PhMe, 90 °C, 3 h                                          | 27 <sup>c</sup>        | 46   |
| Cl               | H              | H              | H               | Bn                                                 | Me              | H                                    | H                                      | PhMe, 90 °C, 3 h                                          | 36 <sup>c</sup>        | 46   |
| Cl               | H              | H              | H               | (S)-CHMePh                                         | Me              | H                                    | H                                      | PhMe, 90 °C, 3 h                                          | 97 <sup>c</sup>        | 46   |
| Cl               | H              | 2-Th           | H               | cyclo-C <sub>5</sub> H <sub>9</sub>                | H               | Ph                                   | H                                      | PhMe, 100 °C, 1 h                                         | 23 <sup>c</sup>        | 47   |
| Cl               | H              | Br             | H               | cyclo-C <sub>5</sub> H <sub>9</sub>                | Bn              | H                                    | H                                      | PhMe, 100 °C, 1 h                                         | 77 <sup>c</sup>        | 47   |
| Cl               | H              | <i>m</i> -Tol  | H               | 3-EtO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>  | Bn              | H                                    | H                                      | PhMe, 100 °C, 1 h                                         | 16 <sup>c</sup>        | 47   |
| Cl               | H              | Ph             | H               | Ph                                                 | Me              | H                                    | H                                      | PhMe, 100 °C, 1 h                                         | 97 <sup>c</sup>        | 47   |
| Cl               | H              | H              | CN              | Me                                                 | H               | H                                    | CO <sub>2</sub> H                      | PhH, 80 °C, 1 h                                           | 65 <sup>c</sup>        | 45   |
| Cl               | H              | H              | CN              | Ph                                                 | H               | H                                    | CO <sub>2</sub> H                      | PhH, 80 °C, 1 h                                           | 71 <sup>c</sup>        | 45   |
| Cl               | H              | H              | CN              | 4-MeC <sub>6</sub> H <sub>4</sub>                  | H               | H                                    | CO <sub>2</sub> H                      | PhH, 80 °C, 1 h                                           | 70 <sup>c</sup>        | 45   |
| Cl               | H              | H              | CN              | 4-MeOC <sub>6</sub> H <sub>4</sub>                 | H               | H                                    | CO <sub>2</sub> H                      | PhH, 80 °C, 1 h                                           | 75 <sup>c</sup>        | 45   |
| Cl               | H              | H              | CN              | 4-EtOC <sub>6</sub> H <sub>4</sub>                 | H               | H                                    | CO <sub>2</sub> H                      | PhH, 80 °C, 1 h                                           | 68 <sup>c</sup>        | 45   |
| Cl               | H              | H              | CN              | 4-BrC <sub>6</sub> H <sub>4</sub>                  | H               | H                                    | CO <sub>2</sub> H                      | PhH, 80 °C, 1 h                                           | 72 <sup>c</sup>        | 45   |
| Cl               | H              | H              | CN              | 4-ClC <sub>6</sub> H <sub>4</sub>                  | H               | H                                    | CO <sub>2</sub> H                      | PhH, 80 °C, 1 h                                           | 96                     | 48   |
| See <sup>a</sup> | H              | H              | MeAll           | 2-MeC <sub>6</sub> H <sub>4</sub>                  | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 89                     | 48   |
| See <sup>a</sup> | H              | H              | MeAll           | 2-MeOC <sub>6</sub> H <sub>4</sub>                 | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 83                     | 48   |
| See <sup>a</sup> | H              | H              | MeAll           | 4-MeOC <sub>6</sub> H <sub>4</sub>                 | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 91                     | 48   |
| See <sup>a</sup> | H              | H              | MeAll           | 4-FC <sub>6</sub> H <sub>4</sub>                   | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 95                     | 48   |
| See <sup>a</sup> | H              | H              | MeAll           | 2-BnC <sub>6</sub> H <sub>4</sub>                  | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 83                     | 48   |
| See <sup>a</sup> | H              | H              | MeAll           | Bn                                                 | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 95                     | 49   |
| See <sup>a</sup> | H              | H              | MeAll           | CHMePh                                             | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 73                     | 49   |
| See <sup>a</sup> | H              | H              | MeAll           | 4-MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>  | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 92                     | 49   |
| See <sup>a</sup> | H              | H              | MeAll           | 4-MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 74                     | 49   |
| Cl               | H              | H              | CN              | 4-ClC <sub>6</sub> H <sub>4</sub>                  | H               | CO <sub>2</sub> (–)-Menth            | H                                      | CHCl <sub>3</sub> , 65 °C, 20 min                         | 65 <sup>c</sup>        | 45   |
| Cl               | H              | H              | Me              | Bn                                                 | CF <sub>3</sub> | H                                    | H                                      | CH <sub>2</sub> Cl <sub>2</sub> , 0 °C, 1 h               | 94                     | 50   |
| Cl               | H              | H              | Pr <sup>i</sup> | Bn                                                 | Me              | H                                    | H                                      | PhMe, 140 °C, 3 h                                         | 97 <sup>c</sup>        | 50   |
| Cl               | H              | H              | Pr <sup>i</sup> | Bn                                                 | CF <sub>3</sub> | H                                    | H                                      | CH <sub>2</sub> Cl <sub>2</sub> , 0 °C, 1 h               | 77                     | 50   |
| Cl               | H              | H              | Ph              | Bn                                                 | Me              | H                                    | H                                      | PhMe, 120 °C, 12 h                                        | 29 <sup>c</sup>        | 50   |
| Cl               | H              | H              | Ph              | Bn                                                 | CF <sub>3</sub> | H                                    | H                                      | CH <sub>2</sub> Cl <sub>2</sub> , 0 °C, 1 h               | 98                     | 50   |
| Cl               | H              | H              | CF <sub>3</sub> | Ph                                                 | Me              | H                                    | H                                      | PhMe, 150 °C, 12 h                                        | 75 <sup>c</sup>        | 50   |
| Cl               | H              | H              | CF <sub>3</sub> | Ph                                                 | CF <sub>3</sub> | H                                    | H                                      | CH <sub>2</sub> Cl <sub>2</sub> , 0 °C, 1 h               | 100                    | 50   |
| OH               | Me             | H              | H               | Bn                                                 | H               | H                                    | BnNHCO                                 | CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 1 h <sup>d</sup> | 65                     | 44   |
| OH               | Me             | H              | H               | Bn                                                 | H               | Ac                                   | H                                      | CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 1 h <sup>d</sup> | 80                     | 44   |
| OH               | Me             | H              | H               | Bn                                                 | H               | CO <sub>2</sub> Et                   | H                                      | CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 1 h <sup>d</sup> | 79                     | 44   |
| OH               | Me             | Me             | H               | Bn                                                 | H               | CO <sub>2</sub> Et                   | H                                      | CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 1 h <sup>d</sup> | 74                     | 44   |
| OH               | Me             | H              | H               | Bn                                                 | H               | H                                    | CO <sub>2</sub> Et                     | CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 1 h <sup>d</sup> | 63                     | 44   |
| OH               | Me             | Me             | H               | Bn                                                 | H               | H                                    | CO <sub>2</sub> Et                     | CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 1 h <sup>d</sup> | 60                     | 44   |
| OH               | Me             | Me             | H               | Bn                                                 | H               | H                                    | BnNHCO                                 | CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 1 h <sup>d</sup> | 64                     | 44   |
| See <sup>a</sup> | Me             | H              | MeAll           | Bn                                                 | H               | H                                    | CO <sub>2</sub> H                      | PhH, <sup>b</sup> 25 °C, 2–7 days                         | 89                     | 49   |

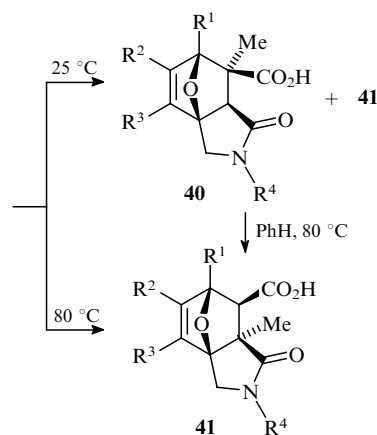
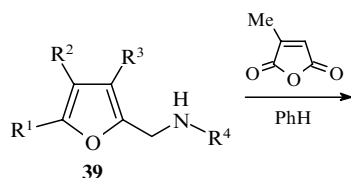
<sup>a</sup> The acylation was carried out using a corresponding anhydride; <sup>b</sup> toluene can also be used as a solvent; <sup>c</sup> the intermediate amide **35** was isolated;<sup>d</sup> a 1,3-diisopropylcarbodiimide (DIC)–diisopropylethylamine (DIEA)–4-dimethylaminopyridine (DMAP) system was used as a catalyst.Abbreviations: Cy is cyclo-C<sub>6</sub>H<sub>11</sub>, Ment is menthyl, 2-Th is 2-thienyl, *m*-Tol is 3-MeC<sub>6</sub>H<sub>4</sub>, MeAll is CH<sub>2</sub>=CMeCH<sub>2</sub>.

A similar intramolecular cycloaddition in *N*-furfuryl- $\beta$ -chloroacrylamides **37** is the key step in the synthesis of the antibiotic ivermectin of the penicillin series possessing a broad spectrum of antiparasitic activities.<sup>54</sup> The chloro-substituted tetracyclic compounds **38** are formed as mixtures of diastereomers.



$R^1 = \text{H, Pr}^i$ ;  $R^2 = \text{Me, CH}_2\text{OBn}$ .

The regioselectivity of the cycloaddition of citraconic (methylmaleic) anhydride to furfurylamines **39** in benzene has been studied.<sup>52, 55</sup> Depending on the temperature and the nature of the substituents in the furan ring, this reaction follows one of two pathways to yield isomeric methyl-substituted epoxyisindolinones **40** and **41** (Table 3).



The yields of the cycloaddition products **40** and **41** depend on the electronic effects of the substituents in the furan ring: donor groups (*e.g.*, SMe) favour the cycloaddition, while electron-withdrawing groups ( $\text{CO}_2\text{Alk}$ ) hinder this process. Their position (3 or 4) has no appreciable effect on the reaction (see Table 3).

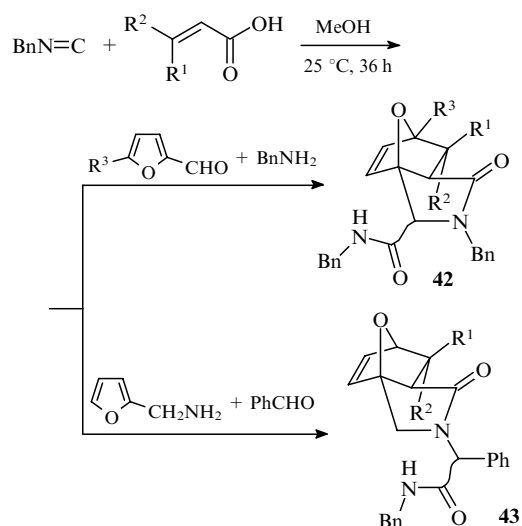
This reaction occurs in two steps. The first step includes the acylation of furfurylamine. NMR spectroscopic studies (the reaction in an NMR tube) have shown that the cycloaddition of citraconic anhydride to *N*-benzylfurfurylamine **39** ( $R^1 = R^2 = R^3 = \text{H}$ ,  $R^4 = \text{Bn}$ ) is reversible.<sup>55</sup> In the majority of cases, the amine attacks both carbonyl groups of the anhydride at room temperature (25 °C), *i.e.*, the acylation is non-regioselective and yields two regioisomers, *i.e.*, **40** and **41**. With an increase in the temperature, the thermodynamically less stable isomer **40** undergoes degradation to the starting furfurylamine **39** which undergoes acylation and cyclisation to yield eventually the isomer **41**. This process is discussed in detail by Murali *et al.*<sup>52</sup>

3*a*,6-Epoxyisindolinones **42** and **43** have recently been synthesised using the four-component Ugi reaction.<sup>56</sup>

**Table 3.** Cycloaddition of citraconic anhydride to furfurylamines **39**.

| $R^1$ | $R^2$              | $R^3$              | $R^4$                                                           | $T / ^\circ\text{C}$ | $t / \text{h}$   | <b>40</b> : <b>41</b> ratio | Yield (%)        | Ref.   |
|-------|--------------------|--------------------|-----------------------------------------------------------------|----------------------|------------------|-----------------------------|------------------|--------|
| H     | H                  | H                  | Cy                                                              | 80                   | < 24             | 0 : 100                     | 76               | 52, 55 |
| H     | H                  | H                  | Bn                                                              | 80                   | < 24             | 0 : 100                     | 84               | 52, 55 |
|       |                    |                    |                                                                 | 25                   | 24               | 65 : 35                     | —                | 52, 55 |
|       |                    |                    |                                                                 | 65                   | 24               | 5 : 95                      | 90 <sup>a</sup>  | 52, 55 |
|       |                    |                    |                                                                 | 25                   | see <sup>b</sup> | 0 : 100                     | 30               | 52, 55 |
| H     | H                  | H                  | 2-MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>               | 80                   | < 24             | 0 : 100                     | 70               | 52, 55 |
| H     | H                  | H                  | 2-HOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>               | 80                   | < 24             | 0 : 100                     | 83               | 52, 55 |
| H     | H                  | H                  | 2-MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>              | 80                   | < 24             | 0 : 100                     | 66               | 52, 55 |
| H     | H                  | H                  | 4-MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>              | 80                   | < 24             | 0 : 100                     | 87               | 52, 55 |
| H     | H                  | H                  | 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> | 80                   | < 24             | 0 : 100                     | 57               | 52, 55 |
| H     | H                  | H                  | 2-NaphCH <sub>2</sub>                                           | 80                   | < 24             | 0 : 100                     | 77               | 52, 55 |
| H     | H                  | Me                 | Bn                                                              | 25                   | 24               | 15 : 85                     | see <sup>c</sup> | 52     |
|       |                    |                    |                                                                 | 65                   | 24               | 85 : 15                     | 82 <sup>a</sup>  | 52     |
| H     | H                  | SMe                | Bn                                                              | 25                   | 24               | 100 : 0                     | —                | 52     |
|       |                    |                    |                                                                 | 65                   | 24               | 100 : 0                     | 80 <sup>a</sup>  | 52     |
| H     | H                  | CO <sub>2</sub> Me | Bn                                                              | 25                   | 24               | —                           | —                | 52     |
|       |                    |                    |                                                                 | 65                   | 24               | 10 : 90                     | 72 <sup>a</sup>  | 52     |
| H     | SMe                | H                  | Bn                                                              | 25                   | 24               | 25 : 75                     | —                | 52     |
|       |                    |                    |                                                                 | 65                   | 24               | 0 : 100                     | 92 <sup>a</sup>  | 52     |
| H     | CO <sub>2</sub> Et | H                  | Bn                                                              | 25                   | 24               | —                           | see <sup>d</sup> | 52     |
|       |                    |                    |                                                                 | 65                   | 24               | —                           | —                | 52     |
| Me    | H                  | H                  | Bn                                                              | 25                   | 24               | 0 : 100                     | —                | 52     |
|       |                    |                    |                                                                 | 65                   | 24               | 0 : 100                     | 92 <sup>a</sup>  | 52     |

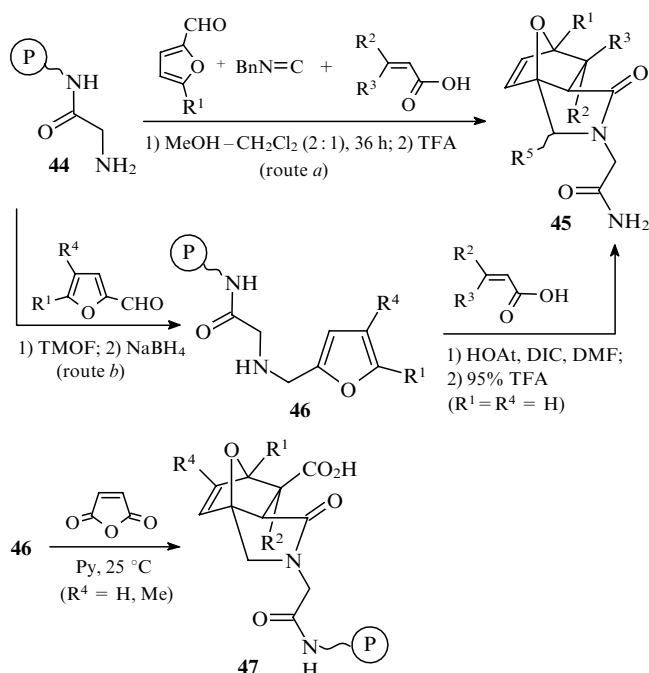
<sup>a</sup> The yield of the isomer **41** is indicated; <sup>b</sup> the reaction is complete within several hours; <sup>c</sup> the conversion of the substrate is 20%; <sup>d</sup> no product was detected. Naph is naphthyl.



| R <sup>1</sup>     | R <sup>2</sup>     | Yield (%)               |                          |    |
|--------------------|--------------------|-------------------------|--------------------------|----|
|                    |                    | 42 (R <sup>3</sup> = H) | 42 (R <sup>3</sup> = Me) | 43 |
| H                  | CO <sub>2</sub> Et | 70                      | 72                       | 75 |
| H                  | CONHBn             | 85                      | 81                       | 88 |
| CO <sub>2</sub> Et | H                  | 89                      | 78                       | 89 |

This multicomponent synthesis is carried out under mild conditions and, depending on the nature of the starting compounds (it is the aldehyde and the amine components that are usually varied), affords high yields of epoxyisindolinones **42** or **43**. The introduction of substituted substrates enables variation of substituents at positions 2, 3, 6 and 7 of the oxazatricyclo[5.2.1.0<sup>1,5</sup>]decene system.

This conversion was also accomplished in a solid-phase version where the AgroGel-Rink resin was used.<sup>56, 57</sup> In this case, the role of the amine component is played by glycineamide **44** bound to the polymeric support.



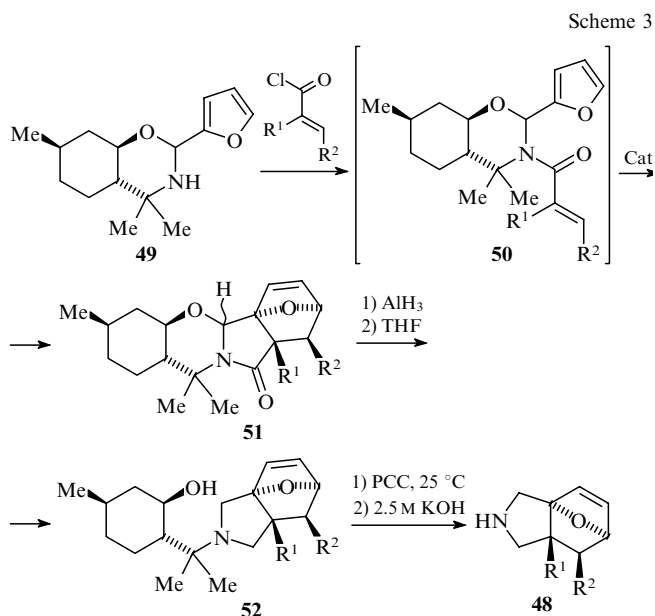
(P) is a polymeric support; TMOF is trimethyl orthoformate; HOAt is 1-hydroxy-7-azabenzotriazole.

| R <sup>2</sup>     | R <sup>3</sup>     | R <sup>5</sup> (route) | Yield of <b>45</b> (%) |                     | Ref. |
|--------------------|--------------------|------------------------|------------------------|---------------------|------|
|                    |                    |                        | R <sup>1</sup> = H     | R <sup>1</sup> = Me |      |
| H                  | CO <sub>2</sub> Et | CONHBn (a)             | 92                     | 88                  | 56   |
|                    |                    | H (b)                  | 95                     | —                   | 57   |
|                    | CONHBn             | CONHBn (a)             | 88                     | 92                  | 56   |
| CO <sub>2</sub> Et | H                  | H (b)                  | 90                     | —                   | 57   |
|                    |                    | CONHBn (a)             | 95                     | 95                  | 56   |
|                    |                    | H (b)                  | 89                     | —                   | 57   |

Two modifications of this reaction exist. One of them represents a solid-phase version of the Ugi reaction (route *a*) with the direct formation of the products **45**; the second variant is a consecutive two-step process (route *b*). In the latter case, the reactions of the intermediate furfurylamine **46** with acrylic acid derivatives also yield epoxyisindolinones **45**. Acylation of the amine with maleic anhydride gives the polymer-bound compounds **47** containing an additional functionalisation site, *i.e.*, a carboxy group. In the final step, the reaction product is liberated from the polymeric substrate by treatment with trifluoroacetic acid. The acids **47** were used as starting compounds for the synthesis of a large library of amides and esters.<sup>57</sup>

A series of original investigations<sup>58–60</sup> have been carried out by Spanish chemists who were the first to perform the synthesis of non-substituted 3-aza-10-oxatricyclo[5.2.1.0<sup>1,5</sup>]dec-8-ene **48** (R<sup>1</sup> = R<sup>2</sup> = H) and to isolate its optical isomers in the individual state.<sup>58</sup> An (–)-8-aminomenthol derivative was used as a chiral inducer in the asymmetric synthesis (Scheme 3).

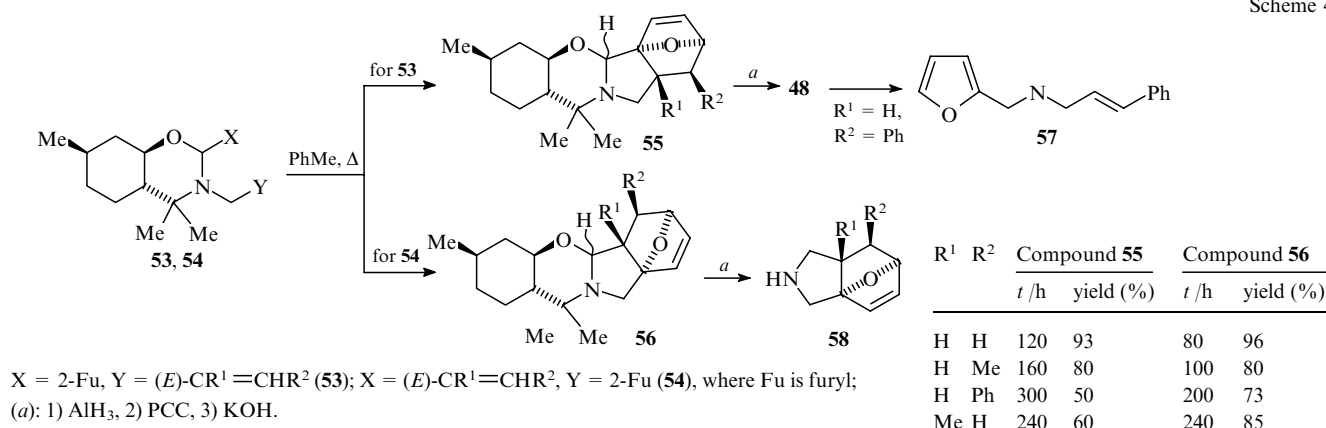
Acylation of optically active 2-furyltetrahydro-1,3-oxazines **49** with unsaturated acid chlorides gives intermediate alkenylfurans **50** which are spontaneously converted into isomeric oxazinoisindoles **51**. The latter are formed in high yields as mixtures of two diastereomers; their ratios depending on the temperature of the reaction, the nature of the solvent and the Lewis acid used as a catalyst. Toluene, CH<sub>2</sub>Cl<sub>2</sub> or hexane are used as solvents; the non-catalysed cycloaddition proceeds smoothly at 0 °C and that in the



R<sup>1</sup>, R<sup>2</sup> = H, Me; Cat = ZnCl<sub>2</sub>, Ti(OPr<sup>i</sup>)<sub>4</sub>, BF<sub>3</sub>·Et<sub>2</sub>O, Et<sub>2</sub>AlCl, Me<sub>3</sub>Al, AlCl<sub>3</sub>; PCC is pyridinium chlorochromate.

| R <sup>1</sup> | R <sup>2</sup> | Yield of <b>48</b> (%) | Ref.   |
|----------------|----------------|------------------------|--------|
| H              | H              | 31–93                  | 58, 59 |
| Me             | H              | 80–89                  | 59     |
| H              | Me             | 80–89                  | 59     |

Scheme 4



presence of catalysts at  $-23^{\circ}\text{C}$ .<sup>59</sup> Reduction of the 1,3-oxazine fragment in the polycycles **51** with aluminium hydride yields individual optically active stereoisomeric amino alcohols **52** (yields 80%–94%). Subsequent oxidation of the hydroxy group with pyridinium chlorochromate and base-catalysed retro-Michael reaction yield the target compounds **48** (see Scheme 3).<sup>58, 59</sup>

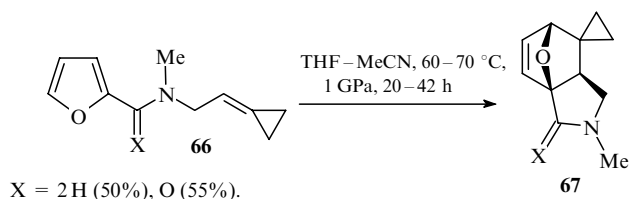
The [4+2]-cycloaddition of the structurally similar isomeric alkenylfurans **53** and **54**, which are devoid of the carbonyl group, takes place only upon long-term boiling in toluene, resulting in fused hexahydroisindoles **55** and **56**, respectively. It is interesting to note that hexahydroepoxyisindole **48** formed upon oxidation and alkaline degradation of the polycycle **55** (R<sup>1</sup> = H, R<sup>2</sup> = Ph) is unstable and undergoes spontaneous retro-Diels–Alder reaction to alkenylfuran **57**. Oxaazatricyclodecenes **58** were obtained from oxasinoisindoles **56** (Scheme 4). Cycloaddition of *N*-furfurylidenetriptamines served as a basis for the development of an elegant procedure for the preparation of fused tetrahydro- $\beta$ -carbolines and the shortest route to the construction of the carbon skeleton of the natural alkaloid noryochimbine.<sup>61, 62</sup>

Acylation of furyl-substituted tetrahydro- $\beta$ -carbolines **59** (synthesised by the Pictet–Spengler method) with maleic anhydride or  $\alpha,\beta$ -unsaturated acid chlorides gives the amides **60** and **61**.<sup>62</sup> Intramolecular cycloaddition in these amides yields the corresponding adducts **62** and **63** containing both tetrahydrocarboline and isindole rings (Table 4, route *a*). Such an approach enables the construction of a noryochimbine skeleton with a broad array of substituents in both the indole and isindole fragments (Scheme 5).

In some cases, furyl-substituted tetrahydro- $\beta$ -carbolines are prepared *in situ* (route *b*). Although this approach has been

applied to compounds that are not characterised by a broad array of substituents, it enabled one-step synthesis of the derivatives **62** (see Table 4).<sup>61</sup> Azomethines derived from tryptophan **64** were acylated with maleic anhydride under mild conditions. The intermediate *N*-acyl derivatives **65** underwent the Pictet–Spengler cyclisation and the intramolecular Diels–Alder cycloaddition to give the heterocyclic adducts **62** in high yields.

An interesting example of an intramolecular attack of an *N*-cyclopropylidene dienophile on the furan ring of the alkenes **66** has been described.<sup>63</sup> This reaction yields epoxyisindolines **67** only at elevated pressure, not at atmospheric pressure.



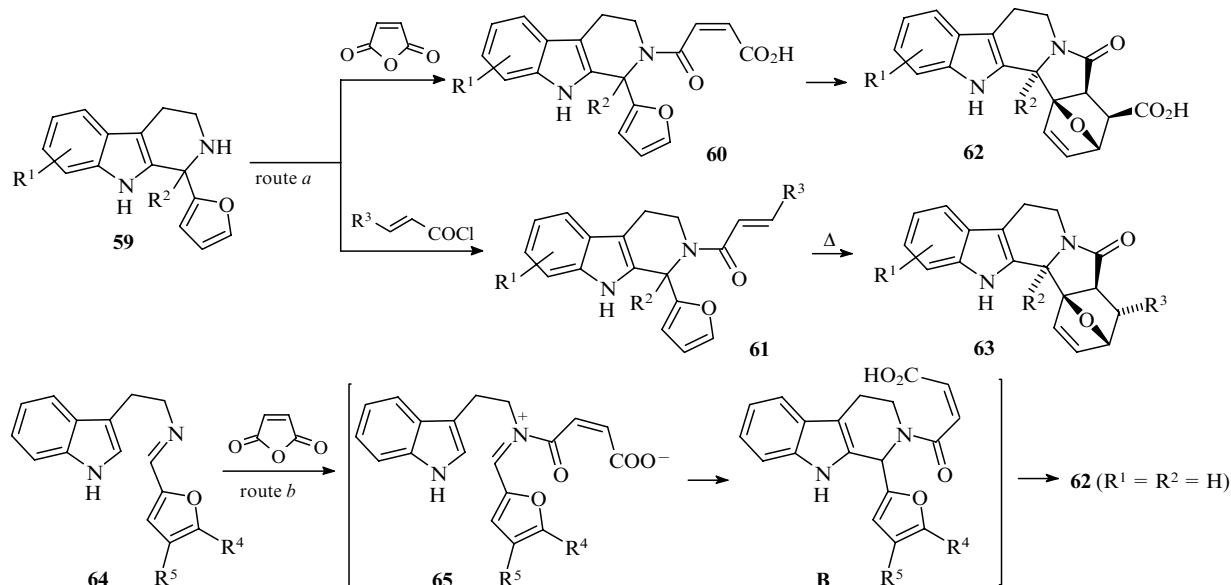
Conversions of 2-alkenylfuran metal complexes are documented.<sup>49, 50, 64</sup> Heating of the coordination molybdenum, tungsten and manganese carbonyl compounds **68** in inert solvents yields hydrogenated epoxyisindoles **69** (Table 5). These complexes are crystalline compounds that are relatively stable in air. No cyclisation of *N*-unsubstituted analogue **68** (R<sup>1</sup>, R<sup>2</sup> = H, X = O) occurs even upon long-term heating; the same was observed with certain metal complexes (see Table 5). The nitrogen atom in the complexes **68** does not undergo inversion, therefore, the derivatives **69** are formed as pairs of geometrical isomers that can be separated by chromatography.

**Table 4.** Preparation of isindolotetrahydrocarbolines **62** and **63**.

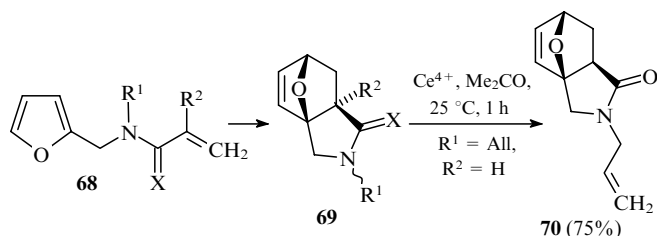
| R <sup>1</sup> | R <sup>2</sup>     | R <sup>3</sup>                                  | R <sup>4</sup>      | R <sup>5</sup> | Route    | Reaction conditions             |        |       | Product<br>[yield (%)] | Ref. |
|----------------|--------------------|-------------------------------------------------|---------------------|----------------|----------|---------------------------------|--------|-------|------------------------|------|
|                |                    |                                                 |                     |                |          | solvent                         | T / °C | t / h |                        |      |
| H              | CO <sub>2</sub> Me | H                                               | H                   | H              | <i>a</i> | DCE                             | 70     | 24    | <b>62</b> [100]        | 62   |
| H              | CO <sub>2</sub> Me | Ph                                              | H                   | H              | <i>a</i> | THF                             | 60     | 4–5   | <b>63</b> [90]         | 62   |
| 6-Cl           | CO <sub>2</sub> Me | Ph                                              | H                   | H              | <i>a</i> | THF                             | 60     | 4–5   | <b>63</b> [94]         | 62   |
| 7-F            | CO <sub>2</sub> Me | 3-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> | H                   | H              | <i>a</i> | THF                             | 60     | 4–5   | <b>63</b> [79]         | 62   |
| 6-OH           | CO <sub>2</sub> Me | Me                                              | H                   | H              | <i>a</i> | THF                             | 60     | 4–5   | <b>63</b> [70]         | 61   |
| 6-OBn          | CO <sub>2</sub> Me | 2-ClC <sub>6</sub> H <sub>4</sub>               | H                   | H              | <i>a</i> | THF                             | 60     | 4–5   | <b>63</b> [86]         | 61   |
| H              | H                  | H                                               | H                   | H              | <i>b</i> | CH <sub>2</sub> Cl <sub>2</sub> | 25     | 24    | <b>62</b> [80]         | 61   |
| H              | H                  | H                                               | Me                  | H              | <i>b</i> | CH <sub>2</sub> Cl <sub>2</sub> | 25     | 24    | <b>62</b> [80]         | 61   |
| H              | H                  | H                                               | CH <sub>2</sub> OAc | H              | <i>b</i> | CH <sub>2</sub> Cl <sub>2</sub> | 25     | 24    | <b>62</b> [76]         | 61   |
| H              | H                  | H                                               | Me                  | Me             | <i>b</i> | CH <sub>2</sub> Cl <sub>2</sub> | 25     | 24    | <b>62</b> [60]         | 61   |

DCE is 1,2-dichloroethane.

Scheme 5

Table 5. Preparation of metallocomplexes **69**.

| R <sup>1</sup>      | R <sup>2</sup> | X                        | Reaction conditions             |               |              | Yield (%) | Ref. |
|---------------------|----------------|--------------------------|---------------------------------|---------------|--------------|-----------|------|
|                     |                |                          | solvent                         | <i>T</i> / °C | <i>t</i> / h |           |      |
| H                   | H              | W(CO) <sub>5</sub>       | PhMe                            | 110           | 3            | 0         | 51   |
| H                   | Me             | W(CO) <sub>5</sub>       | PhMe                            | 110           | 3            | 60        | 51   |
|                     |                |                          | PhMe                            | 90            | 3            | 79        | 64   |
| H                   | Me             | MeCp(CO) <sub>2</sub> Mn | Bu <sub>2</sub> O               | 80            | 24           | 48        | 64   |
| H                   | Me             | Cp(CO)(NO)Mo             | Bu <sub>2</sub> O               | 90            | 3            | 0         | 64   |
|                     |                |                          | Bu <sub>2</sub> O               | 90            | 120          | 0         | 64   |
| All                 | H              | W(CO) <sub>5</sub>       | CH <sub>2</sub> Cl <sub>2</sub> | −30 to 25     | 1            | 38        | 51   |
| Me                  | Me             | W(CO) <sub>5</sub>       | PhMe                            | 90            | 3            | 100       | 64   |
| Me                  | Me             | Cp(CO)(NO)Mo             | Bu <sub>2</sub> O               | 90            | 3            | 22        | 64   |
|                     |                |                          | Bu <sub>2</sub> O               | 70            | 4            | 19        | 64   |
|                     |                |                          | Bu <sub>2</sub> O               | 50            | 24           | 7         | 64   |
| Me                  | Me             | MeCp(CO) <sub>2</sub> Mn | Bu <sub>2</sub> O               | 80            | 6            | 72        | 64   |
| Bn                  | Me             | W(CO) <sub>5</sub>       | PhMe                            | 90            | 3            | 100       | 64   |
| Bn                  | Me             | Cp(CO)(NO)Mo             | Bu <sub>2</sub> O               | 90            | 3            | 50        | 64   |
| Bn                  | Me             | MeCp(CO) <sub>2</sub> Mn | Bu <sub>2</sub> O               | 80            | 4            | 75        | 64   |
| ( <i>S</i> )-CHMePh | Me             | W(CO) <sub>5</sub>       | PhMe                            | 90            | 3            | 100       | 64   |



The cyclisation of tungsten pentacarbonyl complexes occurs most easily. The cyclopentadienyl–molybdenum complex possessing stronger electron-donor properties and manganese carbonyl complexes are characterised by moderate reactivities. The organometallic complex **69** (R<sup>1</sup> = All, R<sup>2</sup> = H) can easily be oxidised to the amide **70** by treatment with (NH<sub>4</sub>)<sub>2</sub>Ce(NO<sub>3</sub>)<sub>6</sub>.

Cyclisation of *N*-furfuryl-*N*-phenylfumaramide acid and the corresponding ethyl ester at high pressures has been studied.<sup>65</sup> The kinetic parameters of this reaction were established at different temperatures and pressures.

#### b. Synthesis of 3,10-dioxatricyclo[5.2.1.0<sup>1,5</sup>]dec-8-enes

The intramolecular cycloaddition of furfuryl esters of α,β-unsaturated acids is more complex than that of their nitrogen analogues and is studied in lesser detail. Like the cyclisation of nitrogen-containing alkenylfurans, this reaction yields only *exo*-isomers of 3,10-dioxatricyclo[5.2.1.0<sup>1,5</sup>]dec-8-enes.

Acylation of furfuryl alcohols with acryloyl chloride and fumaric acid monomethyl ester chloride afforded the unsaturated esters **71** (X = O); their intramolecular cyclisation yielded the diastereomers **72** and **73** (Table 6).<sup>66,67</sup> A similar reaction of the allylic derivative **71** (R<sup>1</sup>–R<sup>3</sup> = H, X = 2 H) (170–200 °C, 18 h) also resulted in a mixture of compounds **72** and **73** (X = 2 H) in a total yield of 35%.<sup>67</sup>

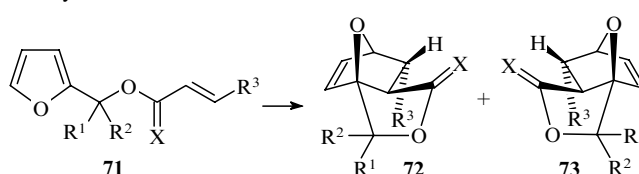


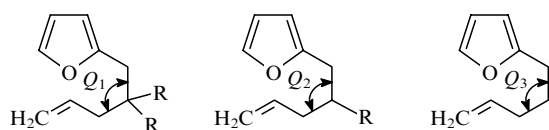
**Table 6.** Intramolecular cyclisation of furfuryl esters **71**.

| R <sup>1</sup> | R <sup>2</sup>                     | R <sup>3</sup>     | X | Reaction conditions |        |          |         | 72 : 73 ratio | Yield (%)        | Ref. |
|----------------|------------------------------------|--------------------|---|---------------------|--------|----------|---------|---------------|------------------|------|
|                |                                    |                    |   | solvent             | T / °C | t        | p / GPa |               |                  |      |
| H              | H                                  | H                  | O | see <sup>a</sup>    | 80     | 60 h     | —       | —             | 50               | 67   |
| H              | H                                  | CO <sub>2</sub> Me | O | CD <sub>3</sub> CN  | 25     | 60 days  | —       | —             | see <sup>b</sup> | 66   |
| Me             | H                                  | CO <sub>2</sub> Me | O | CD <sub>3</sub> CN  | 25     | 11 days  | —       | —             | see <sup>b</sup> | 66   |
| Me             | Me                                 | CO <sub>2</sub> Me | O | CD <sub>3</sub> CN  | 25     | < 1 h    | —       | —             | see <sup>b</sup> | 66   |
|                | (CH <sub>2</sub> ) <sub>4</sub>    | CO <sub>2</sub> Me | O | CD <sub>3</sub> CN  | 25     | < 1 h    | —       | —             | see <sup>b</sup> | 66   |
|                | (CH <sub>2</sub> ) <sub>3</sub>    | CO <sub>2</sub> Me | O | CD <sub>3</sub> CN  | 25     | 11 h     | —       | —             | see <sup>b</sup> | 66   |
|                | (CH <sub>2</sub> ) <sub>2</sub>    | CO <sub>2</sub> Me | O | CD <sub>3</sub> CN  | 25     | 12 days  | —       | —             | see <sup>b</sup> | 66   |
| H              | Me                                 | CO <sub>2</sub> Me | O | Me <sub>2</sub> CO  | 40     | 18 g     | 0.7     | 55 : 45       | 96               | 68   |
| H              | Me                                 | CO <sub>2</sub> Me | O | Me <sub>2</sub> CO  | 40     | 5–7 days | —       | 55 : 45       | 41               | 68   |
| H              | Et                                 | CO <sub>2</sub> Me | O | Me <sub>2</sub> CO  | 40     | 18 h     | 0.7     | 68 : 32       | 36               | 68   |
| H              | Pr <sup>i</sup>                    | CO <sub>2</sub> Me | O | Me <sub>2</sub> CO  | 40     | 18 h     | 0.7     | 90 : 10       | 90               | 68   |
| H              | Pr <sup>i</sup>                    | CO <sub>2</sub> Me | O | Me <sub>2</sub> CO  | 40     | 5–7 days | —       | 78 : 22       | 31               | 68   |
| H              | Bu <sup>t</sup>                    | CO <sub>2</sub> Me | O | Me <sub>2</sub> CO  | 40     | 18 h     | 0.7     | 93 : 7        | 92               | 68   |
| H              | Bu <sup>t</sup>                    | CO <sub>2</sub> Me | O | Me <sub>2</sub> CO  | 40     | 5–7 days | —       | 92 : 8        | 44               | 68   |
| H              | neo-C <sub>5</sub> H <sub>11</sub> | CO <sub>2</sub> Me | O | Me <sub>2</sub> CO  | 40     | 18 h     | 0.7     | 69 : 31       | 93               | 68   |
| H              | Ph                                 | CO <sub>2</sub> Me | O | Me <sub>2</sub> CO  | 40     | 18 h     | 0.7     | 23 : 77       | 49               | 68   |

<sup>a</sup> The reaction was carried out on diatomite in the absence of solvent; <sup>b</sup> the products **72** and **73** were not isolated and their ratio was not determined.

This reaction was studied in an NMR tube (CD<sub>3</sub>CN, 25 °C) by determining the half-conversion times (*t*<sub>1/2</sub>) of the starting compounds **71**. It was found that the cyclisation rates of the non-substituted (R<sup>1</sup> = R<sup>2</sup> = H) and monomethyl-substituted (R<sup>1</sup> = Me, R<sup>2</sup> = H) esters **71** were very low: *t*<sub>1/2</sub> = 665 and 133 h, respectively. In contrast, in the case of dimethyl, cyclobutane and cyclopentane derivatives [R<sup>1</sup>–R<sup>2</sup> = Me<sub>2</sub>, (CH<sub>2</sub>)<sub>3</sub>, (CH<sub>2</sub>)<sub>4</sub>] the intramolecular Diels–Alder reaction occurred fast: the conversion of the starting compounds was complete within less than 11 h. However, the reaction rate dropped drastically (*t*<sub>1/2</sub> = 145 h) on going to the cyclopropane homologue **71** [R<sup>1</sup>–R<sup>2</sup> = (CH<sub>2</sub>)<sub>2</sub>]. These findings led Jung *et al.*<sup>66–68</sup> to suggest that the *gem*-dialkyl substituents R<sup>1</sup> and R<sup>2</sup> strongly influence the formation of the cycloadducts **72** and **73**.

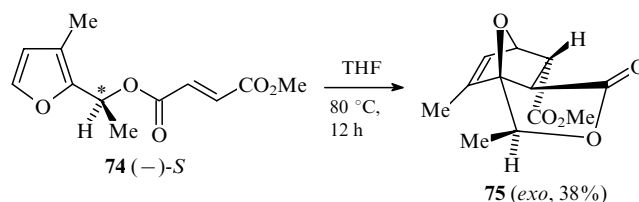
This phenomenon is often referred to as the Thorpe–Ingold effect (or the internal angle compression effect). Its essence is that the so-called internal angle *Q* (*Q*<sub>1</sub> < *Q*<sub>2</sub> < *Q*<sub>3</sub>) decreases with an increase in the number and sizes of substituents at the sp<sup>3</sup>-hybridised carbon atom in the side chain.



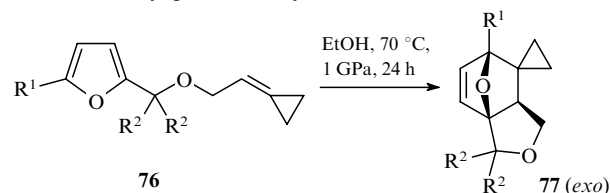
R = Alk.

For the cases under consideration, the magnitude of the internal angle *Q* depends on the nature of the substituents R and decreases in the following order: H, H > H, Alk > Alk, Alk. The ordering of the transition state, *i.e.*, the entropy factor, increases with the decrease in the internal angle *Q*, as a result of which the rate of the intramolecular [4+2]-cycloaddition in this series of compounds also increases.

The cyclisation of optically active furfuryl esters has been studied.<sup>68</sup> At high temperatures and at elevated pressure, the racemic mixtures of the enantiomeric esters **71** are converted into the diastereomeric adducts **72** and **73** (see Table 6), while the cycloaddition of chiral starting compounds occurs stereoselectively. By illustration, the cycloaddition of the *S*-enantiomer **74** gives only one *exo*-isomer **75**.<sup>68</sup>

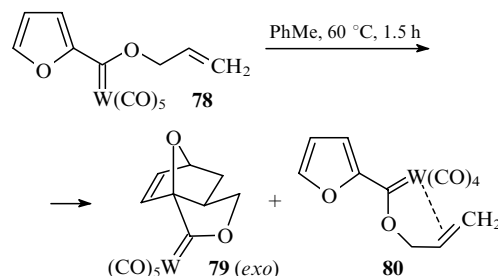


Cyclopropenylideneethyl furfuryl ethers **76** enter into the Diels–Alder reaction in the same manner as their nitrogen analogues **66**, *i.e.*, at elevated pressure. The *exo*-adducts **77** are formed in virtually quantitative yields.<sup>63</sup>



R<sup>1</sup> = H, Me, OMe; R<sup>2</sup> = H, Me.

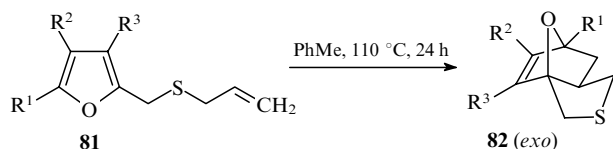
The intramolecular cyclisation in the series of 2-allyloxymethylfuran metal complexes has also been described. However, thermolysis of the tungsten-containing complex **78** yields, in addition to the expected *exo*-adduct **79** (10%), the complex **80** (5%) as a result of extrusion of one CO ligand.<sup>49</sup>



### c. Synthesis of 3-thia-10-oxatricyclo[5.2.1.0<sup>1,5</sup>]dec-8-enes

Before 2003, there were only three publications devoted to the synthesis of oxabicycloheptene systems annulated with the tetrahydrothiophene ring.<sup>69–71</sup> The reason for the low interest in reactions of alkenyl furfuryl sulfides **81** is not clear, since alkyla-

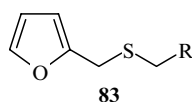
tion of furfurylmethanethiols with alkenyl halides normally proceeds in good yields. Subsequent intramolecular [4 + 2]-cycloaddition affords the Diels–Alder adducts **82**, which are also *exo*-isomers.



| R <sup>1</sup>                                                      | R <sup>2</sup>     | R <sup>3</sup>     | Yield (%) | Ref.   |
|---------------------------------------------------------------------|--------------------|--------------------|-----------|--------|
| H                                                                   | H                  | H                  | 23        | 69     |
| H                                                                   | H                  | Me                 | 77        | 69     |
| H                                                                   | H                  | Br                 | 83        | 69     |
| H                                                                   | Me                 | H                  | 40        | 69     |
| Me                                                                  | H                  | H                  | 18        | 69     |
| BnOCH <sub>2</sub>                                                  | H                  | H                  | 30        | 69     |
| CH <sub>2</sub> OCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Br-2 | H                  | H                  | 33        | 71     |
| H                                                                   | BnOCH <sub>2</sub> | BnOCH <sub>2</sub> | 84        | 69     |
| Me                                                                  | H                  | Me                 | 60        | 69, 70 |
| Me                                                                  | Me                 | H                  | 60        | 69     |
| Me                                                                  | BnOCH <sub>2</sub> | H                  | 48        | 69     |
| Me                                                                  | Me                 | Me                 | 92        | 69     |

It is noteworthy that in the case of 3-substituted furans **81** (R<sup>3</sup> = Alk, Br) the yields of the sulfides **82** are significantly higher. This fact is attributed to the interaction between the bulky sulfur atom and the  $\alpha$ -methylene fragment, on the one hand, and the substituent R<sup>3</sup>, on the other hand, which leads to the approximation of the alkenyl and diene fragments in the starting alkenylfuran. In addition, the structure of the adduct **82** is such that the steric interaction between these substituents decreases.

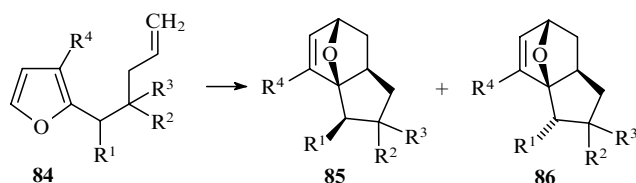
Attempts to perform the cyclisation of sulfides of the type **83** were unsuccessful: the products **82** were either not formed at all, or were formed in trace amounts (< 5%).



R = (*E*)-CH=CHMe, CMe=CH<sub>2</sub>, CH=CHMe<sub>2</sub>,  
(CH<sub>2</sub>)<sub>n</sub>CH=CH<sub>2</sub> (n = 1, 2).

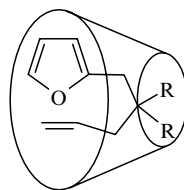
#### d. Synthesis of 10-oxatricyclo[5.2.1.0<sup>1,5</sup>]dec-8-enes

In one of the earliest studies<sup>72</sup> devoted to the synthesis of oxatricyclodecene systems the effects of substituents in the substrate molecule on the intramolecular cyclisation were investigated. It was found that the unsubstituted alkenylfuran **84** could not be converted to the tricyclic compound **85** (and/or **86**). The presence of at least two substituents in the side alkenyl chain is a prerequisite for the cyclisation of compound **84**.



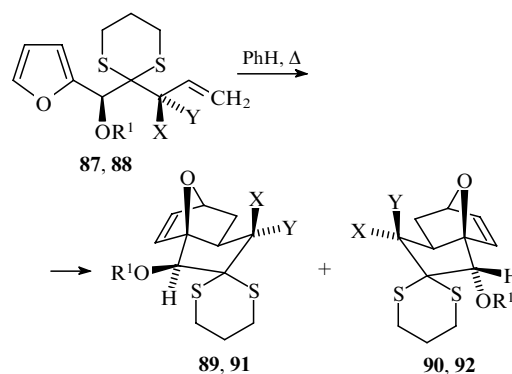
The addition, to the reaction medium, of  $\alpha$ - or  $\beta$ -cyclodextrin ( $\alpha$ -CD or  $\beta$ -CD), a cyclic oligomer built up of six or seven 1,4-linked  $\alpha$ -D-glucopyranose residues, significantly (by 10%–20%) increases the yield of the isomeric cycloadducts **85** and **86**.<sup>72</sup> In the authors' opinion, the effect of cyclodextrins can be attributed to the incorporation of the starting alkene molecule into the cavity of the carbohydrate macromolecule as a result of which the alkene and the furan fragments are brought closer to each other. The size

of the  $\beta$ -cyclodextrin cavity is probably best suited to the binding of 2-alkenylfuran and its use should be preferred.



The effects of solvents on the cyclisation of furan **84** [R<sup>2</sup>–R<sup>3</sup> = S(CH<sub>2</sub>)<sub>3</sub>S] have been studied.<sup>73</sup> The best yields of the epimers **85** and **86** were attained with protic solvents (water–ethanol, ethylene glycol); their ratios do not depend on the nature of the solvent. The cycloaddition rate of alkenylfurans **84** increases with an increase in the size of the substituents R<sup>2</sup> and R<sup>3</sup>, with a concomitant shift of the reaction equilibrium towards the cyclisation products,<sup>74</sup> apparently due to the manifestation of the *gem*-dialkyl effect (see above).

The effect of substituents in the alkyl chain and their relative position on the composition of the intramolecular [4 + 2]-cycloaddition products of the isomeric dithianes **87** (the *syn*-isomer) and **88** (the *anti*-isomer) has been studied.<sup>75</sup> These reactions afford the diastereomeric pairs **89–90** and **91–92**, respectively.



X = OR<sup>2</sup>, Y = H (**87**, **89**, **90**); X = H, Y = OR<sup>2</sup> (**88**, **91**, **92**).

| R <sup>1</sup> | R <sup>2</sup> | t / days | Ratio   |         | Yield (%) |
|----------------|----------------|----------|---------|---------|-----------|
|                |                |          | 89 : 90 | 91 : 92 |           |
| H              | H              | 2        | 1 : 1   | —       | 95        |
|                |                | 4        | —       | 1 : 1   | 95        |
| Bn             | Bn             | 3        | 1 : 99  | —       | 82        |
|                |                | 2        | —       | 1.1 : 1 | 84        |
| Ac             | Ac             | 4        | 1 : 3.4 | —       | 80        |
|                |                | 2        | —       | 2 : 1   | 90        |
| THP            | Bn             | 2        | 1 : 99  | —       | 91        |
|                |                | 3        | —       | 9 : 1   | 89        |

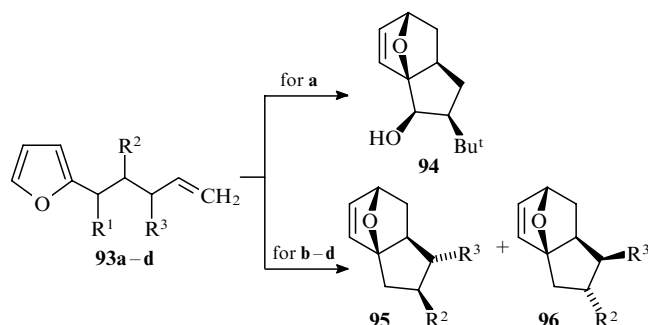
THP is tetrahydropyranyl.

It has been found<sup>75</sup> that an increase in the size of the substituents R<sup>1</sup> and R<sup>2</sup> in *syn*-alkenylfurans **87** favours the formation of the diastereomers **90** with a *trans*, *trans*-configuration of the substituents OR<sup>1</sup> and OR<sup>2</sup> relative to the epoxide bridge. In the case of benzyl substituents, the reaction proceeds in a stereoselective manner and yields only compounds **90**. The stereodirection of the intramolecular cycloaddition of the *anti*-isomers **88** also depends on the size of the substituents R<sup>1</sup> and R<sup>2</sup>, but this effect is not as pronounced as in the previous case and the yield of the adduct **91** is increased. It was found also that the change in the solvent polarity (methylcyclohexanone and aqueous ethanol were used) had no appreciable effect on the stereospecificity of the cycloaddition reaction.

Cyclisation of 4-[(2-furyl)hydroxymethyl]-5,5-dimethylhex-1-ene **93a** in benzene and in toluene at 80 and 111 °C afforded only one geometrical isomer (**94**) in 70% and 60% yields, respectively. The lower yield of the adduct **94** at higher temperatures was



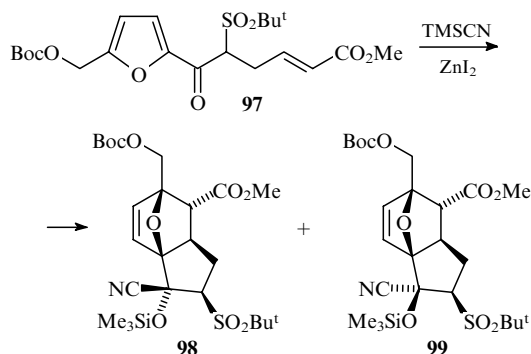
thought to be due to the retro-Diels–Alder reaction.<sup>76</sup> Cyclisation of 5-(2-furyl)pent-1-enes **93b–d** containing a 4-sulfonyl group (benzene, 80 °C) yielded mixtures of isomers **95** and **96**.<sup>77</sup>



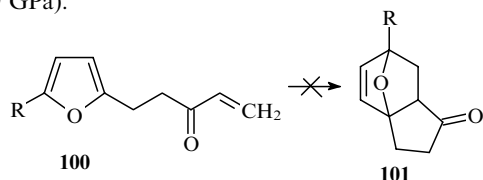
| Compound <b>93</b> | R <sup>1</sup> | R <sup>2</sup>                  | R <sup>3</sup> | Product        | Yield (%) | Ref. |
|--------------------|----------------|---------------------------------|----------------|----------------|-----------|------|
| <b>a</b>           | OH             | Bu <sup>t</sup>                 | H              | <b>94</b>      | 70        | 76   |
| <b>b</b>           | H              | SO <sub>2</sub> Me              | OH             | <b>95 + 96</b> | 78        | 77   |
| <b>c</b>           | H              | SO <sub>2</sub> Ph              | OH             | <b>95 + 96</b> | 93        | 77   |
| <b>d</b>           | H              | SO <sub>2</sub> Bu <sup>t</sup> | OH             | <b>95 + 96</b> | 97        | 77   |

It is of note that  $\delta$ -alkenylfuran **93** (R<sup>1</sup> = OH, R<sup>2</sup> = R<sup>3</sup> = H) gives no intramolecular cycloaddition products.<sup>76</sup>

The addition of trimethylsilyl cyanide (TMSCN) to furyl ketone **97** in the presence of zinc iodide is accompanied by intramolecular cycloaddition.<sup>77</sup> A mixture of the adducts **98** and **99** (1.9:1), which differ in the orientation of the cyano- and TMSO-groups relative to the epoxide bridge, is formed in 61% yield.

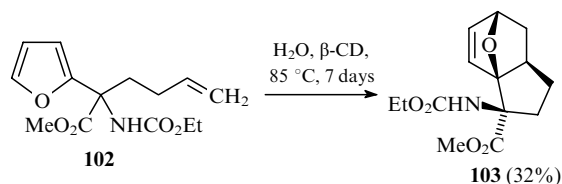


It has been shown<sup>78</sup> that [2-(2-furyl)ethyl] vinyl ketones **100**, the carbonyl group of which is conjugated with the double bond, are not converted into the derivatives **101** either upon long-term heating in toluene or at elevated pressures (CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 24 h, 1.9 GPa).

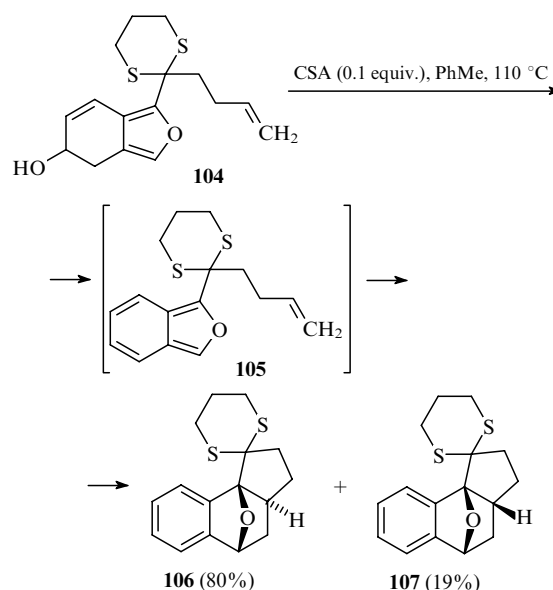


R = H, Me.

Intramolecular cyclisation of alkenylfuran **102** in the presence of  $\beta$ -cyclodextrin occurs in a stereoselective manner and yields the tricyclic *exo*-adduct **103**.<sup>79</sup>

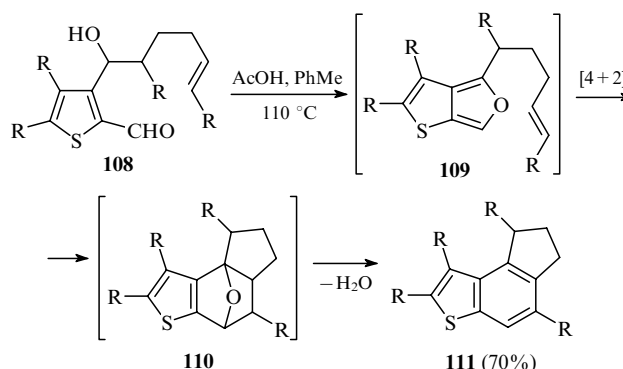


Cyclisation of 2-alkenylfurans [c]-fused to other carbo- and heterocycles has been investigated.<sup>80–87</sup> The cycloaddition of dihydroisobenzofuran **104** is preceded by dehydration by camphorsulfonic acid. The isobenzofuran **105** formed is unstable and is converted into a mixture of *exo*- (**106**) and *endo*-epoxy derivatives (**107**).<sup>80</sup>



CSA is camphorsulfonic acid.

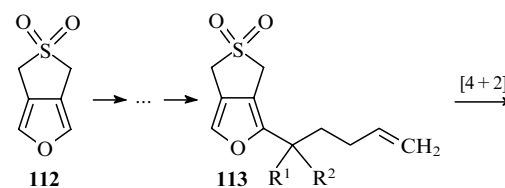
The German chemists Friedrichsen *et al.*<sup>81–83</sup> have carried out the synthesis of 2-alkenylfurans fused to the thiophene ring. These compounds underwent the intramolecular Diels–Alder reaction.

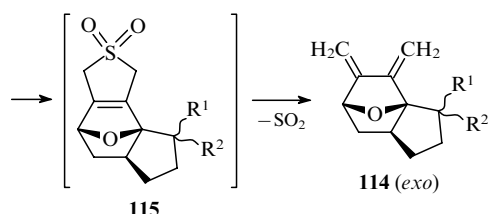


R = H, Me.

Acid-catalysed conversion of unsaturated thiophenecarbaldehydes **108** to intermediate 4-alkenylthieno[2,3-*c*]furans **109** is the key step in this reaction sequence. Further cycloaddition yields the tetracycle **110**, which is immediately dehydrated to yield fused benzothiophenes **111**.

A preparative procedure for the synthesis of 4,6-dihydrothieno[3,4-*c*]furan 1,1-dioxide **112** (see Ref. 84) developed in 1990 has made it possible to study the intramolecular cycloaddition of its derivatives **113**.<sup>85–87</sup>

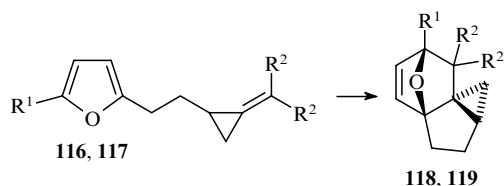




| R <sup>1</sup> –R <sup>2</sup>     | Reaction conditions            | Yield (%) |
|------------------------------------|--------------------------------|-----------|
| O                                  | <i>o</i> -xylene, 140 °C, 48 h | 0         |
| S(CH <sub>2</sub> ) <sub>2</sub> S | <i>o</i> -xylene, 140 °C, 2 h  | 74        |
|                                    | PhMe, 110 °C, 8 h              | 70        |
|                                    | PhH, 80 °C, 144 h              | 70        |
| CN, Me <sub>3</sub> SiO            | PhH, 80 °C, 24 h               | 63        |

It was found that the thermal Diels–Alder reaction is inapplicable to the ketone **113** (R<sup>1</sup>–R<sup>2</sup> = O). The presence of an sp<sup>3</sup>-hybridised carbon atom at the α-position of the substituent at position 2 of the furan ring is a prerequisite for the successful realisation of this reaction. The dienes **114** are formed as a result of sulfur(IV) oxide extrusion from the intermediate Diels–Alder adduct **115**. As the extrusion of SO<sub>2</sub> is carried out at high temperatures, *o*-xylene appears to be the solvent of choice for this reaction (b.p. = 140 °C).

An interesting example of an intramolecular cycloaddition in furans **116** and **117** containing a cyclopropylidene fragment has been described.<sup>88</sup> At elevated pressure, this reaction occurs in a stereoselective manner. X-Ray diffraction analysis revealed that compounds **118** and **119** are *exo*-adducts, the 4,5-methylene groups of which have a *trans*-configuration with respect to the epoxide bridge. The attempts at the intramolecular cyclisation of furans **116** and **117** at normal pressure were unsuccessful.

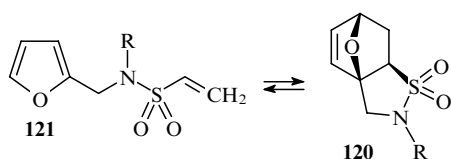


R<sup>1</sup> = H, OMe; R<sup>2</sup> = H (**116**, **118**); R<sup>1</sup> = H, R<sup>2</sup>–R<sup>2</sup> = (CH<sub>2</sub>)<sub>2</sub> (**117**, **119**).

| R <sup>1</sup> | R <sup>2</sup> –R <sup>2</sup>  | Reaction conditions                                            | Yield (%) |
|----------------|---------------------------------|----------------------------------------------------------------|-----------|
| H              | 2 H                             | PhMe, 110 °C                                                   | 0         |
|                |                                 | <i>n</i> -C <sub>5</sub> H <sub>12</sub> , 90 °C, 43 h, 1 GPa  | 32        |
| OMe            | 2 H                             | <i>n</i> -C <sub>5</sub> H <sub>12</sub> , 85 °C, 20 h, 1 GPa  | 95        |
| H              | (CH <sub>2</sub> ) <sub>2</sub> | <i>n</i> -C <sub>5</sub> H <sub>12</sub> , 110 °C, 17 h, 1 GPa | 82        |

#### e. Synthesis of 3-aza- and 3-oxa-4-thia-10-oxatricyclo-[5.2.1.0<sup>1,5</sup>]dec-8-enes

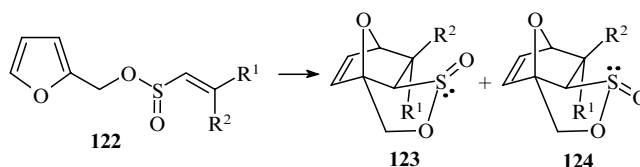
Only two examples of the synthesis of systems containing two additional heteroatoms, *viz.*, N, S or O, S, in the 10-oxatricyclo[5.2.1.0<sup>1,5</sup>]dec-8-ene structure are known. 3-Aza-4-thia-10-oxatricyclo[5.2.1.0<sup>1,5</sup>]dec-8-ene 4,4-dioxides (**120**) were synthesised by Wibbeling *et al.*<sup>89,90</sup>



| R           | Reaction conditions                                    | Yield (%) | Ref. |
|-------------|--------------------------------------------------------|-----------|------|
| H           | PhMe, 110 °C, 12 h                                     | 0         | 89   |
| Me          | PhMe, 110 °C, 7 h                                      | 29        | 89   |
| Bn          | PhMe, 110 °C, 30 h                                     | 91        | 89   |
| S(–)CH*MePh | PhMe, 110 °C, 16 h                                     | 73        | 91   |
|             | CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 14 h, 1.3 GPa | 94        | 91   |

Cyclisation of vinylsulfonamides **121** into tricyclic compounds **120** is reversible; the reaction equilibrium depends on the size of the substituent R at the nitrogen atom: the larger the size the higher the concentration of the *exo*-adduct, sultam **120**.<sup>89</sup> The configuration of a chiral substituent at the nitrogen atom in the sulfonamide **121** is retained in the course of cyclisation; the optically active substrate yields a mixture of diastereomeric adducts.<sup>90</sup>

Furfuryl vinylsulfonates **122** are unstable<sup>91</sup> and cyclise *in situ* into isomeric thiocholanes **123** and **124**, which differ in the position of the oxygen atom at the sulfur atom relative to the epoxide bridge, under very mild conditions. Conditions have been found that favoured stereoselective formation of the epimer **123**. Where the double bond of the alkenyl fragment had the *E*-configuration, the reaction was carried out in the presence of 2,6-di-*tert*-butyl-4-methylphenol, a radical reaction inhibitor and an antioxidant. It is of note that the sulfur atom in the tricycles **123** and **124** is not inverted at room temperature as can be judged from the X-ray diffraction data.<sup>91</sup>

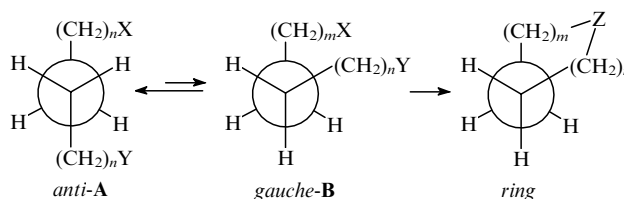


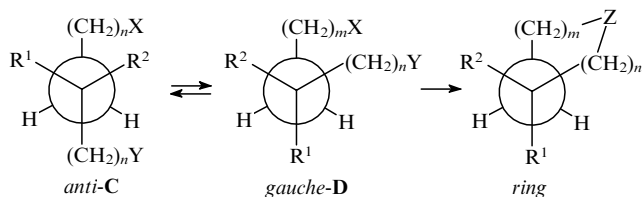
| R <sup>1</sup>     | R <sup>2</sup>     | Reaction conditions                                            | Yield (%) |     |
|--------------------|--------------------|----------------------------------------------------------------|-----------|-----|
|                    |                    |                                                                | 123       | 124 |
| CO <sub>2</sub> Me | H                  | CH <sub>2</sub> Cl <sub>2</sub> , 0.1 equiv. BHT, –30 °C, 19 h | 71        | 12  |
|                    |                    | CH <sub>2</sub> Cl <sub>2</sub> , 0.1 equiv. BHT, –77 °C, 9 h  | 77        | 0   |
| H                  | CO <sub>2</sub> Me | CH <sub>2</sub> Cl <sub>2</sub> , –50 °C, 19 h                 | 47        | 0   |

BHT is 2,6-di-*tert*-butyl-4-methylphenol.

In conclusion, mention should be made of the studies devoted to the theoretical aspects of the intramolecular Diels–Alder reaction of 2-alkenylfurans which yields oxabicycloheptenes fused to five-membered rings.

The dependence of this process on the Thorpe–Ingold effect (changes in the internal angle *Q* as the function of substituents in the alkenyl fragment, see Section IV.1.b) and the ‘reactive rotamer effect’, *i.e.*, the stabilities of the reactive *gauche*-conformers leading to the transition state, was studied by Jung *et al.*<sup>92–95</sup> The latter was demonstrated in the studies of kinetics of the intramolecular cyclisation of ethyl 6-(2-furyl)-6,6-*R,R'*-4-oxohex-2-enoates and furfuryl fumarates. The observed effect can be interpreted in the following way. Alkenylfurans exist predominantly in the *anti*-conformation (X and Y are the diene and the dienophile, respectively).





The cycloaddition occurs when the molecule **A** adopts a much less favourable *gauche*-conformation **B**. The introduction of alkyl substituents at the carbon atoms in the alkenyl chain levels off the energies of the *anti*-(**C**) and *gauche*-(**D**) conformations due to steric interactions, this effect being directly correlated with the size of the substituents. This favours the attainment of the transition state and, correspondingly, the cyclisation.

Dolata<sup>96</sup> has developed an axiomatic model of this reaction which takes into account the energy characteristics of the transition state (a combination of WIZARD and MM2 programmes). This model can be used for predicting the stereochemistry of the adducts formed with a high degree of probability.

It has been demonstrated<sup>97,98</sup> that the rate of intramolecular cyclisation of *N*-alkyl-*N*-furfurylacrylamides increases when the reaction is carried out in water or aqueous alcohols. In the authors' opinion, the abnormally high rate of the cycloaddition in water is due to stabilisation of the transition state as a result of the formation of hydrogen bonds and reduction of the hydrophobic surface of the substrate in the course of activation (since this reaction is accompanied by the reduction of the molecular volume).

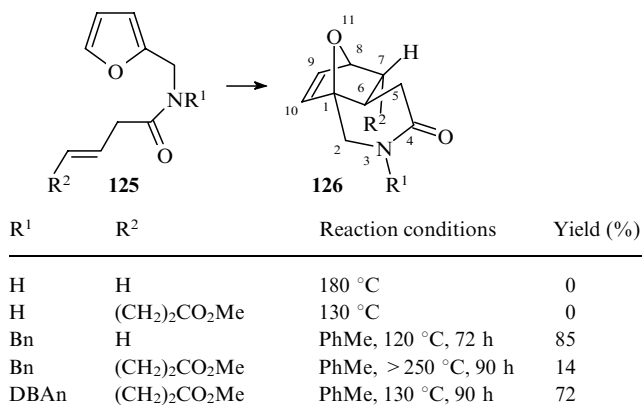
Interesting results illustrating the effect of complexation on the intramolecular cyclisation of (*E*)-3-(*N*-furfurylcarbamoyl)-acrylic acid have been reported.<sup>99</sup> It was found that the cyclisation rate decreased in the presence of *N,N'*-bis(2-methylpyridin-6-yl)terephthalamide and increased in the presence of *N,N'*-bis(2-methylpyridin-6-yl)isophthalamide due to the ability of the latter to stabilise the transition state owing to complexation. Similarly, terephthalamide stabilises the starting *N*-furfurylfumaramide and thus hinders the cyclisation.

## 2. Six-membered rings

### a. Synthesis of 3-aza-11-oxatricyclo[6.2.1.0<sup>1,6</sup>]undec-9-enes

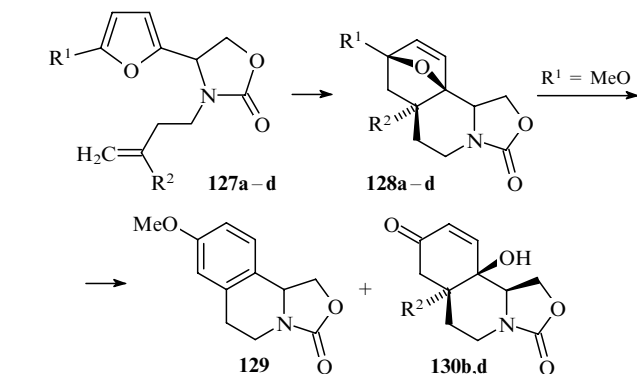
The formation of six-membered nitrogen-containing rings by intramolecular cycloaddition of furan derivatives requires more drastic conditions (*e.g.*, high temperature, high pressure) than the annelation of five-membered rings. The reaction products also contain predominantly *exo*-isomers.

Studies of the intramolecular cycloaddition of *N*-furfurylamides **125** containing a  $\beta,\gamma$ -double bond in the acyl fragment revealed<sup>100</sup> that *N*-unsubstituted derivatives ( $R^1 = H$ ) do not react even under drastic conditions, whereas *N*-substituted furfurylamides **125** yield hydrogenated epoxyisoquinolinones **126**.



DBAn is 10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-yl.

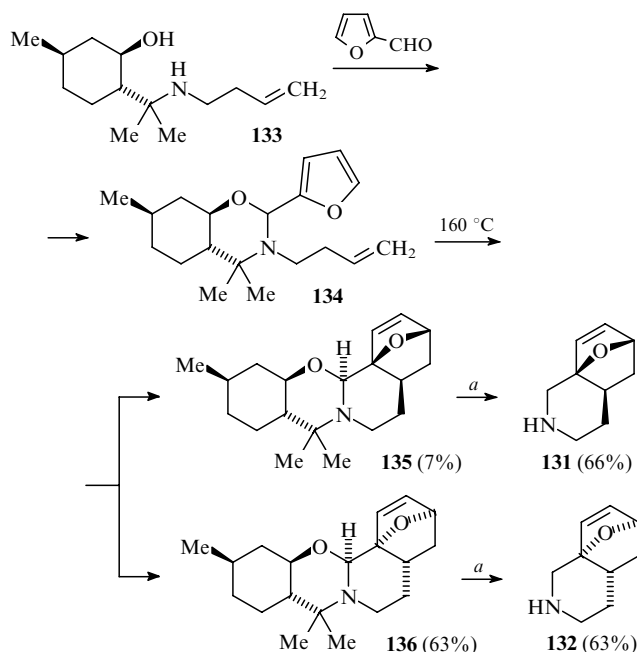
The intramolecular cyclisation of furyloxazolidones **127a–d** containing a non-activated alkenyl fragment at the nitrogen atom has been described.<sup>79</sup> The structure of the cycloadduct depends on the substituents in the furan and alkenyl fragments of the original molecule. In the case of furyloxazolidone **127a** ( $R^1 = H$ ), the reaction stops at the *exo*-tetracycle **128**. In the presence of a methoxy group (compounds **127b,d**) at position 5 of furan, the primary adduct **128** eliminates a molecule of water or methanol to give a mixture of hydrogenated isoquinolinoxazolidones **129** and/or **130**. A phenyl substituent at the double bond of the oxazolidones inhibits this reaction; no cycloadducts are formed from compound **127a**, while oxazolidone **127d** gives a hydroxy derivative **130d** in low yield. All these reactions were carried out in sealed tubes.



| Compound <b>127</b> | $R^1$ | $R^2$ | Reaction conditions                                   | Product [yield (%)]              |
|---------------------|-------|-------|-------------------------------------------------------|----------------------------------|
| <b>a</b>            | H     | H     | PhMe, 200 °C, 130 h                                   | <b>128</b> (56)                  |
|                     |       |       | H <sub>2</sub> O, $\beta$ -CD (1 equiv.) <sup>a</sup> | <b>128</b> (84)                  |
| <b>b</b>            | OMe   | H     | PhH, 165 °C, 120 h                                    | <b>129</b> (40), <b>130</b> (55) |
| <b>c</b>            | H     | Ph    | PhMe, > 250 °C                                        | —                                |
| <b>d</b>            | OMe   | Ph    | PhMe, > 250 °C, 90 h                                  | <b>130</b> (13)                  |

<sup>a</sup> The following temperature conditions were used: 55 °C, 30 h; 75 °C, 60 h; 90 °C, 3 days.

Enantiomers of 3-aza-11-oxatricyclo[6.2.1.0<sup>1,6</sup>]undec-9-ene (**131** and **132**) were synthesised and isolated in the individual state.<sup>101</sup> The starting amino alcohol **133** was synthesised from the optically active (–)-8-aminomenthol. Its reaction with furfural

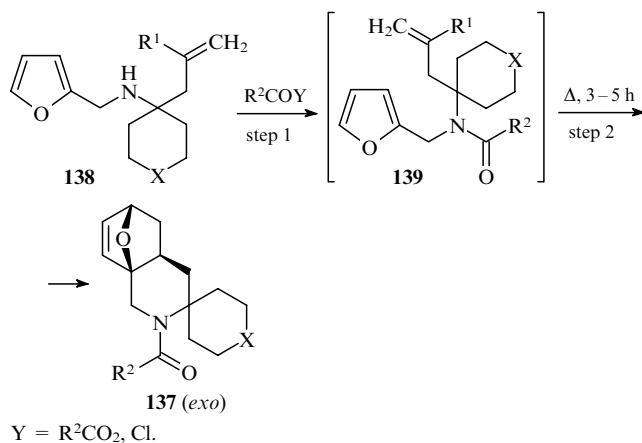


(a): 1) AlH<sub>3</sub>, 2) PCC, 3) KOH.

yields alkenylfuran **134**, which yields a mixture of intramolecular cycloaddition products **135** and **136** upon heating to 160 °C.

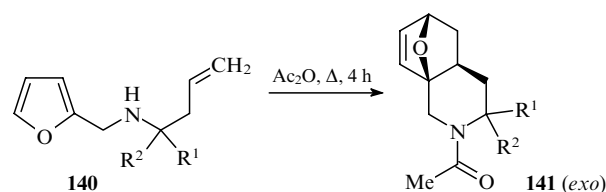
The diastereomers **135** and **136** were separated chromatographically and converted into the target tricycles **131** and **132** using the aforementioned reaction sequence (see Section IV.1.a).

The recently published papers<sup>102, 103</sup> are devoted to the synthesis and analysis of chemical properties<sup>104, 105</sup> of 4-spiroannellated epoxyoctahydroisoquinolines **137** (Table 7).



The formation of compounds **137** from homoallylamines **138** (R<sup>1</sup> = H) occurs under the action of carboxylic anhydrides (or chlorides) *via* the intermediate *N*-acyl derivatives **139**, which could be isolated in none of the cases studied. The best yields (50%–70%) of the Diels–Alder adducts were obtained when the reaction was carried out in boiling acetic anhydride. It was found<sup>102</sup> that the size of the spiro-fused ring and the nature of the acyl radical R<sup>2</sup> have little effect on the reaction (see Table 7). The failure to perform the cyclisation of the methallyl-substituted analogues **138** (R<sup>1</sup> = Me) under identical conditions can be explained by steric reasons. In this case, the reaction stops in the step of formation of the *N*-acetyl derivatives **139**.

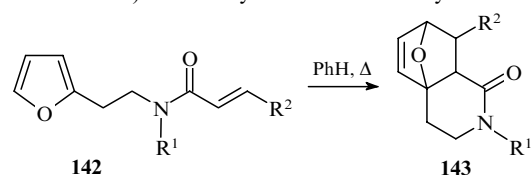
In a similar way, mono- and disubstituted furfurylamines **140** were transformed to hydrogenated epoxyisoquinolines **141** (yields 34%–42%).<sup>102</sup>



R<sup>1</sup> = Ph, 4-PhC<sub>6</sub>H<sub>4</sub>; R<sup>2</sup> = H, Me, Ph.

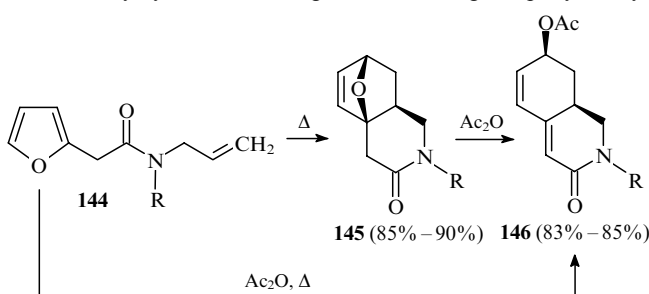
#### b. Synthesis of 4-aza-11-oxatricyclo[6.2.1.0<sup>1,6</sup>]undec-9-en-5-ones

There are only a few examples of the synthesis of these tricyclic systems.<sup>106, 107</sup> One of the first reports describes unsuccessful attempts of monocyclisation of *N*-unsubstituted acrylamide **142** (R<sup>1</sup> = R<sup>2</sup> = H). However, the *N*-methyl derivative gives the tricyclic adduct **143** in quantitative yield. The methyl group at the double bond of the alkenyl substituent considerably hinders this reaction: the expected epoxyoctahydroisoquinolone **143** (R<sup>1</sup> = R<sup>2</sup> = Me) could only be isolated in low yield.



R<sup>1</sup> = Me: R<sup>2</sup> = H (100%), Me (12%).

Synthesis of analogues of berberine alkaloids involved the intramolecular cyclisation of unsaturated furylacetetic amides **144**.<sup>106</sup> They cyclise on heating in toluene to give epoxyoctahydro-



R = H, Me, 3,4-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>(CH<sub>2</sub>)<sub>2</sub>.

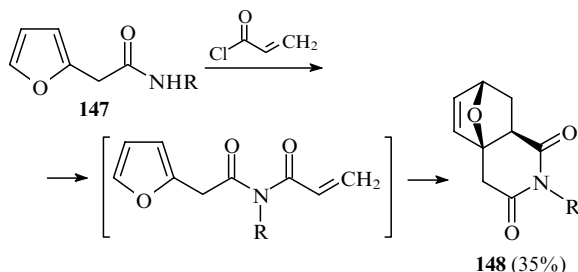
**Table 7.** Preparation of 4-spiroannellated 3-aza-11-oxatricycloundecenes **137**.

| R <sup>1</sup> | R <sup>2</sup>     | X                               | Reaction conditions                                     |               |              | Yield (%)       | Ref.          |
|----------------|--------------------|---------------------------------|---------------------------------------------------------|---------------|--------------|-----------------|---------------|
|                |                    |                                 | reagent (solvent)                                       | <i>T</i> / °C | <i>t</i> / h |                 |               |
| H              | Me                 | —                               | Ac <sub>2</sub> O                                       | 140           | 4            | 48              | 102, 103      |
| H              | Me                 | CH <sub>2</sub>                 | Ac <sub>2</sub> O                                       | 140           | 3            | 68–71           | 102, 103, 105 |
| H              | Me                 | (CH <sub>2</sub> ) <sub>2</sub> | Ac <sub>2</sub> O                                       | 140           | 3            | 66              | 102, 103      |
| H              | Me                 | CHBu <sup>t</sup>               | Ac <sub>2</sub> O                                       | 140           | 5            | 69              | 102, 103      |
| H              | Me                 | NMe                             | Ac <sub>2</sub> O                                       | 140           | 3            | 50              | 102           |
| H              | Me                 | NEt                             | Ac <sub>2</sub> O                                       | 140           | 3            | 48              | 102, 103      |
| H              | H                  | CH <sub>2</sub>                 | HCO <sub>2</sub> H, Ac <sub>2</sub> O (3 : 1)           | 101           | 5            | 22              | 102           |
| H              | Et                 | CH <sub>2</sub>                 | (EtCO) <sub>2</sub> O                                   | 160           | 4            | 52              | 102           |
| H              | CH <sub>2</sub> Cl | CH <sub>2</sub>                 | ClCH <sub>2</sub> COCl, Et <sub>3</sub> N (MeCN)        | 25            | 4            | 40              | 102           |
| H              | Ph                 | CH <sub>2</sub>                 | PhCOCl, Et <sub>3</sub> N (PhMe)                        | 110           | 3            | 61              | 102           |
| H              | CF <sub>3</sub>    | CH <sub>2</sub>                 | (F <sub>3</sub> CCO) <sub>2</sub> O ( <i>o</i> -xylene) | 140           | 5            | 40              | 102           |
| H              | H                  | (CH <sub>2</sub> ) <sub>2</sub> | HCO <sub>2</sub> H, Ac <sub>2</sub> O (3 : 1)           | 101           | 5            | 23              | 102           |
| H              | Et                 | (CH <sub>2</sub> ) <sub>2</sub> | (EtCO) <sub>2</sub> O                                   | 160           | 4            | 56              | 102           |
| H              | CH <sub>2</sub> Cl | (CH <sub>2</sub> ) <sub>2</sub> | ClCH <sub>2</sub> COCl, Et <sub>3</sub> N (MeCN)        | 25            | 4            | 38              | 102           |
| H              | Ph                 | (CH <sub>2</sub> ) <sub>2</sub> | PhCOCl, Et <sub>3</sub> N (PhMe)                        | 110           | 3            | 56              | 102           |
| H              | CF <sub>3</sub>    | (CH <sub>2</sub> ) <sub>2</sub> | (F <sub>3</sub> CCO) <sub>2</sub> O ( <i>o</i> -xylene) | 140           | 5            | 40              | 102           |
| Me             | Me                 | CH <sub>2</sub>                 | Ac <sub>2</sub> O                                       | 140           | 4            | 69 <sup>a</sup> | 102           |
| Me             | Me                 | (CH <sub>2</sub> ) <sub>2</sub> | Ac <sub>2</sub> O                                       | 140           | 4            | 67 <sup>a</sup> | 102           |

<sup>a</sup> The yields of compounds **139** are indicated.

droisoquinolones **145**; opening of the oxygen bridge upon treatment with acetic anhydride results in diene **146**. These compounds can also be prepared in one step by heating alkenylfurans **144** with an excess of acetic anhydride.

Acylation of the amide **147** with acryloyl chloride yields the tricyclic compound **148** in one step. In both cases considered, the [4+2]-cycloaddition is stereoselective: compounds **145** and **148** represent *exo*-adducts.

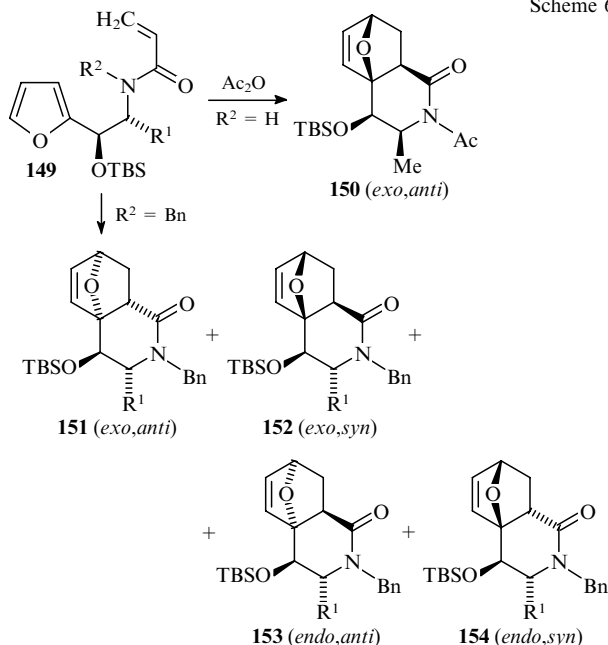


R = 3,4-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>(CH<sub>2</sub>)<sub>2</sub>.

The thermal intramolecular [4+2]-cycloaddition in the amides **149** occurs smoothly; the reaction products are formed in high yields.<sup>107, 108</sup> The hydrogenated *N*-acetyloxyisoquinolone **150** was prepared by treatment of alkenylfuran **149** (R<sup>2</sup> = H) with acetic anhydride (yield 47%) (Scheme 6).

The stereoselectivity of the intramolecular cycloaddition of *N*-acryloylfuryl ethylamine **149** (R<sup>2</sup> = Bn) depends on the steric effect of the substituent R<sup>1</sup>. Of the four possible geometric isomers, in the case of small groups (R<sup>1</sup> = H, Me, CN), the *exo,anti*-adduct **151** is predominant. The selectivity of the cycloaddition decreases with an increase in the size of the substituent. For R<sup>1</sup> = Et, *exo,syn*- (**152**) and *endo,anti*-adducts (**153**) appear; for R<sup>1</sup> = Ph, the latter becomes predominant. It is interesting to

Scheme 6



R<sup>1</sup> = H, Bn; TBS is *tert*-butyldimethylsilyl.

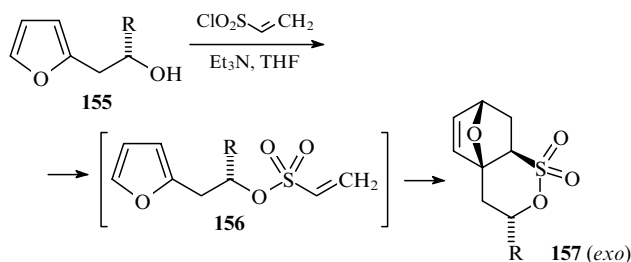
| R <sup>1</sup> | Product [yield (%)]                               |
|----------------|---------------------------------------------------|
| H              | <b>151</b> [90]                                   |
| Me             | <b>151</b> [74]                                   |
| Et             | <b>151</b> [42], <b>152</b> [22], <b>153</b> [20] |
| Ph             | <b>151</b> [8], <b>153</b> [42]                   |
| CN             | <b>151</b> [87]                                   |

note that the *endo,syn*-isomer **154** was found in none of the cases studied. The yields of compounds were determined after separation of the isomers by column chromatography.

### c. Synthesis of 11-oxatricyclo[6.2.1.0<sup>1,6</sup>]undec-9-enes containing heteroatoms

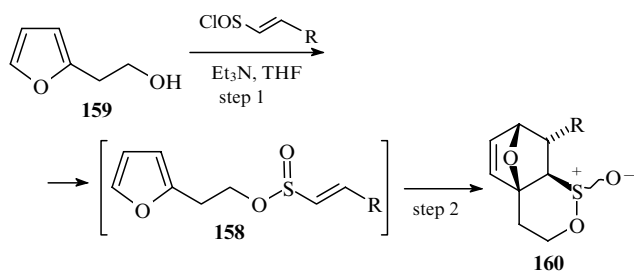
This section considers annelation of an additional six-membered ring containing different heteroatoms (except for nitrogen considered above) to 7-oxabicyclo[2.2.1]hept-2-enes.

Esterification of alcohols **155** with ethylenesulfonyl chloride yields the corresponding esters **156**.<sup>109</sup> However, these undergo intramolecular cycloaddition in the course of isolation; the Diels–Alder *exo*-adducts (sultones **157**) are formed in high yields.



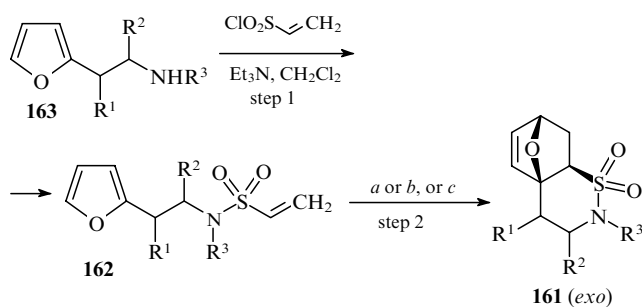
| R               | T / °C | t / h | Yield (%) |
|-----------------|--------|-------|-----------|
| Me              | 25     | 3     | 90        |
| Et              | 25     | 3     | 92        |
| Pr <sup>i</sup> | 0      | 1     | 87        |

A similar conversion of sulfinates **158** prepared from 2-(2-furyl)ethanol **159** and unsaturated sulfinyl chlorides has been described.<sup>91</sup> The presence of tetravalent sulfur hinders the intramolecular cycloaddition in comparison with sulfonates **156**; this reaction occurs either on heating or in the presence of Lewis acids as catalysts. The *exo*-adducts **160** are usually formed as mixtures of two isomers, like compounds **123** and **124** (see above), which differ in the relative positions of the S = O (or S<sup>+</sup>–O<sup>–</sup>) bond and the epoxide bridge. The isomer ratio depends on the reaction conditions and the catalyst used.<sup>91</sup>



| R                  | Conditions of step 2                                                               | Yield (%) |
|--------------------|------------------------------------------------------------------------------------|-----------|
| H                  | PhMe, 68 °C, 24 days                                                               | 54        |
|                    | PhMe, Et <sub>2</sub> AlCl (1.2 equiv.), 62 °C, 7 h                                | 53        |
|                    | CH <sub>2</sub> Cl <sub>2</sub> , Et <sub>2</sub> AlCl (1.2 equiv.), 25 °C, 2 days | 37        |
|                    | PhMe, ZnBr <sub>2</sub> (1.2 equiv.), 25 °C, 5 days                                | 30        |
| CO <sub>2</sub> Me | CH <sub>2</sub> Cl <sub>2</sub> , –30 °C, 19 h                                     | 42        |
|                    | CH <sub>2</sub> Cl <sub>2</sub> , ZnBr <sub>2</sub> (1.2 equiv.), 25 °C, 3.5 h     | 63        |

A two-step synthesis of sultams **161**, which includes the [4+2]-cycloaddition of vinylsulfonylamides **162** (see also Section IV.1.d, synthesis of compound **120**), has been described.<sup>89, 90</sup> *N*-Benzylvinylsulfonamide derivatives **162** prepared from substituted 2-(2-furyl)ethylamines **163** undergo cyclisation to *exo*-δ-sultams **161** even at room temperature.

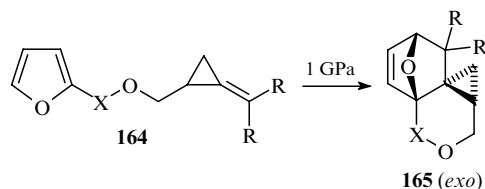


(a) Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 to 25 °C, 3 h; (b) PhMe, 110 °C, 16 h;  
(c) CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 1.3 GPa, 14 h.

| R <sup>1</sup> | R <sup>2</sup> | R <sup>3</sup>       | Conditions of step 2 | Yield (%) | Ref. |
|----------------|----------------|----------------------|----------------------|-----------|------|
| H              | Me             | Bn                   | <i>a</i>             | 78        | 89   |
| H              | Me             | ( <i>S</i> )-C*HMePh | <i>b</i>             | 85–87     | 90   |
|                |                |                      | <i>c</i>             | 98        | 90   |
| Me             | H              | Bn                   | <i>a</i>             | 92        | 89   |

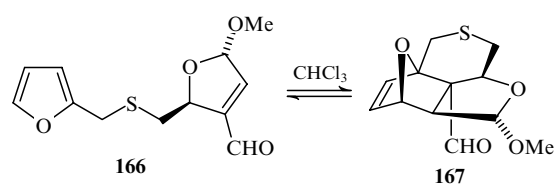
The stereochemistry of the intramolecular Diels–Alder reaction of diastereomeric amides **162** (R<sup>2</sup> = Me) prepared from the optically active (*S*)-(–)- $\alpha$ -methylbenzylamine has been studied. A detailed analysis of the diastereomeric composition of the tricyclic sultams **161** formed is carried out.<sup>90</sup> It is noteworthy that the cyclisation of *N*-phenethyl-substituted alkenylfurans **162** requires more drastic conditions than that of their *N*-benzyl analogues;<sup>89</sup> however, the yields of the adducts **161** are high in all cases.

A series of novel oxabicycloheptanes containing an oxygen atom or oxygen and silicon atoms in the annelated six-membered rings were prepared by intramolecular cycloaddition of methyl-enecyclopropylmethyl furyl ethers **164** at elevated pressure.<sup>88</sup> As in the previous cases, *exo*-3,11-dioxatricyclo[6.2.1.0<sup>1,6</sup>]undec-9-enes **165**, the fused cyclopropane ring of which occupies the *trans*-position relative to the epoxide bridge, are formed selectively.

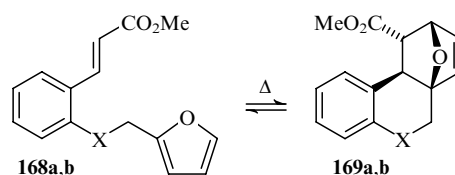


| R–R                                    | X                 | Solvent           | <i>T</i> / °C | <i>t</i> / h | Yield (%) |
|----------------------------------------|-------------------|-------------------|---------------|--------------|-----------|
| 2 H                                    | CH <sub>2</sub>   | MeCN–THF (1 : 1)  | 85            | 45           | 47        |
|                                        |                   | MeCN–THF (1 : 1)  | 100           | 20           | 50        |
| 2 H<br>(CH <sub>2</sub> ) <sub>2</sub> | SiMe <sub>2</sub> | Et <sub>2</sub> O | 125           | 30           | 25        |
|                                        |                   | MeCN–THF (1 : 1)  | 70            | 48           | 46        |
| (CH <sub>2</sub> ) <sub>2</sub>        | CH <sub>2</sub>   | MeCN–THF (1 : 1)  | 75            | 70           | 42        |
|                                        |                   | MeCN–THF (1 : 1)  | 75            | 70           | 42        |
| (CH <sub>2</sub> ) <sub>2</sub>        | SiMe <sub>2</sub> | Et <sub>2</sub> O | 130           | 20           | 83        |

The equilibrium between the sulfide **166** and the intramolecular cycloaddition product **167** in chloroform has been studied at different temperatures.<sup>110</sup> It was found that the equilibrium is established slowly and the concentration of the Diels–Alder adduct **167** increases with a decrease in the temperature. After 70 h at 25 °C, the ratio **166**:**167** was 72 : 28, whereas after 53 h at 60 °C it had changed to 56 : 44. The adduct **167** formed with diastereoselectivity > 99% was isolated by column chromatography on silica gel (eluent, heptane–Et<sub>3</sub>N) (yield 71%).

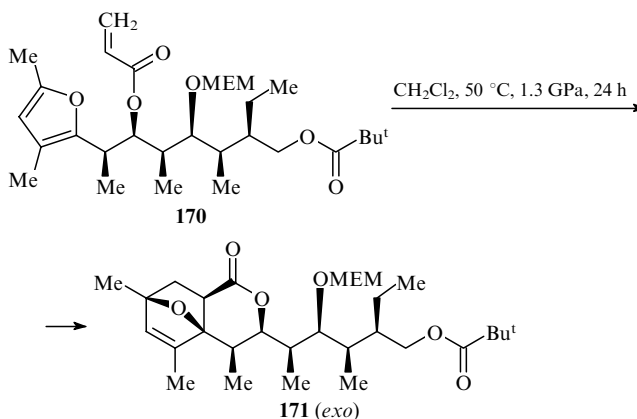


A similar reversible intramolecular [4 + 2]-cycloaddition was described for the *ortho*-substituted cinnamates **168a,b**.<sup>111</sup> Upon boiling in toluene (**168b**, 7 h) or xylene (**168a**, 47 h), these compounds are converted to fused heterocycles **169** in low yields.



X = O (**a**, 8%), NEt (**b**, 34%).

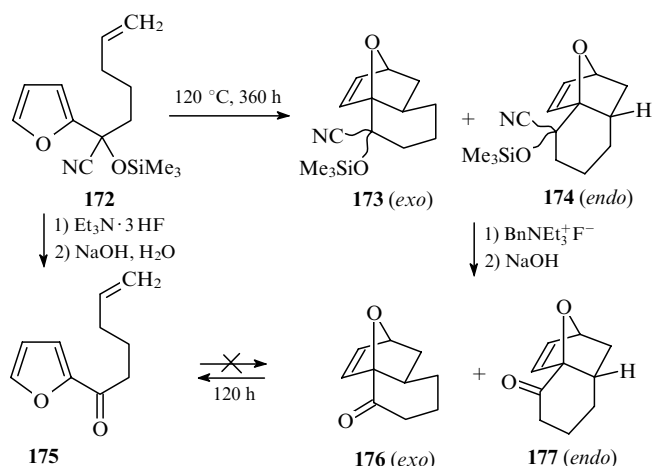
The cyclisation of unsaturated furan derivative **170** can be achieved only at elevated pressure.<sup>112</sup> The *exo*-adduct **171**, which represents an individual stereoisomer, is formed in 28% yield.



MEM = CH<sub>2</sub>O(CH<sub>2</sub>)<sub>2</sub>OMe.

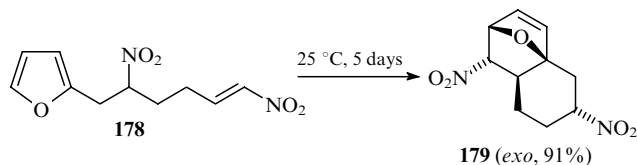
#### d. Synthesis of 11-oxatricyclo[6.2.1.0<sup>1,6</sup>]undec-9-enes

The intramolecular Diels–Alder reaction of unsaturated furan derivatives that results in 11-oxatricyclo[6.2.1.0<sup>1,6</sup>]undec-9-enes is explored much better (in a large measure, owing to the studies by Keay *et al.* and by De Clercq *et al.*) than the cyclisation of their aforementioned heterocyclic analogues. This can be attributed to the fact that the hydrogenated epoxynaphthalenes thus formed are easily converted into polysubstituted decalins which represent structural fragments of steroids and terpenes. This reaction is attractive from the synthetic standpoint, since the formation of *exo*-adducts occurs with high stereoselectivity with only few exceptions. Successful intramolecular cycloaddition usually requires the presence of electron-withdrawing groups at the double bond of the alkenyl substituent. There are only a few examples concerning successful cyclisation of alkenylfurans containing non-activated unsaturated fragments.<sup>113, 114</sup> Thus cyanotrimethylsilyloxyhexenyl derivative **172** undergoes slow cyclisation on heating at 120 °C to yield a mixture of isomers **173** and **174**. The stereoselectivity of this reaction is rather low: the *exo:endo* ratio is 88 : 12 and the total yield is 77%.<sup>114</sup>



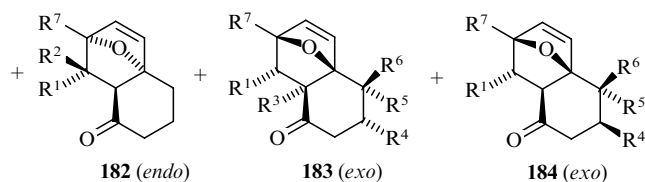
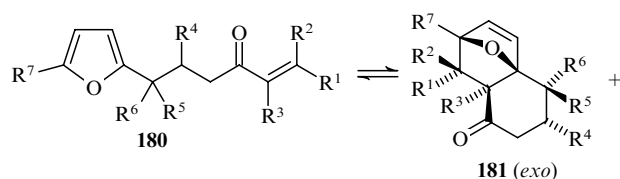
Attempts to perform the intramolecular cycloaddition of acylfuran **175**, which is a furan **172** analogue, failed. Epoxyoctahydronaphthalenes **176** and **177**, which represent the desilylation products of the isomers **173** and **174**, are quantitatively converted into acylfuran **175** upon retro-Diels–Alder reaction at high temperatures.

Stereoselective cyclisation of 2-alkenylfuran **178**, which contains a dienophile fragment activated by a nitro group, occurs smoothly even at 25 °C and yields tricyclic *exo*-adduct **179**.<sup>115</sup> In all probability, the transition state that would yield the *endo*-isomer is destabilised by the 1,3-diaxial interaction of the oxygen atom of the epoxide bridge with the nitro group.



In one of the pioneering works<sup>116</sup> devoted to the synthesis of unsubstituted 11-oxatricyclo[6.2.1.0<sup>1,6</sup>]undec-9-ene, the thermal intramolecular cyclisation of 3-furylpropylvinyl ketone **180** ( $\text{R}^1\text{--}\text{R}^7 = \text{H}$ ) under variable conditions was studied. This reaction was found to be reversible; the best yield of the adduct **181** (> 70%) was attained in boiling  $\text{CH}_2\text{Cl}_2$  or at room temperature in the presence of Florisil® (a weak Lewis acid which represents a mixture of magnesium silicates). The equilibrium could be shifted towards the adduct **181** ( $\text{R}^1\text{--}\text{R}^7 = \text{H}$ ) only at elevated pressure.<sup>78, 117</sup> Using NMR spectroscopy, it was shown that 10 min exposure of the ketone **180** ( $\text{R}^1\text{--}\text{R}^7$ ) at room temperature and 1 GPa resulted in its quantitative cyclisation to yield a mixture of *exo*- and *endo*-epoxyoctahydronaphthalenes **181** and **182** (95 : 5).<sup>78, 117</sup>

The intramolecular Diels–Alder reaction of substituted 3-furylalkylvinyl ketones **180** yields four stereoisomeric cycloadducts, *viz.*, compounds **181**–**184** (in the absence of substituents, the *exo*-structures are degenerate). This process was studied in great detail (see Table 8; the cited data were predominantly taken from the works by Keay *et al.*).



In addition to the experimental work,<sup>118–125</sup> the same group of investigators have performed a series of theoretical calculations<sup>127, 128</sup> of the effects of substituents  $\text{R}^1\text{--}\text{R}^7$  and reaction conditions (*e.g.*, the use of Lewis acids as catalysts, variation of temperature) on the intramolecular Diels–Alder reactions of methyl-substituted 3-furylpropylvinyl ketones **180**, which yield 11-oxatricyclo[6.2.1.0<sup>1,6</sup>]undec-9-enes.

Based on the data obtained (Table 8), the following conclusions can be made. Lewis acids shift the equilibrium of the intramolecular cycloaddition of alkenylfurans **180** towards the adducts **181** and **182**. These included  $\text{ZnI}_2$  (see Refs 121 and 125),  $\text{SnCl}_4$ ,  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{TiCl}_4$ ,<sup>121</sup>  $\text{Et}_2\text{AlCl}$ ,  $\text{MeAlCl}_2$ ,<sup>120–123</sup> 2 M  $\text{CaCl}_2$ ,<sup>118, 119, 121</sup> Florisil,<sup>120, 121, 123, 124</sup> molecular sieves 3 Å<sup>125</sup> and some other catalysts in various solvents in the temperature interval from –78 to 80 °C (see Table 8). Hexane and toluene are undesirable as solvents for this reaction. Dichloromethane proved to be the solvent of choice, while ethyl- and methylaluminium dichlorides ( $\text{RAlCl}_2$ ,  $\text{R} = \text{Me}, \text{Et}$ ) and Florisil were the most efficient catalysts. A high degree of conversion of the substrates was also observed in the presence of titanium chloride or boron trifluoride etherate, but this was accompanied by resinification even at low temperatures.<sup>121</sup>  $\text{MeAlCl}_2$  manifested the highest catalytic activity from –78 to 65 °C,<sup>120</sup> while Florisil ensures good yields of the Diels–Alder adducts **183** and **184** at room or elevated temperatures (25–40 °C).

Interestingly, the cyclisation rate depended on the amount of the catalyst used. For example, the yield of the Diels–Alder adducts with 10 mol.% of  $\text{MeAlCl}_2$  was higher than in the presence of its 110% molar excess.<sup>121</sup> In this case, the equilibrium  $\text{183} \rightleftharpoons \text{180}$  was established after 5 min and the product : substrate ratio was ~1 : 2. A second stereoisomer (compound **184**, 14%) was detected in the reaction medium after 5 min in the presence of 0.1 equiv. of  $\text{MeAlCl}_2$ ; its concentration dropped to zero with time.<sup>121–123</sup> The NMR<sup>127</sup> and quantum chemical calculations<sup>128</sup> suggest that the position of equilibrium of the cycloaddition is controlled by the Lewis acid. The amount of catalyst required for this reaction is determined by the relative basicities of the functional groups in the starting compounds and cyclisation products, since the latter form complexes with the Lewis acid. If the basicities of the functional groups in the final product are lower than in the original alkenylfuran **180**, the epoxyoctahydronaphthalene–Lewis acid complex formed easily dissociates with the regeneration of the catalyst. In this case, the latter should be used in catalytic amounts in order to promote the reaction. If the basicities of the functional groups in the product exceed those in the original alkenylfuran **180**, the complex formed is stable and 1 equiv. of the Lewis acid should be added.

No unambiguous conclusions concerning the effect of substituents on the cyclisation of alkenylfurans **180** can be made. It is evident, however, that the introduction of methyl groups ( $\text{R}^5 = \text{R}^6 = \text{Me}$ ) into the alkenyl fragment of furan **180** favours the reaction due to manifestation of the *gem*-dialkyl effect.

It was demonstrated<sup>124</sup> that in the presence of a 10-fold excess (by weight) of Florisil an equilibrium was established between alkenylfuran **180** and the *exo*-adducts **181** and **183**; the yields of the latter increase with temperature and reaction time.

The cyclisation of methyl-substituted alkenylfurans **180** [ $\text{R}^1(\text{R}^3, \text{R}^7) = \text{Me}$ ] was studied under varied conditions including aqueous media and elevated pressure.<sup>118, 119</sup> These studies showed that the presence of methyl groups in both the furan ring and at the double bond of the starting compounds prevents the formation of

**Table 8.** Cyclisation of 3-furylpropyl vinyl ketones **180**.

| R <sup>1</sup> | R <sup>2</sup> | R <sup>3</sup> | R <sup>4</sup> | R <sup>5</sup> | R <sup>6</sup> | R <sup>7</sup> | Reaction conditions                                                                                                  | Composition of the reaction mixture [product, yield (%)] <sup>a</sup> | Ref.         |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|--------------|
| H              | H              | H              | H              | H              | H              | H              | H <sub>2</sub> O, 25 °C, 4 days                                                                                      | <b>181</b> : <b>180</b> = 1 : 1 (69) <sup>b</sup>                     | 119          |
|                |                |                |                |                |                |                | CaCl <sub>2</sub> (2 M), 25 °C, 4–6 days                                                                             | <b>181</b> : <b>180</b> = 1 : 1 (66) <sup>b</sup>                     | 118, 119     |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 6 days                                                            | <b>181</b> : <b>180</b> = 9 : 1 ( <b>181</b> , 62–72)                 | 116, 118–121 |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 1 h                                      | <b>181</b> (99)                                                       | 120, 121     |
|                |                |                |                |                |                |                | CH <sub>2</sub> Cl <sub>2</sub> , 0.5 GPa, 20 °C, 12 h                                                               | <b>181</b> (65)                                                       | 118          |
|                |                |                |                |                |                |                | CH <sub>2</sub> Cl <sub>2</sub> , 1 GPa, 20 °C, 10 min                                                               | <b>181</b> : <b>182</b> = 95 : 5                                      | 78           |
|                |                |                |                |                |                |                | CH <sub>2</sub> Cl <sub>2</sub> , 1.2 GPa, 25 °C, 25 h                                                               | <b>181</b> (51)                                                       | 118, 120     |
| H              | H              | H              | H              | H              | H              | Me             | H <sub>2</sub> O, 25 °C, 4 days                                                                                      | <b>181</b> : <b>180</b> = 1 : 3 ( <b>181</b> , 72)                    | 119          |
|                |                |                |                |                |                |                | CaCl <sub>2</sub> (2 M), 25 °C, 4–6 days                                                                             | <b>181</b> : <b>180</b> = 1 : 2 (68–78) <sup>b</sup>                  | 118, 119     |
|                |                |                |                |                |                |                | fluorosil, <sup>c</sup> CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 14 days                                             | <b>181</b> : <b>180</b> = 7 : 1 ( <b>181</b> , 65)                    | 119          |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 14 days                                                          | <b>181</b> : <b>180</b> = 88 : 12 ( <b>181</b> , 65)                  | 121          |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 14 days                                                           | <b>181</b> : <b>180</b> = 88 : 12 ( <b>181</b> , 52)                  | 120          |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 1 h                                      | <b>181</b> (99)                                                       | 120, 121     |
|                |                |                |                |                |                |                | CH <sub>2</sub> Cl <sub>2</sub> , 1 GPa, 20 °C, 10 min                                                               | <b>181</b> (100)                                                      | 78           |
|                |                |                |                |                |                |                | CH <sub>2</sub> Cl <sub>2</sub> , 1.25 GPa, 25 °C, 24 h                                                              | <b>181</b> (56)                                                       | 118, 120     |
| H              | H              | Me             | H              | H              | H              | H              | H <sub>2</sub> O, 25 °C, 4 days                                                                                      | <b>181</b> : <b>180</b> = 2 : 1 (70) <sup>b</sup>                     | 119          |
|                |                |                |                |                |                |                | fluorosil, <sup>c</sup> CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 14 days                                             | see <sup>d</sup>                                                      | 119          |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 14 days                                                           | <b>181</b> : <b>180</b> = 7 : 1 (65)                                  | 118          |
|                |                |                |                |                |                |                | CaCl <sub>2</sub> (2 M), 25 °C, 4–6 days                                                                             | <b>181</b> : <b>180</b> = 1 : 2 (68) <sup>b</sup>                     | 118          |
|                |                |                |                |                |                |                | CaCl <sub>2</sub> (2 M), 25 °C, 4 days                                                                               | <b>181</b> : <b>180</b> = 4 : 1 (73) <sup>b</sup>                     | 119          |
|                |                |                |                |                |                |                | CaCl <sub>2</sub> (2 M), 25 °C, 4 days                                                                               | <b>181</b> : <b>180</b> = 1 : 1                                       | 121          |
|                |                |                |                |                |                |                | ZnI <sub>2</sub> , CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 1 h                                                     | see <sup>d</sup>                                                      | 121          |
|                |                |                |                |                |                |                | ZnI <sub>2</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 3 h                                                      | <b>181</b> : <b>180</b> = 31 : 69                                     | 121          |
|                |                |                |                |                |                |                | ZnI <sub>2</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 39 h                                                     | <b>181</b> : <b>180</b> = 35 : 65                                     | 121          |
|                |                |                |                |                |                |                | SnCl <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 1 h                                                    | <b>181</b> : <b>180</b> = 76 : 24                                     | 121          |
|                |                |                |                |                |                |                | BF <sub>3</sub> ·OEt <sub>2</sub> , CH <sub>2</sub> Cl <sub>2</sub> ,<br>–78 or –50 °C, 2.5–3.5 h                    | <b>181</b> : <b>180</b> = 72 : 28                                     | 121          |
|                |                |                |                |                |                |                | TiCl <sub>4</sub> ·Ti(OPr <sup>i</sup> ) <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> ,<br>–78 or 50 °C, 2.5–4.5 h | <b>181</b> : <b>180</b> = 68 : 32                                     | 121          |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> , CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 2.5 h                                                | <b>181</b> : <b>180</b> = 78 : 22 ( <b>181</b> , 76)                  | 120          |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> ,<br>–78 or –50 °C, 2.5 h                          | <b>181</b> : <b>180</b> = 65 : 35 ( <b>181</b> , 63)                  | 121          |
|                |                |                |                |                |                |                | EtAlCl <sub>2</sub> , CH <sub>2</sub> Cl <sub>2</sub> , –78 or –50 °C, 2.5 h                                         | <b>181</b> : <b>180</b> = 65 : 35                                     | 121          |
|                |                |                |                |                |                |                | Me <sub>2</sub> AlCl, CH <sub>2</sub> Cl <sub>2</sub> , –50 °C, 2.5 h                                                | <b>181</b> : <b>180</b> = 68 : 32                                     | 121          |
|                |                |                |                |                |                |                | Et <sub>2</sub> AlCl, CH <sub>2</sub> Cl <sub>2</sub> , –50 °C, 2.5 h                                                | <b>181</b> : <b>180</b> = 65 : 35                                     | 121          |
|                |                |                |                |                |                |                | CH <sub>2</sub> Cl <sub>2</sub> , 0.5 GPa, 20 °C, 12 h                                                               | see <sup>d</sup>                                                      | 118          |
|                |                |                |                |                |                |                | CH <sub>2</sub> Cl <sub>2</sub> , 1.25 GPa, 20 °C, 24 h                                                              | <b>181</b> (55)                                                       | 118          |
| H              | Ac             | H              | H              | H              | H              | H              | CH <sub>2</sub> Cl <sub>2</sub> , 1.9 GPa, 20 °C, 24 h                                                               | <b>181</b> : <b>182</b> = 15 : 85                                     | 78           |
| Me             | H              | H              | H              | H              | H              | H              | H <sub>2</sub> O, 25 °C, 4 days                                                                                      | <b>181</b> : <b>180</b> = 2 : 1 (70) <sup>b</sup>                     | 119          |
|                |                |                |                |                |                |                | Florisil or fluorosil, <sup>c</sup> CH <sub>2</sub> Cl <sub>2</sub> ,<br>–78 or 25 °C, 14 days                       | see <sup>d</sup>                                                      | 118–121      |
|                |                |                |                |                |                |                | CaCl <sub>2</sub> (2 M), 25 °C, 4–6 days                                                                             | <b>181</b> : <b>180</b> = 4 : 1 (73)                                  | 118          |
|                |                |                |                |                |                |                | CaCl <sub>2</sub> (2 M), 25 °C, 4 days                                                                               | <b>181</b> : <b>180</b> = 2 : 1 (69) <sup>b</sup>                     | 119          |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> , CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 8 h                                                  | <b>181</b> : <b>180</b> = 22 : 78 ( <b>181</b> , 11)                  | 120          |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 8 h                                      | <b>181</b> : <b>180</b> = 22 : 78 ( <b>181</b> , 11)                  | 121, 122     |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> ,<br>–65 or –78 °C, 2 h                            | <b>181</b> : <b>180</b> = 69 : 31 ( <b>181</b> , 66–69)               | 121, 122     |
|                |                |                |                |                |                |                | CH <sub>2</sub> Cl <sub>2</sub> , 1.25 GPa, 20 °C, 24 h                                                              | <b>181</b> (52)                                                       | 118          |
| Ac             | H              | H              | H              | H              | H              | H              | CH <sub>2</sub> Cl <sub>2</sub> , 1.9 GPa, 20 °C, 24 h                                                               | <b>181</b> : <b>182</b> : <b>180</b> = 70 : 15 : 15                   | 78           |
| H              | H              | H              | H              | H              | Me             | Me             | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 13 days                                                           | <b>183</b> : <b>181</b> = 87 : 13 ( <b>183</b> , 70)                  | 123          |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 40 °C, 24 h                                                              | <b>183</b> : <b>181</b> : <b>180</b> = 84 : 16 : 1 ( <b>183</b> , 67) | 123          |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 40 °C, 2 days                                                            | <b>183</b> : <b>181</b> : <b>180</b> = 75 : 18 : 7 ( <b>183</b> , 60) | 123          |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 15 min                                   | <b>183</b> : <b>181</b> = 9 : 1 ( <b>183</b> , 88)                    | 123          |
| H              | H              | H              | H              | Me             | H              | Me             | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h                                                               | <b>181</b> : <b>183</b> : <b>180</b> = 21 : 73 : 6                    | 124          |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 12 h                                                              | <b>181</b> : <b>183</b> : <b>180</b> = 43 : 43 : 14                   | 124          |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 40 °C, 24 h                                                              | <b>181</b> : <b>183</b> : <b>180</b> = 78 : 15 : 7                    | 124          |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 40 °C, 2 days                                                            | <b>181</b> : <b>183</b> : <b>180</b> = 75 : 18 : 7                    | 124          |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 14 days                                                           | <b>181</b> : <b>183</b> : <b>180</b> = 85 : 13 : 2                    | 124          |
| H              | H              | H              | H              | Me             | Me             | H              | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 6 days<br>or –78 °C, 12 h                                         | <b>181</b> (88)                                                       | 120, 121     |
| H              | H              | H              | Me             | H              | H              | Me             | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 12 h                                                              | <b>181</b> (100)                                                      | 124          |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 6 days                                                            | <b>183</b> (85)                                                       | 123          |



Table 8 (continued).

| R <sup>1</sup> | R <sup>2</sup> | R <sup>3</sup> | R <sup>4</sup> | R <sup>5</sup> | R <sup>6</sup> | R <sup>7</sup> | Reaction conditions                                                                    | Composition of the reaction mixture [product, yield (%)] <sup>a</sup> | Ref.          |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------|---------------|
| H              | H              | Me             | H              | H              | H              | Me             | H <sub>2</sub> O, 25 °C, 4 days                                                        | <b>181</b> : <b>180</b> = 1 : 1 (71) <sup>b</sup>                     | 119           |
|                |                |                |                |                |                |                | CaCl <sub>2</sub> (2 M), 25 °C, 4–6 days                                               | <b>181</b> : <b>180</b> = 2 : 1 (69–78) <sup>b</sup>                  | 118, 119      |
|                |                |                |                |                |                |                | CH <sub>2</sub> Cl <sub>2</sub> , 1.25 GPa, 20 °C, 24 h                                | <b>181</b> (50)                                                       | 118           |
| H              | H              | Me             | H              | H              | Me             | Me             | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 24 h                                | <b>183</b> : <b>181</b> : <b>180</b> = 27 : 1 : 73 ( <b>183</b> , 22) | 123           |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 4 days                              | <b>183</b> : <b>181</b> : <b>180</b> = 35 : 1 : 65 ( <b>183</b> , 28) | 123           |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 13 days                             | <b>183</b> : <b>181</b> : <b>180</b> = 47 : 4 : 48 ( <b>183</b> , 38) | 123           |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 5 min      | <b>183</b> : <b>181</b> : <b>180</b> = 88 : 3 : 9 ( <b>183</b> , 81)  | 123           |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 8 h        | <b>181</b> : <b>180</b> = 81 : 19 ( <b>181</b> , 80)                  | 120–122       |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 °C, 2 h        | <b>181</b> (98)                                                       | 122           |
| H              | H              | Me             | H              | H              | H              | Me             | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 2 h        | <b>181</b> (99)                                                       | 121           |
| H              | Ac             | H              | H              | H              | H              | Me             | CH <sub>2</sub> Cl <sub>2</sub> , 1.9 GPa, 20 °C, 24 h                                 | <b>181</b> : <b>182</b> = 34 : 30                                     | 78, 117       |
| Me             | H              | H              | H              | H              | H              | Me             | CaCl <sub>2</sub> (2 M), 25 °C, 4–6 days                                               | <b>181</b> : <b>180</b> = 1 : 2 (61) <sup>b</sup>                     | 118, 119      |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 or –78 °C, 6 days                       | see <sup>d</sup>                                                      | 118, 120, 121 |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 8 h        | <b>181</b> : <b>180</b> = 18 : 82 ( <b>181</b> , 18)                  | 120–122       |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 °C, 2 h        | <b>181</b> : <b>180</b> = 76 : 24 ( <b>181</b> , 73)                  | 122           |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 2 h        | <b>181</b> : <b>180</b> = 76 : 24 ( <b>181</b> , 74)                  | 121           |
|                |                |                |                |                |                |                | CH <sub>2</sub> Cl <sub>2</sub> , 1.25 GPa, 20 °C, 24 h                                | <b>181</b> (43)                                                       | 118           |
| Ac             | H              | H              | H              | H              | H              | Me             | CH <sub>2</sub> Cl <sub>2</sub> , 1.9 GPa, 20 °C, 24 h                                 | <b>181</b> : <b>182</b> = 95 : 5                                      | 78, 117       |
| Ac             | H              | H              | H              | H              | OMe            | H              | CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 24 h                                          | see <sup>d</sup>                                                      | 125           |
|                |                |                |                |                |                |                | Et <sub>2</sub> O, SiO <sub>2</sub> , 20 °C, 0.5 h                                     | <b>181</b> (15)                                                       | 125           |
|                |                |                |                |                |                |                | 3 Å sieves, PhMe, 110 °C, 24 h                                                         | see <sup>d</sup>                                                      | 125           |
|                |                |                |                |                |                |                | 3 Å sieves, CH <sub>2</sub> Cl <sub>2</sub> , 0 °C, 6 h                                | <b>181</b> (27)                                                       | 125           |
|                |                |                |                |                |                |                | 3 Å sieves, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 24 h                              | <b>181</b> (40)                                                       | 125           |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 2 days                              | <b>181</b> (44)                                                       | 125           |
|                |                |                |                |                |                |                | ZnI <sub>2</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 2 days                     | <b>181</b> (67)                                                       | 125           |
| Me             | H              | H              | Me             | H              | H              | H              | MeAlCl <sub>2</sub> , CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 5 h                    | <b>181</b> : <b>184</b> = 8.6 : 1 (92)                                | 126           |
| Me             | H              | Me             | H              | H              | H              | H              | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 2 h        | see <sup>d</sup>                                                      | 121           |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 2 h        | <b>181</b> : <b>180</b> = 5 : 95 ( <b>181</b> , 4)                    | 121           |
| H              | H              | H              | H              | Me             | Me             | Me             | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 12 h                                | <b>181</b> (96)                                                       | 120           |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 12 h                               | <b>181</b> (96)                                                       | 121           |
| H              | H              | Me             | Me             | H              | H              | Me             | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 5 days                              | <b>183</b> : <b>180</b> = 38 : 62                                     | 123, 124      |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 9 days                              | <b>183</b> : <b>180</b> = 48 : 52                                     | 123, 124      |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 19 days                             | <b>183</b> : <b>180</b> = 50 : 50                                     | 123, 124      |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 40 °C, 24 h                                | <b>183</b> : <b>180</b> = 45 : 55                                     | 123, 124      |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 40 °C, 2 days                              | <b>183</b> : <b>180</b> = 44 : 56 ( <b>183</b> , 37)                  | 123, 124      |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 5 min      | <b>183</b> : <b>180</b> = 89 : 11 ( <b>183</b> , 88)                  | 124           |
| H              | H              | Me             | H              | Me             | Me             | H              | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 24 h                                | <b>181</b> : <b>180</b> = 17 : 83 ( <b>181</b> , 6)                   | 120           |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 24 h                               | <b>181</b> : <b>180</b> = 17 : 83 ( <b>181</b> , 16)                  | 121           |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 8 h        | <b>181</b> : <b>180</b> = 32 : 68 ( <b>181</b> , 31)                  | 120–122       |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 °C, 2 h        | <b>181</b> : <b>180</b> = 6 : 4 ( <b>181</b> , 58)                    | 122           |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 2 h        | <b>181</b> : <b>180</b> = 60 : 40 ( <b>181</b> , 60)                  | 121           |
| Me             | H              | H              | H              | Me             | Me             | H              | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 192 h                               | <b>181</b> : <b>180</b> = 13 : 87 ( <b>181</b> , 12)                  | 120, 121      |
|                |                |                |                |                |                |                | or –78 °C, 8 days                                                                      |                                                                       |               |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 8 h        | <b>181</b> : <b>180</b> = 27 : 73 ( <b>181</b> , 22)                  | 120–122       |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 or –78 °C, 2 h | <b>181</b> : <b>180</b> = 73 : 27 ( <b>181</b> , 70)                  | 121, 122      |
| Me             | H              | H              | H              | Me             | H              | Me             | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 24 h                                | <b>183</b> : <b>180</b> = 69 : 3                                      | 123           |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 4 days                              | <b>183</b> : <b>181</b> : <b>180</b> = 11 : 1 : 89 ( <b>183</b> , 9)  | 123           |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 13 days                             | <b>183</b> : <b>181</b> : <b>180</b> = 19 : 8 : 73 ( <b>183</b> , 15) | 123           |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 5 min      | <b>183</b> : <b>181</b> : <b>180</b> = 16 : 5 : 79 ( <b>183</b> , 15) | 123           |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 °C, 2 h        | <b>183</b> : <b>181</b> : <b>180</b> = 75 : 4 : 17 ( <b>183</b> , 74) | 123           |
| Me             | H              | H              | Me             | H              | H              | Me             | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 40 °C, 24 h                                | <b>183</b> : <b>180</b> = 15 : 85 ( <b>183</b> , 13)                  | 123, 124      |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 5 days                              | <b>183</b> : <b>180</b> = 17 : 83                                     | 123, 124      |
|                |                |                |                |                |                |                | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 8 days                              | <b>183</b> : <b>180</b> = 1 : 4 ( <b>183</b> , 16)                    | 123, 124      |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 °C, 5 min      | <b>183</b> : <b>184</b> : <b>180</b> = 31 : 8 : 61 ( <b>183</b> , 30) | 122, 123      |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 °C, 15 min     | <b>183</b> : <b>180</b> = 19 : 81                                     | 122           |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 °C, 30 min     | <b>183</b> : <b>180</b> = 22 : 78                                     | 122           |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 °C, 1 h        | <b>183</b> : <b>180</b> = 33 : 67                                     | 122           |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 °C, 2 h        | <b>183</b> : <b>180</b> = 28 : 72                                     | 122           |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 °C, 4 h        | <b>183</b> : <b>180</b> = 30 : 70                                     | 122           |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 °C, 5 min      | <b>183</b> : <b>184</b> : <b>180</b> = 14 : 14 : 72                   | 122           |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 °C, 15 min     | <b>183</b> : <b>184</b> : <b>180</b> = 27 : 18 : 55                   | 122           |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 °C, 30 min     | <b>183</b> : <b>184</b> : <b>180</b> = 41 : 27 : 32                   | 122           |

Table 8 (continued).

| R <sup>1</sup> | R <sup>2</sup> | R <sup>3</sup> | R <sup>4</sup> | R <sup>5</sup> | R <sup>6</sup> | R <sup>7</sup> | Reaction conditions                                                                    | Composition of the reaction mixture [product, yield (%)] <sup>a</sup> | Ref.     |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------|----------|
| Me             | H              | H              | Me             | H              | H              | Me             | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 °C, 1 h        | <b>183</b> : <b>184</b> : <b>180</b> = 58:13:29                       | 122      |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 °C, 2 h        | <b>183</b> : <b>184</b> : <b>180</b> = 87:2:11 ( <b>183</b> , 83)     | 122, 123 |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 °C, 4 h        | <b>183</b> : <b>184</b> : <b>180</b> = 77:6:17                        | 122      |
| H              | H              | Me             | H              | Me             | Me             | Me             | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 10 days                             | <b>181</b> : <b>180</b> = 23:77 ( <b>181</b> , 19)                    | 120, 121 |
|                |                |                |                |                |                |                | or –78 °C, 10 days                                                                     |                                                                       |          |
| H              | H              | Me             | H              | Me             | Me             | Me             | MeAlCl <sub>2</sub> , CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 8 h                    | <b>181</b> : <b>180</b> = 23:78 ( <b>181</b> , 22)                    | 120      |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 8 h        | <b>181</b> : <b>180</b> = 22:78 ( <b>181</b> , 18–22)                 | 121, 122 |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 to –78 °C, 2 h | <b>181</b> : <b>180</b> = 77:23 ( <b>181</b> , 75)                    | 121, 122 |
| Me             | H              | H              | H              | Me             | Me             | Me             | Florisil, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 14 days                             | <b>181</b> : <b>180</b> = 15:85 ( <b>181</b> , 13)                    | 121, 122 |
|                |                |                |                |                |                |                | or –78 °C, 14 days                                                                     |                                                                       |          |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 8 h        | <b>183</b> : <b>184</b> : <b>180</b> = 18:6:78 ( <b>181</b> , 15–18)  | 120, 122 |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 2 h        | <b>181</b> : <b>180</b> = 31:69 ( <b>181</b> , 30)                    | 121      |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –65 °C, 2 h        | <b>183</b> : <b>184</b> : <b>180</b> = 79:4:17 ( <b>181</b> , 81)     | 122      |
| Me             | H              | Me             | H              | Me             | Me             | H              | MeAlCl <sub>2</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 2 h        | see <sup>d</sup>                                                      | 121      |
|                |                |                |                |                |                |                | MeAlCl <sub>2</sub> (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , –78 °C, 2 h        | see <sup>d</sup>                                                      | 121      |

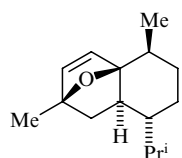
<sup>a</sup> The yields of isolated products are indicated; the compositions of the reaction mixtures were determined by <sup>1</sup>H NMR spectroscopy; <sup>b</sup> the yield of the adduct **181** calculated with respect to the amount of alkenylfuran **180** introduced into the reaction is indicated; <sup>c</sup> fluorosil is fluoroalkylsilicon; <sup>d</sup> the reaction does not occur.

the Diels–Alder adducts (see Table 8). The reaction equilibrium can be shifted towards the tricycles **181** either by increasing the pressure (1.25 GPa) or by conducting the reaction at room temperature in water with the addition of 2 M calcium chloride. It is interesting to note that no epoxynaphthalene **181** is formed in the presence of β-cyclodextrin or upon boiling in 2 M CaCl<sub>2</sub>.<sup>119</sup>

The cyclisation of alkenylfurans **180** containing an acetyl group at the double bond [R<sup>1</sup>(R<sup>2</sup>) = Ac] occurs at 1.9 GPa and yields a mixture of the *exo*- and *endo*-adducts **181** and **182**. The latter revert to the starting compounds at atmospheric pressure.<sup>78, 117</sup>

The cyclisation of 1,4-diketone **180** (R<sup>1</sup> = Ac, R<sup>6</sup> = OMe) was studied in detail.<sup>125</sup> It was established that the cycloaddition is successful only in the presence of Lewis acids, ZnI<sub>2</sub> being the most active (the yield of the adduct **181** was 67%).

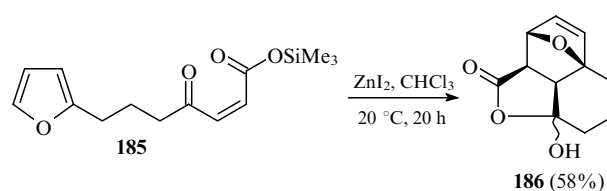
These results were successfully applied to the total synthesis of 1,4-epoxycadinane, a terpene isolated from the brown alga *Dilophus fasciola*.<sup>123, 124</sup>



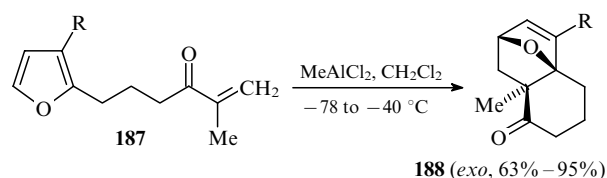
1,4-Epoxycadinane

Some chemical properties of 11-oxatricyclo[6.2.1.0<sup>1,6</sup>]undec-9-enes have been studied. Thus the reactions of epoxyoctahydronaphthalenes **181** and **183** (see Refs 118, 121, 124 and 125) with nucleophiles (primarily, with organolithium and organomagnesium derivatives),<sup>129</sup> and the Wagner–Meerwein rearrangement of compounds **181** were reported.<sup>130</sup>

The intramolecular cycloaddition in the keto ester **185**, a structural analogue of the above-described ketones **180**, in the presence of ZnI<sub>2</sub> is accompanied by desilylation. This reaction yields the tetracyclic lactone **186**.<sup>125</sup>



Only one paper<sup>131</sup> describes the effects of the substituents at position 3 of the furan ring on the course of the intramolecular Diels–Alder reaction of furylpropyl isopropenyl ketones **187**. In the presence of methylaluminium dichloride, the cyclisation proceeds stereoselectively and yields the *exo*-adducts **188**. For R = CH<sub>2</sub>OAlk, the yield of the product **188** was nearly quantitative. However, the reaction did not go to completion if an ester group (CO<sub>2</sub>Pr<sup>i</sup>) was introduced into the furan ring. In this case, the tricyclic ketone **188** was isolated from the reaction mixture in a moderate yield.

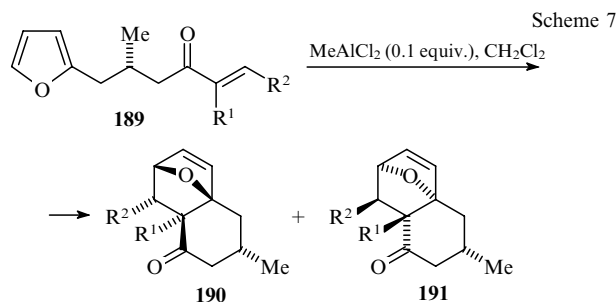


R = CH<sub>2</sub>OMe, CH<sub>2</sub>OBn, CO<sub>2</sub>Pr<sup>i</sup>.

The catalytic cyclisation of the optically active alkenylfuran **189** yields a mixture of diastereomeric methyl-substituted 11-oxatricyclo[6.2.1.0<sup>1,6</sup>]undec-9-enes **190** and **191** (Scheme 7).<sup>132</sup>

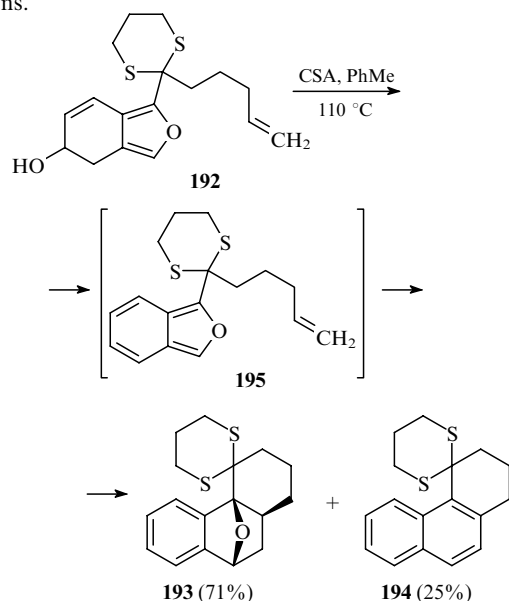
Several publications are devoted to the intramolecular cyclisation of furans [c]-annulated to partially hydrogenated benzene or thiophene rings.<sup>80, 85, 133</sup>

Upon boiling in toluene in the presence of catalytic amounts of camphorsulfonic acid, dihydroisobenzofuran **192** is converted into a mixture of spirans **193** and **194**.<sup>80</sup> Initially, dehydration results in unstable isobenzofuran **195**, which undergoes further rapid intramolecular cyclisation to the spiro-annulated octahydroepoxyphenanthrene **193**. The latter is partly aromatised

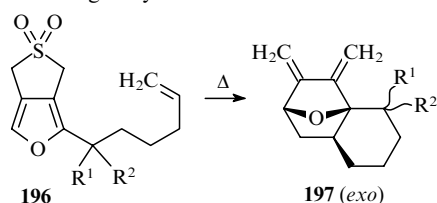


| R <sup>1</sup> | R <sup>2</sup> | T / °C | t / h | Ratio of<br>189 : 190 : 191 | Product [yield (%)]                           |
|----------------|----------------|--------|-------|-----------------------------|-----------------------------------------------|
| H              | H              | –78    | —     | 10 : 61 : 15                | <b>189</b> [10], <b>190</b> + <b>191</b> [76] |
| Me             | H              | –78    | 2     | 0 : 74 : 26                 | —                                             |
|                |                | –78    | 5.5   | 0 : 100 : 0                 | <b>190</b> [96]                               |
| H              | Me             | –78    | 2     | 10 : 55 : 35                | —                                             |
|                |                | –78    | 5.5   | 9 : 81 : 10                 | <b>190</b> + <b>191</b> [92]                  |
|                |                | –60    | 0.1   | 34 : 47 : 19                | —                                             |
|                |                | –60    | 0.5   | 6 : 83 : 11                 | —                                             |
|                |                | –60    | 2     | 4 : 92 : 4                  | —                                             |

into the tetrahydrophenanthrene **194** under the reaction conditions.



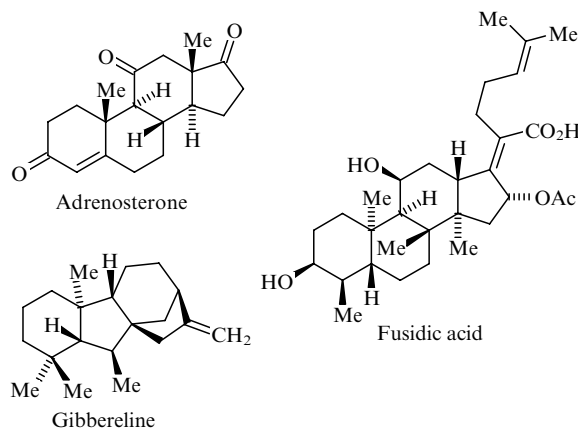
Thienofurans **196** are converted into the *exo*-adducts **197** upon boiling in xylene or benzene.<sup>85</sup>



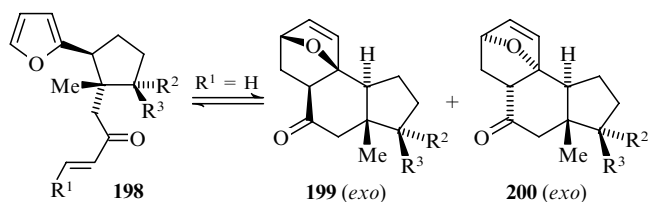
| R <sup>1</sup> –R <sup>2</sup>     | Reaction conditions  | Yield (%) |
|------------------------------------|----------------------|-----------|
| O                                  | xylene, 140 °C, 48 h | 0         |
| S(CH <sub>2</sub> ) <sub>2</sub> S | xylene, 140 °C, 2 h  | 70        |
| O(CH <sub>2</sub> ) <sub>3</sub> O | xylene, 140 °C, 2 h  | 74        |
| CN, OSiMe <sub>3</sub>             | PhH, 80 °C, 24 h     | 59        |

The stereodirection of the cycloaddition of furyl-substituted cyclopentanes has been studied by De Clercq *et al.*<sup>134–139</sup> This reaction is the key step in the total synthesis of a series of tetracyclic natural compounds, *e.g.*, 11-ketosteroids (including

adrenosterone) and diterpenoids. The natural antibiotic fusidic acid (ent-fusidic acid) and substituted gibberelins (ent-gibberellins) that possess phytohormonal properties and are used as plant growth factors provide illustrative examples of such compounds.



The intramolecular cyclisation of the water-soluble hydroxy ketones **198** into diastereomeric *exo*-adducts **199** and **200** was studied.<sup>134,135</sup> For compound **198** (R<sup>1</sup> = R<sup>2</sup> = H, R<sup>3</sup> = OH), this reaction is stereoselective and yields only the *exo*-adduct **200**. Water appeared to be the best solvent for this reaction. NMR studies have shown that compound **200** (R<sup>2</sup> = H, R<sup>3</sup> = OH) is formed in water within 10 min, whereas in chloroform or dichloromethane the equilibrium is shifted towards the starting furyl-containing cyclopentane **198**.<sup>134</sup>

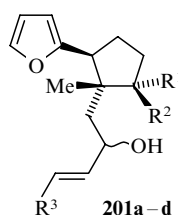


R<sup>1</sup> = H, Me.

| R <sup>2</sup>                     | R <sup>3</sup> | Reaction conditions                               | Ratio<br>198 : 199 : 200 | Product<br>[yield (%)] | Ref. |
|------------------------------------|----------------|---------------------------------------------------|--------------------------|------------------------|------|
| H                                  | OH             | CDCl <sub>3</sub> , 25 °C, 3 days                 | 0 : 0 : 100              | <b>200</b> [<10]       | 134  |
|                                    |                | (CD <sub>3</sub> ) <sub>2</sub> SO, 25 °C, 3 days | 0 : 0 : 100              | <b>200</b> [50]        | 134  |
|                                    |                | D <sub>2</sub> O, 25 °C, 10 min                   | 0 : 0 : 100              | <b>200</b> [>95]       | 134  |
| O(CH <sub>2</sub> ) <sub>2</sub> O |                | CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 7 days   | 25 : 20 : 55             | —                      | 135  |
|                                    |                | PhH, 80 °C, 24 h                                  | 13 : 80 : 5              | —                      | 135  |

In the case of the dioxolane derivative **198** [R<sup>1</sup> = H, R<sup>2</sup>–R<sup>3</sup> = O(CH<sub>2</sub>)<sub>2</sub>O], the ratio of the substrate and the cyclisation products **199** and **200** in the reaction mixture depends on the reaction conditions.<sup>135</sup> The methyl group at the double bond of the vinyl fragment (R<sup>1</sup> = Me) fully inhibits the [4 + 2]-cycloaddition.<sup>134</sup>

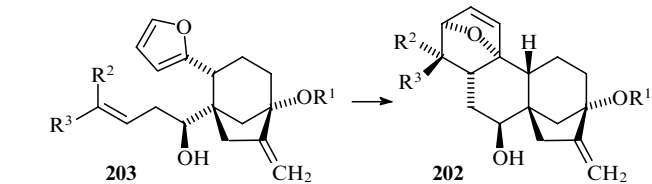
It is of note that attempts to perform cycloaddition in compounds **201a–d**, the precursors of unsaturated ketones **198**, failed.



R<sup>3</sup> = H: R<sup>1</sup> = H, R<sup>2</sup> = OH (**a**), OTBS (**b**);

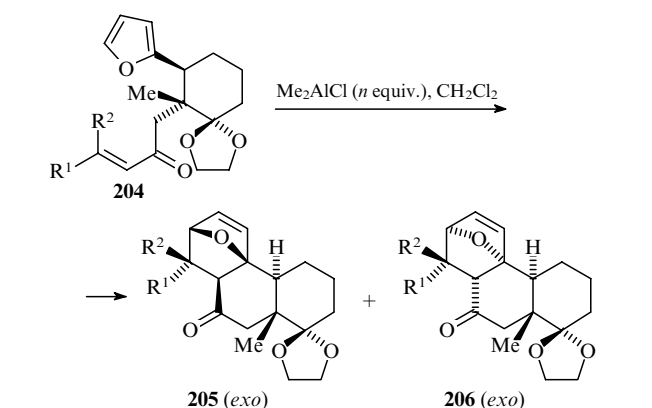
R<sup>1</sup>–R<sup>2</sup> = O (**c**); R<sup>1</sup> = H, R<sup>2</sup> = OTBS, R<sup>3</sup> = Ac (**d**).

Epoxy derivatives of diterpenes of the gibberellin series **202** were prepared in high yields from furyl-substituted bicyclo[3.2.1]octanes **203**.<sup>136–138</sup> This reaction occurred stereospecifically as *exo*-cycloaddition in boiling benzene or upon heating in aqueous solutions in the presence of  $\beta$ -cyclodextrin.



| R <sup>1</sup> | R <sup>2</sup>     | R <sup>3</sup>     | Reaction conditions                        | Yield (%) | Ref.     |
|----------------|--------------------|--------------------|--------------------------------------------|-----------|----------|
| H              | H                  | CO <sub>2</sub> Me | PhH, 80 °C, 96 h                           | 75        | 136      |
| H              | CO <sub>2</sub> Me | H                  | PhH, 80 °C, 40 h                           | 95        | 136      |
| H              | CO <sub>2</sub> Me | H                  | H <sub>2</sub> O, $\beta$ -CD, 50 °C, 12 h | 92        | 136      |
| H              | CO <sub>2</sub> Me | H                  | H <sub>2</sub> O, $\beta$ -CD, 90 °C, 90 h | 72        | 137      |
| TBS            | CO <sub>2</sub> Me | H                  | H <sub>2</sub> O, $\beta$ -CD, 55 °C, 90 h | 80        | 137, 138 |

In conclusion of this section, let us consider the synthesis of homoketosteroid precursors, *viz.*, hydrogenated epoxyphenanthrenes, by catalytic cycloaddition of ketones **204**.<sup>139</sup> Dimethylaluminium chloride proved to be the best catalyst for this reaction. The ratio and the yield of the *exo*-addition products **205** and **206** depended on the amount of the catalyst and the reaction temperature.



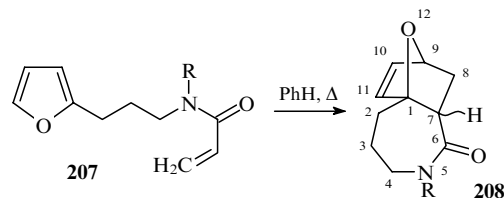
| R <sup>1</sup> | R <sup>2</sup> | n   | T / °C | t / h | Product [(yield (%))]             |
|----------------|----------------|-----|--------|-------|-----------------------------------|
| H              |                | 1.1 | –35    | 24    | <b>205</b> [23]                   |
| H              |                | 2   | –78    | 2     | <b>206</b> [53]                   |
|                | H              | 0.1 | –25    | 2     | <b>206</b> [86]                   |
|                | H              | 0.1 | 25     | 24    | <b>206</b> [29] + <b>205</b> [54] |

### 3. Seven-membered rings

There are very a few examples of the annelation of seven-membered rings **4** upon the intramolecular Diels–Alder reaction in the series of 2-alkenylfurans. This may be due to enhanced (in comparison with five- and six-membered analogues) effects of entropic factors upon closure of seven-membered rings. Very often, such conversions require elevated pressure; the polycycles **4** formed are not always stable under ordinary conditions (see also Section II, synthesis of compound **6**). Moreover, in this case the intramolecular cycloaddition occurs with a rather low stereoselectivity and yields *exo*- and *endo*-adducts. Before 2003, there were no reports of successful annelation of eight-membered rings to 7-oxabicyclo[2.2.1]hept-2-ene by intramolecular [4 + 2]-cycloaddition.

#### a. Synthesis of 5-aza-12-oxatricyclo[7.2.1.0<sup>1,7</sup>]dodec-10-en-6-ones

A description of this heterocyclic system, which has been prepared by the cyclisation of *N*-(3-furylpropyl)acrylamides **207** in boiling benzene, can be found in only one early publication.<sup>140</sup> This reaction did not occur if the double bond in the alkenyl fragment of the molecule **207** (*e.g.*, crotylamide derivatives) was not terminal. No spectral confirmation of the structure and stereochemistry of the tricyclic lactams **208** synthesised was provided.

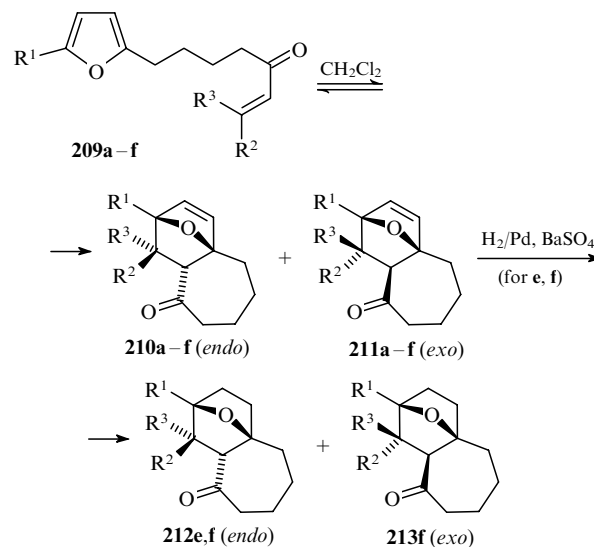


R = Me (45%), Bn (75%).

#### b. Synthesis of 12-oxatricyclo[7.2.1.0<sup>1,7</sup>]dodec-10-en-6-ones

The first synthesis of tricyclic 12-oxatricyclo[7.2.1.0<sup>1,7</sup>]dodec-10-en-6-ones by intramolecular cyclisation of 4-furfurylbutyl vinyl ketones **209a–f** was carried out in 1985.<sup>141</sup> The isomeric cycloaddition products *endo*- (**210**) and *exo*-adducts (**211**) (see compounds **209a–f**, Table 9) appeared to be unstable and rapidly reverted to the starting ketones **209** at atmospheric pressure. The half-life of the more stable *endo*-adduct **210a** (R<sup>1</sup>–R<sup>3</sup> = H) was 1100 min, that of the *exo*-isomer **211a** was 90 min.

The double bonds in the adducts **210e,f** and **211e,f** were reduced under conditions of catalytic hydrogenation without isolation of the adducts from the reaction mixture. Interestingly, these compounds were not detected later<sup>78</sup> (see Table 9). The hydrogenated derivatives **212** and **213** are fairly stable and were used for the preparation of terpenoids of the daphnane series.<sup>78, 117</sup>



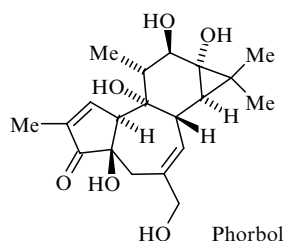
In addition to high pressure, the efficiency of the cycloaddition of alkenylfurans **209** can be increased if methylaluminium dichloride is used as a catalyst.<sup>121, 122</sup> The degree of conversion of the non-substituted compound **209a** at low temperature in the presence of 0.1 equiv. of MeAlCl<sub>2</sub> reaches >90%. The ratio of the *endo*- and *exo*-adducts is variable in this case, but the *endo*-isomers usually predominate.

A series of interesting experiments aimed at the annelation of seven-membered rings upon [4 + 2]-cycloaddition have been carried out by Harwood *et al.*<sup>142–144</sup> In elaborating a new approach to the synthesis of phorbol-type diterpenes (irrigants isolated from different species of the African spurge, *Euphorbia coerulescens*, *E. coperi*, *E. frankian*, *E. resinifera*), these authors investigated the intramolecular Diels–Alder reaction of ketals **214** (see Table 9).

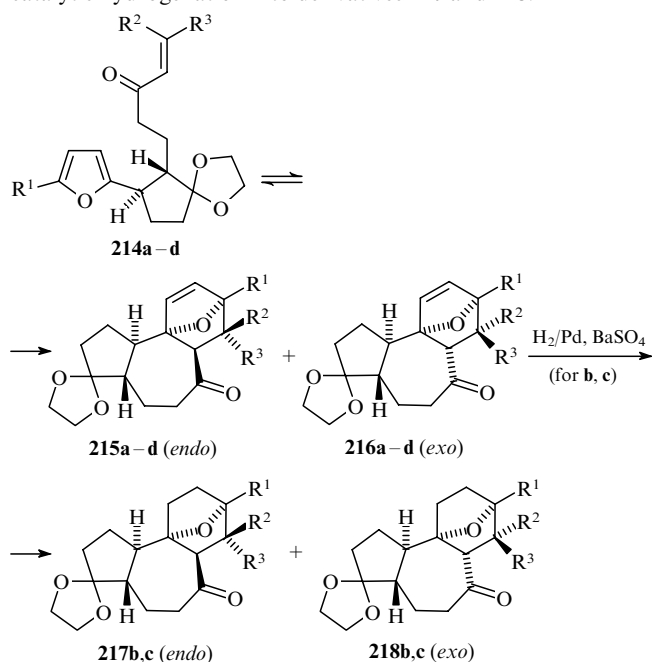
**Table 9.** Cyclisation of substituted 7-(2-furyl)hept-1-en-3-ones.

| Substrate   | R <sup>1</sup>      | R <sup>2</sup>     | R <sup>3</sup>     | Reaction conditions <sup>a</sup>                                                                                       | Composition of the reaction mixture <sup>b</sup><br>[product, yield (%)]                                                                                                           | Ref.                  |
|-------------|---------------------|--------------------|--------------------|------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| <b>209a</b> | H                   | H                  | H                  | 1.2 GPa, 20 °C, 24 h<br>MeAlCl <sub>2</sub> (0.1 equiv.), –65 °C, 2 h<br>MeAlCl <sub>2</sub> (0.1 equiv.), –78 °C, 2 h | <b>210a</b> : <b>211a</b> = 1 : 1<br><b>210a</b> : <b>211a</b> : <b>209a</b> = 81 : 11 : 8 ( <b>210</b> + <b>211</b> , 91)<br><b>210a</b> : <b>211a</b> : <b>209a</b> = 84 : 8 : 8 | 78<br>121, 122<br>121 |
| <b>209b</b> | H                   | H                  | Ac                 | 1.9 GPa, 20 °C, 24 h                                                                                                   | see <sup>c</sup>                                                                                                                                                                   | 78                    |
| <b>209c</b> | H                   | Ac                 | H                  | 1.9 GPa, 20 °C, 24 h                                                                                                   | <b>210c</b> : <b>211c</b> : <b>209c</b> = 2 : 3 : 5                                                                                                                                | 78                    |
| <b>209d</b> | Me                  | H                  | H                  | 1.2 GPa, 20 °C, 24 h<br>1.4 GPa, 20 °C                                                                                 | <b>210d</b> : <b>211d</b> : <b>209d</b> = 5 : 4 : 1<br>( <b>210d</b> + <b>211d</b> )                                                                                               | 78<br>141             |
| <b>209e</b> | Me                  | H                  | Ac                 | 1.9 GPa, 20 °C, 24 h<br>1.9 GPa, 20 °C, 24 h (see <sup>d</sup> )                                                       | see <sup>c</sup><br>( <b>212e</b> , 35)                                                                                                                                            | 78<br>117             |
| <b>209f</b> | Me                  | Ac                 | H                  | 1.9 GPa, 20 °C, 24 h<br>1.9 GPa, 20 °C, 24 h (see <sup>d</sup> )                                                       | see <sup>c</sup><br>( <b>212f</b> , 25) + ( <b>213f</b> , 5)                                                                                                                       | 78<br>117             |
| <b>214a</b> | H                   | H                  | H                  | SiO <sub>2</sub> , 25 °C, 16 h (see <sup>e</sup> )<br>SiO <sub>2</sub> , –12 °C, 7 days (see <sup>e</sup> )            | <b>216a</b> : <b>215a</b> : <b>214a</b> = 1 : 2 : 1<br><b>215a</b> : <b>216a</b> = 1 : 2                                                                                           | 142<br>142            |
| <b>214b</b> | H                   | H                  | CO <sub>2</sub> Et | 1.9 GPa, 20 °C, 5 min (see <sup>d</sup> )                                                                              | ( <b>217b</b> , 11) + ( <b>218b</b> , 48)                                                                                                                                          | 143                   |
| <b>214c</b> | H                   | CO <sub>2</sub> Et | H                  | 1.9 GPa, 20 °C, 5 min (see <sup>d</sup> )                                                                              | ( <b>217c</b> , 38) + ( <b>218c</b> , 18)                                                                                                                                          | 143                   |
| <b>214d</b> | SCH <sub>2</sub> Me | CO <sub>2</sub> Et | H                  | 1.9 GPa, 20 °C, 13 h                                                                                                   | ( <b>215d</b> , 68)                                                                                                                                                                | 144                   |

<sup>a</sup> CH<sub>2</sub>Cl<sub>2</sub> was used as solvent; <sup>b</sup> the compositions of the reaction mixtures were determined using <sup>1</sup>H NMR spectroscopy; <sup>c</sup> the reaction does not occur; <sup>d</sup> hydrogenation *in situ*; <sup>e</sup> CHCl<sub>3</sub> was used as solvent.

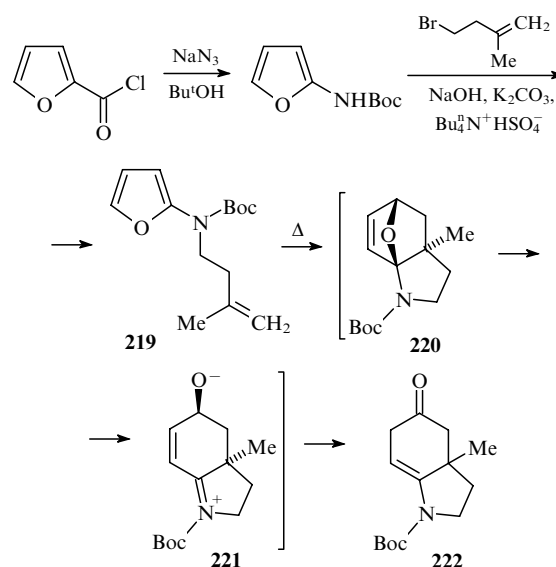


As for the above-described conversions of alkenylfurans **209**, in certain cases (*e.g.*, for derivatives **214b,c**), the cycloadducts **215** and **216** formed were not isolated in the individual state, but their equilibrium mixture with the starting compound was subjected to catalytic hydrogenation into derivatives **217** and **218**.



## V. Intramolecular cyclisation of *N*-alkenyl-2-aminofurans

Several novel types of intramolecular cycloaddition of substituted furans were disclosed in the past 8 years. It is well-known that, *N*-unsubstituted 2-furylamines are unstable under ordinary conditions, therefore, their reactions are virtually unexplored. In 1997, Padwa and coworkers developed a simple preparative procedure for the synthesis of unsaturated 2-furylcarbamates **219**,<sup>145, 146</sup> which proved to be exceptionally reactive dienes.

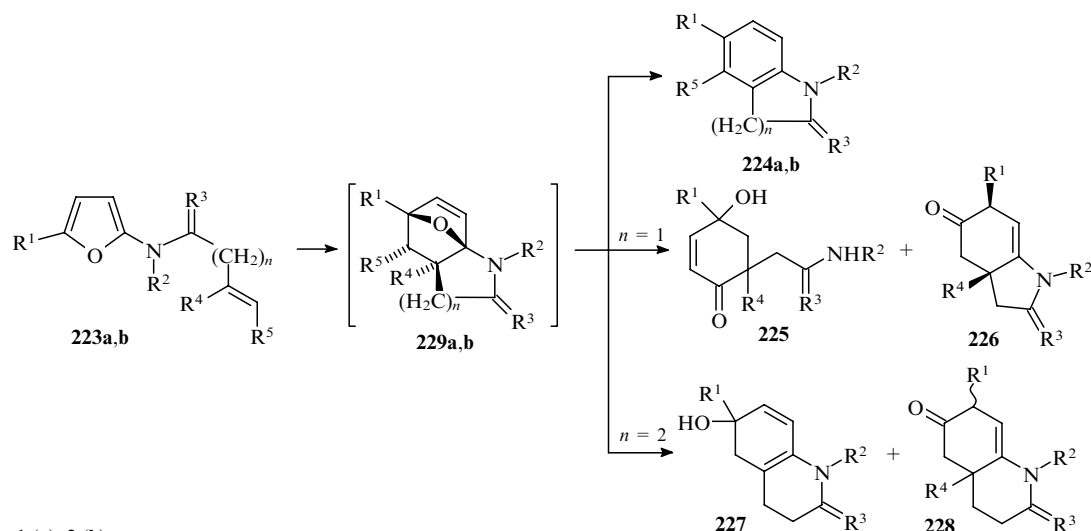


Boc is *tert*-butoxycarbonyl.

In contrast to the above-considered cyclisation reactions, the intramolecular cycloaddition of *N*-substituted 2-furylcarbamates **219** seldom yields the annelated oxabicycloheptene **220**. The latter undergoes spontaneous opening of the epoxide bridge; the ambident ion **221** formed is stabilised in various ways, *e.g.*, by conversion into hexahydroindolone **222**.

In the majority of cases, the intramolecular cycloaddition in *N*-alkenyl-2-furylamides and -carbamates **223a,b** differing in the lengths of the alkenyl chains occurs in boiling benzene or toluene; sometimes, this is carried out in a sealed tube. In the presence of 4–5 M ethereal lithium perchlorate, the temperature can be

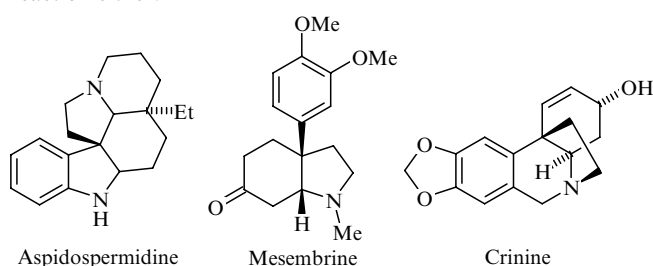
Scheme 8



reduced; sterically hindered alkenylfurans react under these conditions.<sup>147</sup> The mechanism of the catalytic effects of ethereal  $\text{LiClO}_4$  and other examples are considered in a review.<sup>148</sup>

Depending on the nature of substituents  $\text{R}^1 - \text{R}^5$  in the starting furans **223a,b**, eight products **224–229** can be obtained,<sup>147, 149–158</sup> six of which are formed upon cleavage of the epoxide bridge in the primary adducts **229a,b**, (Scheme 8). It is of note that the intermediate epoxyindole **229a** could be isolated in only one case.<sup>151</sup> The intramolecular cycloaddition always proceeds *via* the intermediate *exo*-transition state. The reaction conditions and the product yields are presented in Table 10.

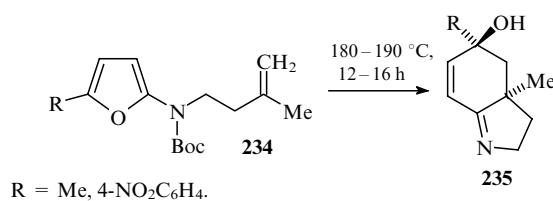
Based on these data, the following general conclusions have been made. The annelation of five-membered rings to oxabicycloheptene proceeds more smoothly than that of six-membered rings, which often results in mixtures of reaction products. The reaction occurs with furans containing both electron-withdrawing ( $\text{CO}_2\text{Alk}$ ) and electron-donor ( $\text{SMe}$ ) groups. Thus, the nature of the substituent at position 5 of the furan ring affects neither the reaction conditions nor the yield of the cycloadducts. Bulky substituents at the amide nitrogen atom ( $\text{R}^2$ ) and radicals at the double bond ( $\text{R}^4$  and  $\text{R}^5$ ) of the dienophile do not inhibit this reaction either.



In the case of  $\text{R}^4 = 3,4-(\text{MeO})_2\text{C}_6\text{H}_3$  [or  $3,4-(\text{OCH}_2\text{O})\text{C}_6\text{H}_3$ ], compounds **226**, which represent close precursors of the alkaloids mesembrine and crinine, respectively, are formed. The former were isolated from South African plants of the Mesembryanthemaceae family (genus *Sceletium*); the latter were found in the bulbs and seeds of the African lily *Crinum bulbispermum* (Amaryllidaceae). Total synthesis of these and other structurally similar alkaloids by intramolecular cycloaddition of *N*-alkenylaminofurans **223** has been described.<sup>19, 153, 154</sup>

The Diels–Alder reaction of 5-substituted *N*-alkenyl-*N*-furyl-sulfonamides is also accompanied by conversions of the primary adducts.<sup>147, 150</sup> In the case of 5-nitro derivatives, **230a,b**, the elimination or migration of the nitro group in the intermediate tricycles **231a,b** and subsequent oxygen-induced aromatisation result in a mixture of mono- (**232a,b**) and disubstituted (**233a,b**) indolines ( $n = 1$ ) or tetrahydroquinolines ( $n = 2$ ) (Scheme 9).<sup>147</sup>

An unexpected elimination of the *N*-*tert*-butoxycarbonyl group was observed in the cyclisation of 5-methyl- and 5-nitro-phenyl-substituted furylcarbamates **234** leading to 3,3a,4,5-tetrahydro-2*H*-indoles (**235**) in good yields.<sup>150</sup>



It is interesting to note that the thermal cyclisation of the *N*-butenyl analogue yields an unstable adduct of the type **229a** (see above); the latter is further aromatised into the corresponding indoline.<sup>152</sup>

Scheme 9

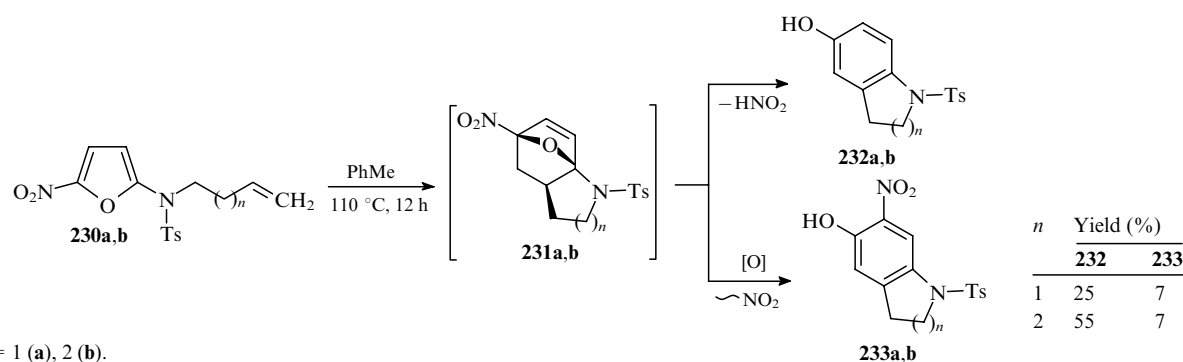
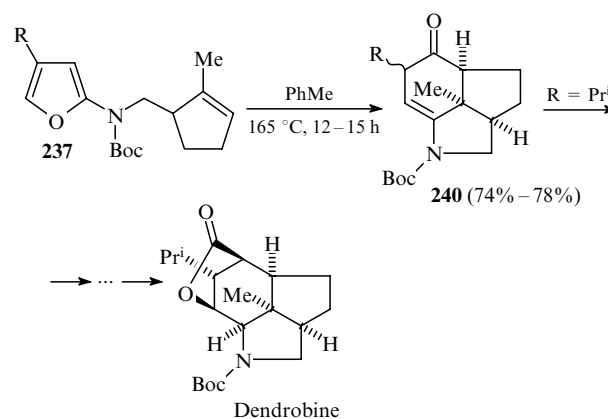
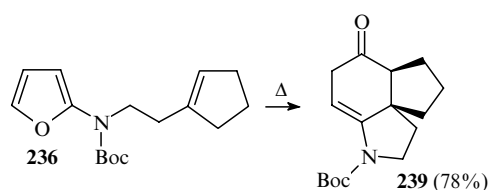


**Table 10.** Cyclisation of acylated (*N*-alkenyl)aminofurans **223a,b**.

| Com-<br>pound | R <sup>1</sup>                                  | R <sup>2</sup>                                                                       | R <sup>3</sup> | R <sup>4</sup>                                        | R <sup>5</sup>     | Product                  | Yield<br>(%) | Reaction conditions                                                      | Ref.     |
|---------------|-------------------------------------------------|--------------------------------------------------------------------------------------|----------------|-------------------------------------------------------|--------------------|--------------------------|--------------|--------------------------------------------------------------------------|----------|
| <b>223a</b>   | H                                               | CO <sub>2</sub> Me                                                                   | 2 H            | 3,4-(OCH <sub>2</sub> O)C <sub>6</sub> H <sub>3</sub> | H                  | <b>226</b>               | 85           | PhMe, 180 °C, 15 h                                                       | 153      |
|               | H                                               | CO <sub>2</sub> Et                                                                   | 2 H            | Me                                                    | H                  | <b>226</b>               | 90           | PhH, 165 °C, 14 h                                                        | 150      |
|               | H                                               | CO <sub>2</sub> Et                                                                   | 2 H            | CO <sub>2</sub> Me                                    | H                  | <b>226</b>               | 80           | PhH, 80 °C, 6 h                                                          | 150      |
|               | H                                               | CO <sub>2</sub> Et                                                                   | 2 H            | 3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>  | H                  | <b>226</b>               | 78           | PhMe, 155 °C, 20 h                                                       | 153      |
|               | OH <sup>a</sup>                                 | CO <sub>2</sub> Et                                                                   | 2 H            | Br                                                    | H                  | <b>224a</b>              | 80           | PhH, 160 °C, 7 h                                                         | 152      |
|               | H                                               | CO <sub>2</sub> Bu <sup>t</sup>                                                      | 2 H            | H                                                     | H                  | <b>224a</b>              | 16           | PhH, 165 °C, 16 h                                                        | 149, 152 |
|               | H                                               | CO <sub>2</sub> Bu <sup>t</sup>                                                      | 2 H            | Me                                                    | H                  | <b>226</b>               | 71           | PhH, 165 °C, 14 h                                                        | 149, 152 |
|               | OH <sup>a</sup>                                 | CO <sub>2</sub> Bu <sup>t</sup>                                                      | 2 H            | Br                                                    | H                  | <b>224a</b>              | 5            | thermolysis                                                              | 152      |
|               | OH <sup>a</sup>                                 | CO <sub>2</sub> Bu <sup>t</sup>                                                      | 2 H            | SPh                                                   | H                  | <b>224a</b>              | 87           | PhH, 160 °C, 6 h                                                         | 152      |
|               | H                                               | CO <sub>2</sub> Bu <sup>t</sup>                                                      | 2 H            | CO <sub>2</sub> Me                                    | H                  | <b>226</b>               | 87           | PhH, 80 °C, 6 h                                                          | 149, 150 |
|               | H                                               | CO <sub>2</sub> Bu <sup>t</sup>                                                      | 2 H            | OBO <sup>b</sup>                                      | H                  | <b>226</b>               | 70           | PhH, 165 °C, 14 h                                                        | 150      |
|               | H                                               | CO <sub>2</sub> Bu <sup>t</sup>                                                      | 2 H            | 3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>  | H                  | <b>226</b>               | 77           | PhH, 165 °C                                                              | 149      |
|               | Me                                              | CF <sub>3</sub> CO                                                                   | 2 H            | H                                                     | H                  | <b>224a</b>              | —            | PhMe, 130 °C, 4 h                                                        | 151      |
|               | Me                                              | CO <sub>2</sub> Bu <sup>t</sup>                                                      | 2 H            | H                                                     | H                  | <b>224a</b>              | 77           | PhH, 160 °C, 15 h                                                        | 152      |
|               | Me                                              | SO <sub>2</sub> CF <sub>3</sub>                                                      | 2 H            | H                                                     | H                  | <b>224a</b>              | 96           | PhMe, 130 °C, 4 h                                                        | 151      |
|               | Me                                              | SO <sub>2</sub> CF <sub>3</sub>                                                      | 2 H            | Me                                                    | H                  | <b>229</b>               | 85           | PhMe, 130 °C, 4 h                                                        | 151      |
|               | CO <sub>2</sub> Me                              | CO <sub>2</sub> Et                                                                   | 2 H            | H                                                     | H                  | <b>224a</b>              | 66           | 4 M LiClO <sub>4</sub> , <sup>c</sup> 100 °C, 26 h                       | 147      |
|               | CO <sub>2</sub> Me                              | PhCO                                                                                 | 2 H            | H                                                     | H                  | <b>224a</b> <sup>d</sup> | 25           | PhMe, 190 °C, 19 h                                                       | 147      |
|               | CO <sub>2</sub> Me                              | 2-Br-3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>2</sub> CO                         | 2 H            | H                                                     | H                  | <b>224a</b>              | 79           | 4 M LiClO <sub>4</sub> , <sup>c</sup> 100 °C, 36 h                       | 147      |
|               | CO <sub>2</sub> Me                              | 2-Br-3,4-(OCH <sub>2</sub> O)C <sub>6</sub> H <sub>2</sub> CO                        | 2 H            | H                                                     | H                  | <b>224a</b>              | 80           | 5 M LiClO <sub>4</sub> , <sup>c</sup> 100 °C, 36 h                       | 147      |
|               | 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> | CO <sub>2</sub> Bu <sup>t</sup>                                                      | 2 H            | H                                                     | H                  | <b>224a</b>              | 57           | PhH, 165 °C, 15 h                                                        | 152      |
|               | CO <sub>2</sub> Me                              | PhCO                                                                                 | 2 H            | H                                                     | Me                 | <b>224a</b>              | 73           | CSA, 4 M LiClO <sub>4</sub> , <sup>c</sup> 100 °C, 48 h                  | 147      |
|               | CO <sub>2</sub> Me                              | PhCO                                                                                 | 2 H            | H                                                     | MeO <sub>2</sub> C | <b>224a</b>              | 70           | 4 M LiClO <sub>4</sub> , <sup>c</sup> 100 °C, 24 h or PhMe, 160 °C, 24 h | 147      |
|               | CO <sub>2</sub> Me                              | PhCO                                                                                 | 2 H            | Me                                                    | H                  | <b>225</b>               | 68           | 4 M LiClO <sub>4</sub> , <sup>c</sup> 95 °C, 24 h                        | 147      |
|               | MeS                                             | Me                                                                                   | O              | H                                                     | H                  | <b>226</b>               | 72           | PhMe, 110 °C, 2 h                                                        | 158      |
|               | MeS                                             | 3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> | O              | H                                                     | H                  | <b>226</b>               | 63           | PhMe, 110 °C, 3 h                                                        | 157      |
|               | MeS                                             | Me                                                                                   | O              | Me                                                    | H                  | <b>226</b>               | 42           | PhMe, 110 °C, 3 h                                                        | 158      |
|               | MeS                                             | Me                                                                                   | O              | Ph                                                    | H                  | <b>226</b>               | 61           | PhH, 80 °C, 8 h                                                          | 157      |
|               | MeS                                             | Me                                                                                   | O              | CO <sub>2</sub> Me                                    | H                  | <b>226</b>               | 68           | MeCN, 25 °C, < 1 h                                                       | 158      |
| <b>223b</b>   | H                                               | CO <sub>2</sub> Et                                                                   | 2 H            | Me                                                    | H                  | <b>228</b>               | 68           | PhH, 200 °C, 36 h                                                        | 150      |
|               | H                                               | CO <sub>2</sub> Bu <sup>t</sup>                                                      | 2 H            | H                                                     | H                  | <b>224b</b> + <b>227</b> | 28 + 33      | PhH, 165 °C, 18 h                                                        | 149, 152 |
|               | CO <sub>2</sub> Me                              | PhCO                                                                                 | 2 H            | H                                                     | H                  | <b>224b</b> + <b>227</b> | 33 61        | PhMe, 190 °C, 20 h                                                       | 147      |
|               | H                                               | H                                                                                    | O              | H                                                     | Me                 | <b>224b</b>              | 89           | PhH, 200 °C, 36 h                                                        | 152      |
|               | H                                               | 4-(MeO)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>                                 | O              | H                                                     | Me                 | <b>224b</b>              | 80           | PhH, 160 °C, 24 h                                                        | 152      |
|               | CO <sub>2</sub> Me                              | H                                                                                    | O              | H                                                     | H                  | <b>224b</b>              | 66           | PhMe, 200 °C, 24 h                                                       | 147      |
|               | CO <sub>2</sub> Me                              | Me                                                                                   | O              | H                                                     | H                  | <b>224b</b> + <b>227</b> | 13 + 77      | PhMe, 160 °C, 24 h                                                       | 147      |
|               | MeS                                             | Me                                                                                   | O              | H                                                     | H                  | <b>228</b>               | 0            | PhMe, 200 °C, > 2 h                                                      | 158      |

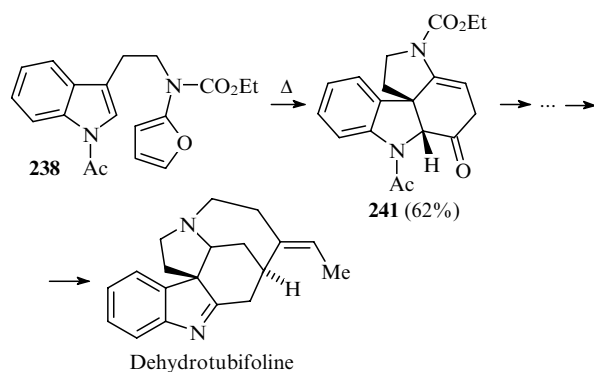
<sup>a</sup> The substituent R<sup>1</sup> for the reaction product is indicated; in the starting furan, R<sup>1</sup> = H; <sup>b</sup> OBO is 2,6,7-trioxabicyclo[2.2.2]octane; <sup>c</sup> the concentration of LiClO<sub>4</sub> in diethyl ether is indicated; <sup>d</sup> the yield of methyl 1-benzoyl-5-hydroxy-2,3,4,5-tetrahydro-1*H*-indole-5-carboxylate was also obtained, yield 52%.

Alkylfurylcarbamates **236** and **237** and a tryptamine derivative **238** underwent intramolecular cycloaddition.<sup>140, 153</sup> These conversions yield the adducts **239–241**, which represent synthons for the preparation of the polycyclic alkaloids dendrobine (found in the Chinese orchid *Dendrobium nobile*), aspidospermidine and dehydrotubifoline isolated from South American tree-frogs.

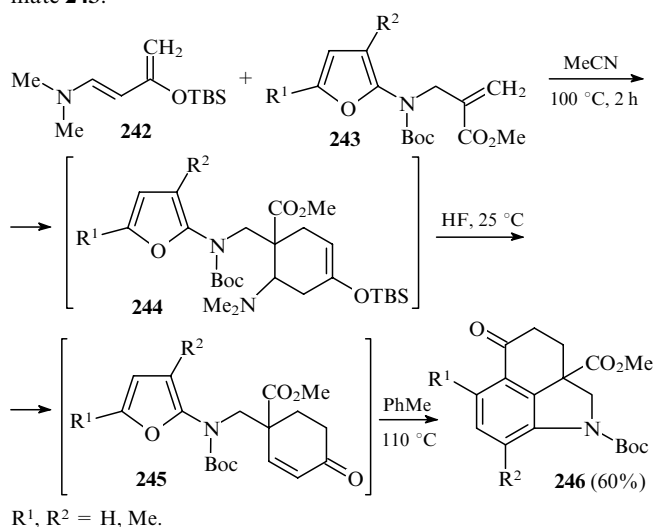


R = H, Pr<sup>i</sup>

Dendrobine

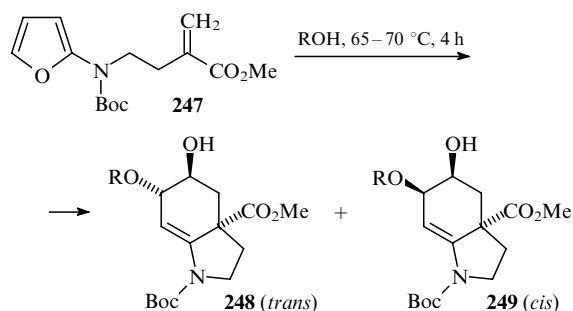


Alkenylfurylcarbamates for intramolecular Diels–Alder reactions can be prepared *in situ*. The sequence of transformations<sup>155</sup> begins with the intermolecular [4 + 2]-cycloaddition of protected 4-dimethylaminobuta-1,3-dien-2-ol **242** to furylcarbamate **243**.



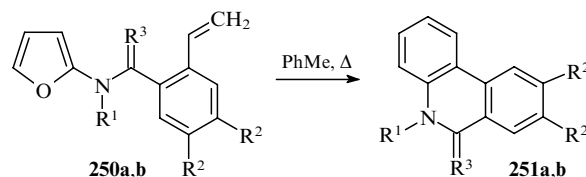
Dimethylamine and the protecting silyl group are eliminated from compound **244** under the action of hydrofluoric acid resulting in cyclohexenone **245**. The latter undergoes thermal cycloaddition to be further converted into the tricyclic indole derivatives **246**.

The cycloaddition of a carbamate **243** homologue, *viz.*, methyl 4-(*tert*-butoxycarbonyl-2-furyl)amino-2-methylenbutyrate (**247**), carried out in an alcoholic medium (MeOH or BnOH) yields mixtures of monoalkylated 5,6-dihydroxy derivatives **248** and **249** (but not the ketones of the type **228**, see above).<sup>150, 154</sup> The total yield of these compounds is 80%–85%; the ratio of the *trans*- and *cis*-isomers is 3 : 1 in both cases.



The cyclisation of 2-aminofurans can be used for the synthesis of azaphenanthrene systems.<sup>152</sup> Thus the cyclisation of the *N*-non-substituted alkenylfuran **250a** occurs under more drastic conditions (160 °C, 4 days) than that of its ethoxycarbonyl analogue

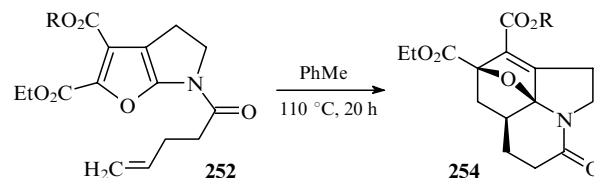
**250b** (110 °C, 24 h). The yields of the substituted phenanthridines **251** are high in both cases.



$R^1 = R^2 = \text{H, } R^3 = \text{O (a, 97\%); } R^1 = \text{CO}_2\text{Et, } R^2 = \text{OCH}_2\text{O, } R^3 = 2 \text{ H (b, 79\%)}$

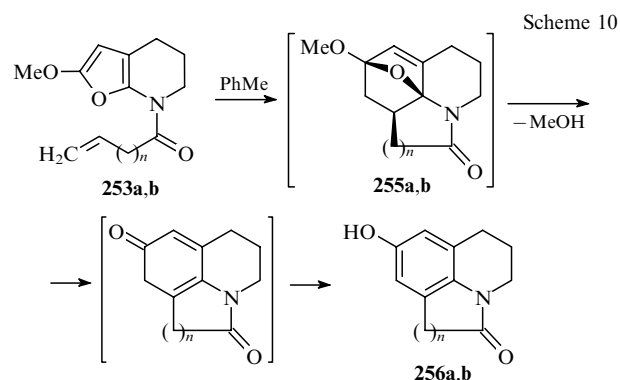
The intramolecular Diels–Alder reaction in the series of furan derivatives annelated to nitrogen-containing heterocycles with *N*-alkenyl substituents, *viz.*, furopyrrrolines **252** and furotetrahydropyridines **253**, has been described.<sup>156–160</sup> Conversions of such systems lead to polyheterocyclic compounds. Unfortunately, the starting fused heterocycles are not easily accessible, which restricts significantly prospects of their practical application in the synthesis of biologically active compounds.

If the furan ring contains electron-withdrawing groups ( $\text{CO}_2\text{Alk}$ ), the cycloaddition stops at the formation of epoxy derivatives of the tetracyclic compounds **254**.



**254:**  $R = \text{Bu}^t$  (70%), Me (24%).

Contrariwise, electron-donor groups (*e.g.*, MeO) make the Diels–Alder adducts **255** unstable, which results in spontaneous cleavage of the epoxide bridge. These compounds are stabilised upon elimination of methanol.<sup>156, 157</sup> It was shown that the formation of hydrogenated pyridoquinoline from methoxy-substituted furotetrahydropyridine occurs under more drastic conditions than that of pyrrolo[3,2,1-*ij*]quinoline **256a** (Scheme 10).



| Compound <b>256</b> | <i>n</i> | Reaction conditions | Yield (%) |
|---------------------|----------|---------------------|-----------|
| <b>a</b>            | 1        | 110 °C, 0.5 h       | 58        |
| <b>b</b>            | 2        | 180 °C, 12 h        | 30        |

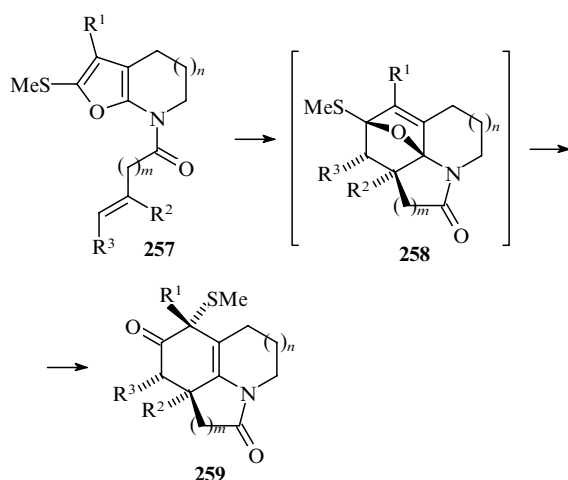
The [4 + 2]-cycloaddition of various *N*-acylazinofurans **257** [*e.g.*, hydrogenated furopyridines ( $n = 1$ ) and furoazepines ( $n = 2$ )] containing an electron-donor MeS group at position 5 of the furan ring was studied.<sup>158–160</sup> These compounds afforded both the Diels–Alder adducts and their subsequent conversion products. It is interesting to note that, in contrast to the methoxy derivatives **255**, the sulfur-containing analogues **258** undergo a 1,2-shift of the thiomethyl group to yield oxo amides **259** (Table 11).



**Table 11.** Cyclisation of *N*-acylazinofurans **257**.

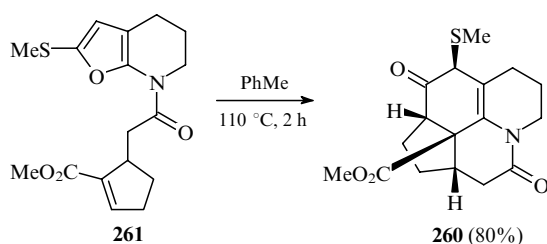
| R <sup>1</sup> | R <sup>2</sup>     | R <sup>3</sup>                     | <i>n</i> | <i>m</i> | Reaction conditions                         | Product                 | Yield (%) | Ref. |
|----------------|--------------------|------------------------------------|----------|----------|---------------------------------------------|-------------------------|-----------|------|
| H              | H                  | H                                  | 1        | 1        | PhMe, 110 °C, 1 h                           | <b>259</b>              | 92        | 158  |
| H              | H                  | H                                  | 1        | 2        | PhMe, 150 °C, 15 h                          | <b>259</b>              | 76        | 158  |
| H              | H                  | CH <sub>2</sub> CO <sub>2</sub> Me | 1        | 1        | PhMe, 110 °C, 3 h                           | <b>259</b>              | 66        | 160  |
| H              | Me                 | H                                  | 1        | 1        | PhMe, 110 °C, 7 h                           | <b>259</b>              | 61        | 158  |
| H              | CO <sub>2</sub> Me | H                                  | 1        | 1        | PhH, 80 °C, 1 h                             | <b>259</b>              | 77        | 158  |
| H              | CO <sub>2</sub> Me | H                                  | 1        | 1        | CH <sub>2</sub> Cl <sub>2</sub> , 0 °C, 3 h | <b>258</b>              | 77        | 158  |
| Et             | H                  | H                                  | 1        | 1        | PhMe, 110 °C, 1 h                           | <b>259</b>              | 70        | 158  |
| H              | H                  | H                                  | 2        | 1        | MeCN, 25 °C, < 1 h                          | <b>259</b> <sup>a</sup> | 64        | 158  |
| H              | H                  | H                                  | 2        | 2        | PhMe, 150 °C, 4 h                           | <b>258</b>              | 75        | 158  |
| H              | H                  | CH <sub>2</sub> CO <sub>2</sub> Me | 2        | 1        | MeCN, 25 °C, < 1 h                          | <b>259</b> <sup>a</sup> | 79        | 160  |

<sup>a</sup> The configuration of the SMe group was not determined.



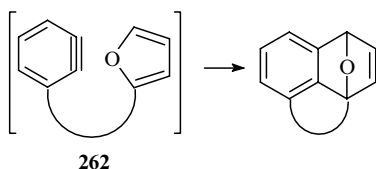
Substituents at the double bond of the unsaturated fragment in the fused furans **257** and the size of the annelated ring have no appreciable effect on the yield of the tricyclic compounds **258** and **259**.

An elegant stereoselective synthesis of the tetracyclic system **260** upon heating of furotetrahydropyridine **261** can be mentioned in conclusion of this section.<sup>158</sup>

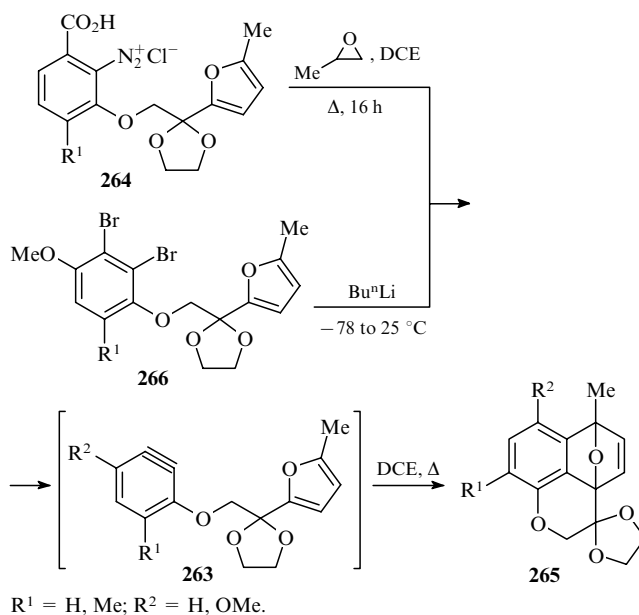


## VI. Intramolecular cycloaddition in furylalkyldehydrobenzenes

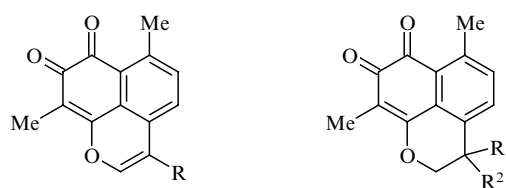
This is one of the least investigated intramolecular cycloaddition reactions in the furan series; the first report appeared in 1981.<sup>161</sup> It is of note that no information about this type of cyclisation is given in a recent review<sup>162</sup> of dehydrobenzene reactions published in 2003.



Several approaches to the generation of furylalkyldehydrobenzenes of the type **262** exist. The two major types include decomposition of the corresponding diazonium salts prepared from substituted anthranilic acids and dehalogenation of furyl-containing *ortho*-dihalobenzenes. The intermediate dehydrobenzenes **263** are formed smoothly upon heating of the diazonium salts **264** in the presence of propylene oxide which binds the evolving hydrogen chloride. Further boiling in dichloroethane gives the thermal cyclisation products, *viz.*, the epoxytetracycles **265** (yields 74%–90%). Similar compounds are formed in good yields upon treatment of dibromo-derivatives **266** with butyllithium.



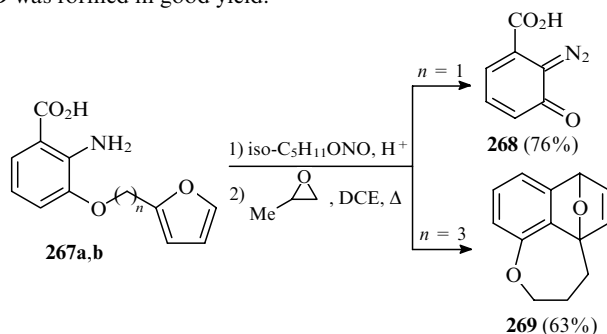
Both approaches were employed by Australian chemists in the synthesis of naphtho[1,8-*bc*]pyran,<sup>161, 163, 164</sup> which is a skeleton of isoprenoids biflorin and mansonones E, I and F possessing a rare *o*-quinonoid structure. Biflorin was isolated from the blossoms and leaves of *Capraria biflora* L., while mansonones E, I and F



R = (CH<sub>2</sub>)<sub>2</sub>CH=CHMe<sub>2</sub> (biflorin), Me (mansonone F);  
R<sup>1</sup> = Me: R<sup>2</sup> = H (mansonone E), OH (mansonone I).

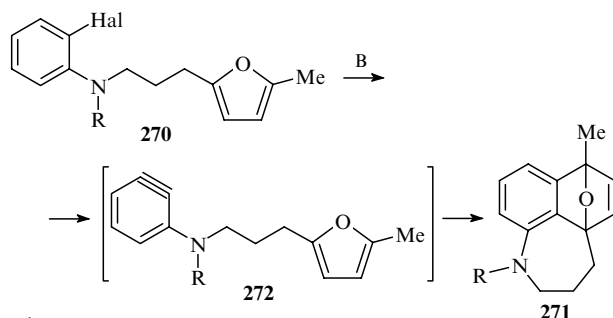
were isolated from the wood of the African tree *Mansonia altissima*.

The length of the chain linking the dehydrobenzene fragment to the furan ring is critical for the cyclisation.<sup>161</sup> No intramolecular Diels–Alder cyclisation occurred of furylalkoxydehydrobenzene formed upon diazotisation of anthranilic acid **267a** with isoamyl nitrite; instead, only diazoquinone **268** was obtained as the elimination product of the furfuryl substituent. However, the annelation of the seven-membered ring in a diazonium salt prepared from the derivative **267b** was more successful: the adduct **269** was formed in good yield.<sup>161</sup>



$n = 1$  (a),  $3$  (b).

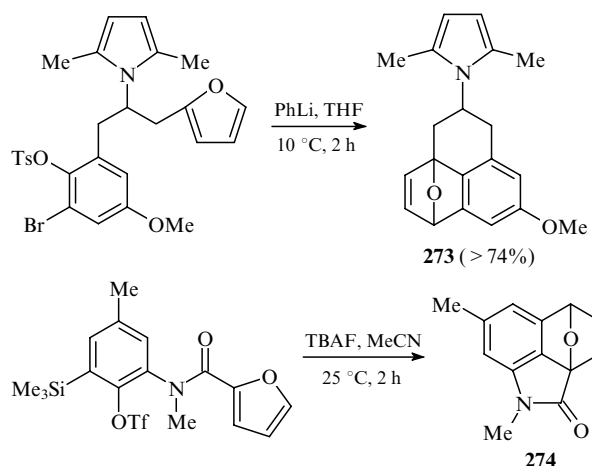
The conversion of *o*-furylpropylaminohalobenzenes **270** into fused azepines **271** (Table 12) containing an epoxynaphthalene fragment has been described.<sup>165</sup> Lithium diisopropylamide (LDA) and lithium-2,2,6,6-tetramethylpiperidide (LiTMP) in THF proved to be the most suitable bases for generating dehydrobenzene **272**. The yields of naphthoazepines **271** were low.



B is a base.

Short communications<sup>166, 167</sup> outline approaches to the synthesis of the partly hydrogenated phenalenes **273** and the fused indole systems **274**, respectively. These syntheses employed con-

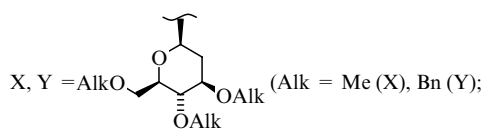
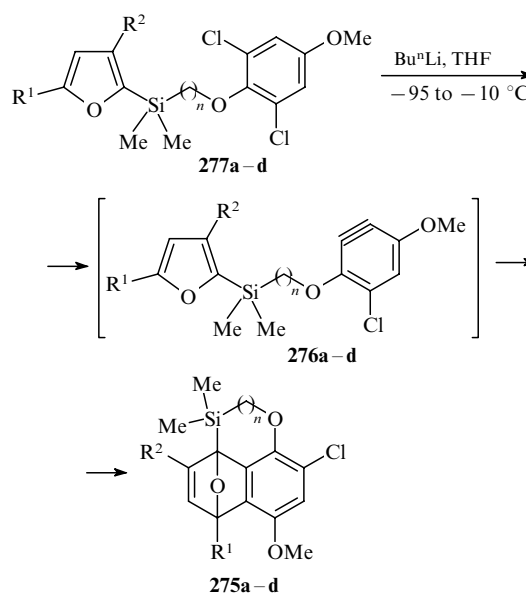
ventional techniques for the generation of the dehydrobenzene intermediates.



Tf is trifluoromethylsulfonyl,  
TBAF is tetrabutylammonium fluoride.

The labile adduct **274** was synthesised in quantitative yield.

Intramolecular cyclisation in epoxynaphthalenes **275a–d** fused to a silaoxacyclohex(hept)ane fragment has recently been described.<sup>168</sup> The intermediate furyl-substituted dehydrobenzenes **276** were generated by treatment of compounds **277** with *tert*- or *sec*-butyllithium in THF from  $-95$  to  $-10$  °C.



| Compound <b>275</b> | $n$ | R <sup>1</sup> | R <sup>2</sup> | Yield (%) |
|---------------------|-----|----------------|----------------|-----------|
| <b>a</b>            | 1   | X              | H              | 68        |
| <b>b</b>            | 2   | X              | H              | 81        |
| <b>c</b>            | 1   | H              | Z              | 91        |
| <b>d</b>            | 1   | X              | Y              | 61        |

**Table 12.** Preparation of epoxynaphthazepines **271**.

| Hal | R <sup>2</sup> | Reaction conditions <sup>a</sup>                   |                    |              | Yield (%) |
|-----|----------------|----------------------------------------------------|--------------------|--------------|-----------|
|     |                | base (equiv.)                                      | $T/^\circ\text{C}$ | $t/\text{h}$ |           |
| Cl  | Me             | Bu <sup>n</sup> Li (4)                             | –78 to 25          | 24           | 10        |
|     |                | LDA (4)                                            | –40 to 25          | 20           | 40        |
|     |                | LiTMP (4)                                          | –78 to 25          | 24           | 49        |
| Br  | Me             | NaNH <sub>2</sub> (5)                              | 25                 | 20           | 0         |
|     |                | NaNH <sub>2</sub> (5.5) + NaOBu <sup>t</sup> (1.1) | –60                | 60           | 0         |
| Cl  |                | NaCH <sub>2</sub> SOMe (3.5) <sup>b</sup>          | 100                | 16           | < 5       |
|     |                | Bu <sup>n</sup> Li (3.5)                           | –78 to 25          | 24           | 0         |
|     |                | LDA (3.5)                                          | –40 to 25          | 20           | 29        |
|     |                | LiTMP (3.5)                                        | –78 to 25          | 24           | 34        |

<sup>a</sup> THF was used as solvent; <sup>b</sup> DMSO was used as solvent.

\* \* \*

The data reviewed clearly demonstrate that the intramolecular Diels–Alder reactions of alkenylfurans provide an efficient and often the only way to fused 7-oxabicycloheptane systems.

The best results are achieved with substrates containing a three-membered chain between the dienophile (alkenyl) and the diene (furan) fragments (annulation of five-membered rings). The cyclisation that yields six-membered derivatives is less smooth. In any case, a decrease in the degree of freedom of unsaturated fragments (e.g., as a result of introduction of additional substituents, complex formation or the presence of sp<sup>2</sup>-hybridised atoms) favours cyclisation. The contribution of electronic factors that is critical for intermolecular interactions from the standpoint of boundary orbital theory fades into the background in the case of intramolecular interactions. With rare exception, the stereochemistry of intramolecular [4 + 2]-cycloaddition usually follows the Diels–Alder *endo*-rule.

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# Polyquinolines and polyanthrazolines: synthesis and properties

A L Rusanov, L G Komarova, M P Prigozhina, D Yu Likhatchev

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**Abstract.** The advances in the synthesis and studies of the properties of polyquinolines and polyanthrazolines are reviewed. The main attention is given to polymers prepared by the Friedlander reaction from the AB- and AA–BB-type monomers, *viz.*, rigid-rod polyquinolines, polyether quinolines, cardo polyquinolines and polymers containing tetraphenylsilyl and perfluorotetramethylene fragments. The approaches to the design of reactive oligo- and polyquinolines, the terminal groups of which have a curing effect on these systems, are considered. The use of polyquinolines for the preparation of composite and electroluminescent materials is discussed. The bibliography includes 155 references.

## I. Introduction

Polyheteroarylenes (PHA) based on quinolines (polyquinolines, PQ) and anthrazolines (polyanthrazolines, PAZ) present substantial interest for both fundamental and applied investigations<sup>1–6</sup> due to their high heat resistances and high thermal stabilities.<sup>7</sup>

In the early stage (the 1970's), PQ and PAZ were used predominantly for the preparation of polymeric materials (films, fibres, composites, *etc.*) for the aerospace industry. Later (the 1990's), more attention was placed on their use for the preparation of materials for high-tech industrial domains, for optoelectronics, in particular.<sup>8,9</sup>

The results obtained in both stages of the investigations of these compounds are considered in this review.

**A L Rusanov, L G Komarova, M P Prigozhina** A N Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, 119991 Moscow, Russian Federation.

Fax (7-095) 135 50 85, tel. (7-095) 135 63 72, e-mail: alrus@ineos.ac.ru (A L Rusanov), tel. (7-095) 135 93 27, e-mail: komarova@ineos.ac.ru (L G Komarova, M P Prigozhina)

**D Yu Likhatchev** Materials Research Institute, National Autonomous University of Mexico, Circuito Exterior s/n, CU, Apdo Postal 70-360 Coyoacan, 04510 Mexico City, Mexico. Fax (52-555) 616 12 01, tel. (52-555) 622 45 87, e-mail: likhach@serviodor.unam.mx

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## II. Synthesis of polyquinolines and polyanthrazolines manifesting high heat resistances and high thermal stabilities

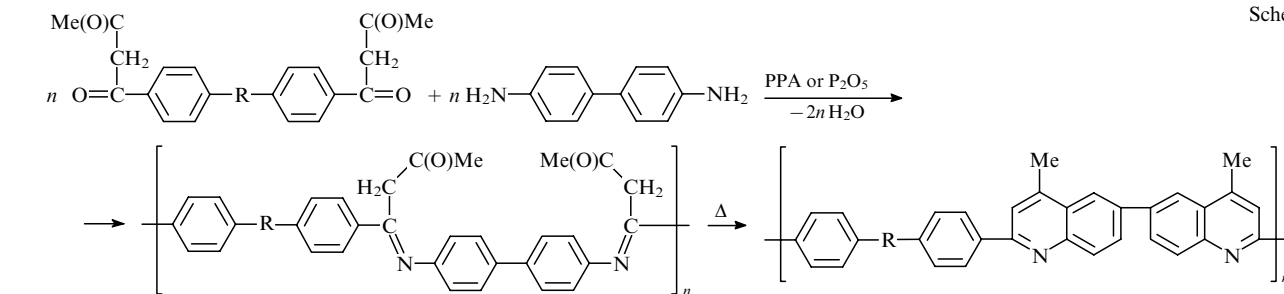
The past four decades have been marked by the synthesis of diverse PHA.<sup>10–19</sup> Some of them, *e.g.*, polyimides,<sup>20–25</sup> polyazoles,<sup>26–30</sup> polyphenylquinoxalines,<sup>31–33</sup> *etc.*), have found application in the design of materials retaining their operating characteristics at temperatures around 300 °C. To a considerable extent, such compounds satisfied the needs of the aircraft industry and rocket engineering for thermostable polymeric materials, but more recent demands are for materials able to withstand higher temperatures. Therefore, the efforts of investigators have switched over to a search for polymers surpassing the well-known PHA in heat resistances and thermal stabilities. Identification of the least stable fragments in the polymeric chains of conventional PHA and their replacement by more thermostable units seemed to be the most rational solution to this problem.

In-depth studies of the decomposition mechanisms of different classes of PHA have shown that the decomposition involves predominantly the heterocyclic fragments,<sup>34–42</sup> which suggests that it is the heterocyclic fragments of PHA that should be replaced by more thermostable components. A comparison of the thermal stabilities of various carbo- and heterocycles<sup>43,44</sup> has shown that quinoline is one of the most heat-resistant compounds.<sup>44</sup> The first attempt at synthesising polymers containing quinoline rings in the main chains starting from benzidine and bis( $\beta$ -diketones), *viz.*, 4,4'-bis(acetoacetyl)diphenyloxide and 4,4'-bis(acetoacetyl)diphenylethane, was undertaken by Korshak *et al.*<sup>45</sup> (Scheme 1).

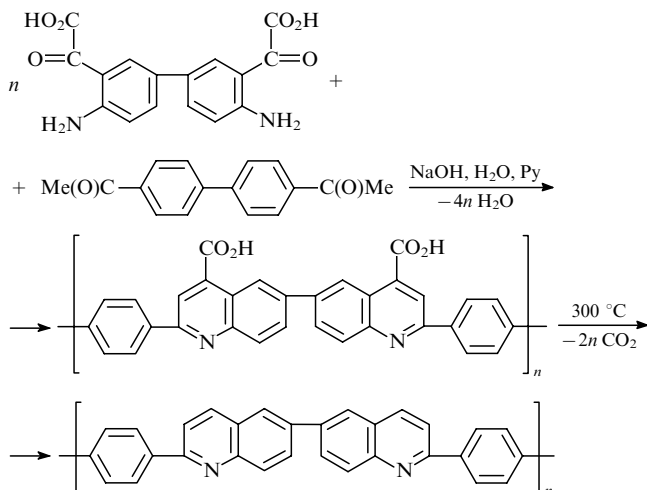
The polyanils formed in the first step were soluble in cresol, DMSO and H<sub>2</sub>SO<sub>4</sub> (the reduced viscosities of their solutions in H<sub>2</sub>SO<sub>4</sub> were 0.6–0.8 dl g<sup>–1</sup>), while polyquinolines prepared by thermal cyclisation of polyanils *in vacuo* were insoluble in either of these solvents, which significantly limited their processing into articles.

Some time later, Shopov<sup>46</sup> succeeded in obtaining a soluble PQ by extrapolation of the Pfitzinger reaction<sup>47</sup> to the polymer synthesis.

Scheme 1

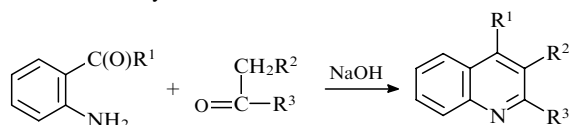


R = O, CH<sub>2</sub>CH<sub>2</sub>; PPA is polyphosphoric acid.



The carboxy-substituted PQ represented a dark-brown powder which was soluble in DMF, pyridine, DMSO and aqueous alkali and underwent decarboxylation to the target PQ upon heating to 300 °C. Unfortunately, no comprehensive analysis of the properties of the polymers obtained was reported.<sup>45, 46</sup>

Yet another approach to the synthesis of PQ was realised by Stille *et al.*,<sup>1–5, 48–52</sup> this was based on the Friedlander reaction.<sup>1–5, 53–56</sup> In its classical version, this reaction consists of an alkali-catalysed condensation of aromatic *o*-aminocarbonyl compounds with methylene ketones.<sup>54–56</sup>



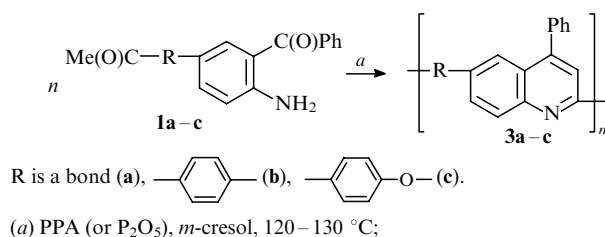
Formally, this reaction results in a Schiff base which undergoes subsequent aldol condensation<sup>57</sup> with involvement of the carbonyl group and the reactive methylene group.<sup>58</sup> It was shown<sup>59–64</sup> that acids are as effective as catalysts of the formation of the quinoline rings as alkalis.

The preparation of PQ by the Friedlander reaction may include both homocondensation of compounds containing *o*-aminocarbonyl and oxomethylene fragments<sup>51, 65–68</sup> and co-condensation of bis(*o*-aminocarbonyl) and bis(oxomethylene) derivatives.<sup>48–52</sup> In both cases, synthesis of the starting compounds presents the major problem, since substituted *o*-aminocarbonyl derivatives are difficult to access.<sup>58, 64</sup>

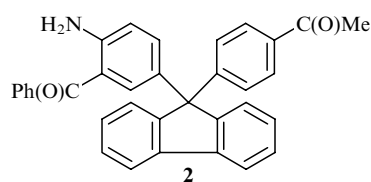
### 1. Synthesis of polyquinolines by homocondensation of AB-type monomers

5-Acetyl-2-aminobenzophenone (**1a**),<sup>51, 65, 69</sup> 4'-acetyl-4-amino-3-benzoylbiphenyl (**1b**),<sup>65</sup> 4'-acetyl-4-amino-3-benzoyldiphenyl oxide (**1c**)<sup>66</sup> and 9-(4-acetylphenyl)-9-(4-amino-3-benzoylphenyl)fluorene (**2**) were used as the AB monomers in the synthesis of PQ.<sup>68</sup> Homocondensation of the first three compounds in

*m*-cresol – polyphosphoric acid (PPA) or *m*-cresol – P<sub>2</sub>O<sub>5</sub> mixtures (according to <sup>31</sup>P NMR data, these systems represent mixtures of mono- and di-*m*-cresyl phosphate)<sup>52</sup> at 120–130 °C yielded the fibre-forming PQ **3a–c** containing lateral phenyl groups.



(a) PPA (or P<sub>2</sub>O<sub>5</sub>), *m*-cresol, 120–130 °C;



5-Acetyl-2-aminobenzophenone (**1a**) yielded the polyquinoline **3a**, which precipitated from the reaction mixture after 24–30 h. The intrinsic viscosities of its solutions in sulfuric acid were 1.3–3.6 dl g<sup>–1</sup>. According to X-ray diffraction data, the crystallinity of the polymer **3a** was close to 65%, as a result of which it was soluble only in sulfuric acid. The high crystallinity of the polymer **3a** is largely determined by the symmetry of its macromolecule due to the formation of only one geometric isomer of the PQ in the Friedlander reaction,<sup>51, 54</sup> while three isomers of polyquinolines, which are structurally similar to polyquinolines, are formed.<sup>31–33</sup>

Dynamic thermogravimetric analysis (TGA, ΔT = 5 °C min<sup>–1</sup>) revealed that the mass loss of the polymer **3a** began at 520 °C in air and at 570 °C in nitrogen; at 800 °C, the mass losses were 20%. Such a high thermal stability of polymer **3a** is explicable, especially if one takes into consideration the high extent of cyclisation<sup>51</sup> and high thermal stability of the quinoline ring.<sup>44</sup> The high rigidity and crystallinity of the PQ formed account for its high glass-transition (T<sub>g</sub> = 415 °C) and melting (T<sub>m</sub> = 552 °C) temperatures<sup>1, 49, 65</sup> and limited solubility significantly complicates its processing into articles.

The PQ **3b**, the homocondensation product of 4'-acetyl-4-amino-3-benzoylbiphenyl (**1b**), manifests similar characteristics. The comparative characteristics of the polymers **3a, b** are listed in Table 1.

Somewhat better solubilities of rigid-rod homocondensation products of the AB-type monomers could be achieved if copolycondensation of compounds **1a** and **1b** was carried out. Thus the random copolymer of 5-acetyl-2-aminobenzophenone (**1a**) with 4'-acetyl-4-amino-3-benzoylbiphenyl (**1b**) was soluble not only in sulfuric acid, but also in trifluoroacetic acid (see Table 1). The observed better solubilities of rigid-rod random copolymers in comparison with those of homopolymers is in keeping with previously reported data.<sup>70, 71</sup>

**Table 1.** Some characteristics of polyquinolines **3a,b**.<sup>65</sup>

| Polymer          | Solubility <sup>a</sup>                                              | [ $\eta$ ]/dl g <sup>-1</sup><br>(see <sup>b</sup> ) | $T_g$ /°C<br>(DSC <sup>c</sup> ) | $T_m$<br>/°C | $T_d$ /°C (see <sup>d</sup> )<br>(TGA) |                |
|------------------|----------------------------------------------------------------------|------------------------------------------------------|----------------------------------|--------------|----------------------------------------|----------------|
|                  |                                                                      |                                                      |                                  |              | air                                    | N <sub>2</sub> |
| <b>3a</b>        | H <sub>2</sub> SO <sub>4</sub>                                       | 3.6                                                  | 415                              | 552          | 520                                    | 570            |
| <b>3b</b>        | H <sub>2</sub> SO <sub>4</sub>                                       | 11.6                                                 | —                                | 580          | 605                                    | 610            |
| See <sup>e</sup> | CF <sub>3</sub> CO <sub>2</sub> H,<br>H <sub>2</sub> SO <sub>4</sub> | 4.9                                                  | 330                              | 520          | 555                                    | 580            |

<sup>a</sup> In this case, the ability of the solvent to form 5% solutions of polymers is meant.

<sup>b</sup> The intrinsic viscosities [ $\eta$ ] were measured in concentrated H<sub>2</sub>SO<sub>4</sub> at 25 °C.

<sup>c</sup> DSC is differential scanning calorimetry.

<sup>d</sup> The temperature at which the initial mass loss of the polymer was observed.

<sup>e</sup> A random copolymer (1 : 1) of the monomers **1a** and **1b**.

The polyquinoline **3c** based on 4'-acetyl-4-amino-3-benzoyldiphenyl oxide (**1c**) is soluble in chloroform, THF and DMF, and holds more promise as regards its processing. The high solubility of this polyheteroarylene may be attributed to the presence of ether bonds, which is consistent with the results of other authors.<sup>72</sup> The glass-transition temperature ( $T_g$ ) of polymer **3c** is 235 °C; however, this compound has an amorphous structure and does not melt according to data from differential scanning calorimetry (DSC); its initial decomposition temperature is 513 °C.

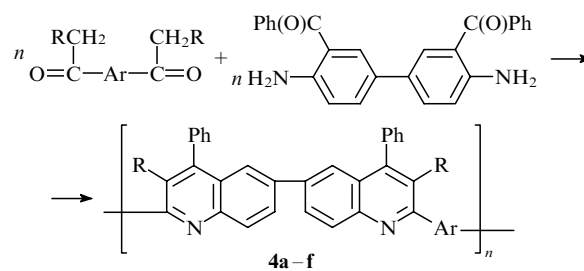
The introduction of 'cardo' groups,<sup>73</sup> of fluorene groups in particular, is yet another approach to the enhancement of the solubilities of PQ derived from AB-type monomers.<sup>68</sup> The corresponding monomer, 9-(4-acetylphenyl)-9-(4-amino-3-benzoylphenyl)fluorene (**2**) was prepared by an eight-step synthesis starting from fluorenone. Homocondensation of this monomer in a mixture of *m*-cresol with di-*m*-cresyl phosphate afforded a cardo polyquinoline containing fluorene groups. This polymer is amorphous, it is soluble in strong acids and *m*-cresol, and its  $T_g$  is 365 °C. However, the low characteristic viscosity of solutions of this polymer ([ $\eta$ ] = 0.24 dl g<sup>-1</sup>) is its drawback.

A much larger panel of PQ has been synthesised by reactions of bis(*o*-aminocarbonyl) compounds with diacylarylenes and diphenacylarylenes.

## 2. Synthesis of polyquinolines by co-condensation of bis(*o*-aminocarbonyl) compounds with diacyl- and diphenacylarylenes

### a. Rigid-rod polyquinolines

Polycondensation of 3,3'-dibenzoylbenzidine with various diacylarylenes affords rigid-rod poly(2,6-quinolines) with high glass-transition temperatures and limited solubilities.<sup>65</sup>

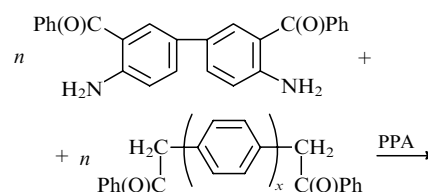


R = H, Ar =  $\text{—}(\text{C}_6\text{H}_4)_x\text{—}$ , where  $x = 1$  (**a**), 2 (**b**), 3 (**c**), 4 (**d**);

R = Ph, Ar =  $\text{—}(\text{C}_6\text{H}_4)_y\text{—}$ , where  $y = 1$  (**e**), 2 (**f**).

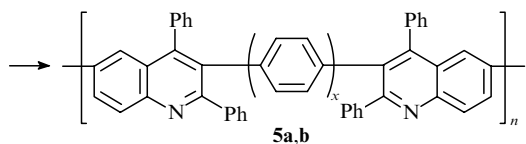
Some characteristics of rigid-rod PQ **4a–f** are listed in Table 2. Anisotropic solutions of these polymers in a *m*-cresol–di-*m*-cresyl phosphate mixture were used for the spinning of high-quality fibres.<sup>65</sup>

Poly(3,6-quinolines) **5a,b** were prepared by the reaction of 3,3'-dibenzoylbenzidine with diphenacylarylenes, viz., 1,4-diphenacylbenzene and 4,4'-diphenacylbiphenyl in a *m*-cresol–di-*m*-cresyl phosphate mixture.<sup>74</sup>

**Table 2.** Some characteristics of rigid-rod poly(2,6-quinolines) **4a–f**.<sup>65</sup>

| Polymer   | R  | Ar | Solubility <sup>a</sup>        |                                   | [ $\eta$ ]/dl g <sup>-1</sup><br>(see <sup>b</sup> ) | $T_g$ /°C<br>(DSC) | $T_m$ /°C | $T_d$ /°C (TGA) |                |
|-----------|----|----|--------------------------------|-----------------------------------|------------------------------------------------------|--------------------|-----------|-----------------|----------------|
|           |    |    | H <sub>2</sub> SO <sub>4</sub> | CF <sub>3</sub> CO <sub>2</sub> H |                                                      |                    |           | air             | N <sub>2</sub> |
| <b>4a</b> | H  |    | ps                             | s                                 | 7.0                                                  | 350                | —         | 570             | 595            |
| <b>4b</b> | H  |    | ins                            | s                                 | 14.5–26.0                                            | 340                | 500       | 570             | 580            |
| <b>4c</b> | H  |    | ins                            | s                                 | 22.0                                                 | 345                | 540       | 525             | 600            |
| <b>4d</b> | H  |    | ins                            | ins                               | —                                                    | 350                | —         | 580             | 600            |
| <b>4e</b> | Ph |    | ins                            | s                                 | 17.0                                                 | 370                | 555       | 580             | 590            |
| <b>4f</b> | Ph |    | ps                             | s                                 | 22.0                                                 | 360                | —         | 570             | 595            |

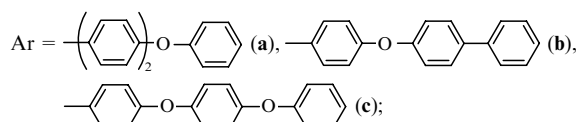
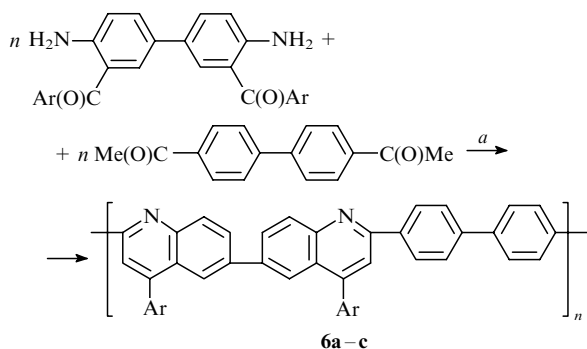
<sup>a</sup> Hereinafter, ps is partly soluble, s is soluble, ins is insoluble. <sup>b</sup> The intrinsic viscosities [ $\eta$ ] were measured in CF<sub>3</sub>CO<sub>2</sub>H at 25 °C.



| Polymer   | <i>x</i> | Solubility                                          | $[\eta]$<br>/dl g <sup>-1</sup> | $T_g$ /°C<br>(DSC) | $T_m$ /°C | $T_d$ /°C |                |
|-----------|----------|-----------------------------------------------------|---------------------------------|--------------------|-----------|-----------|----------------|
|           |          |                                                     |                                 |                    |           | air       | N <sub>2</sub> |
| <b>5a</b> | 1        | H <sub>2</sub> SO <sub>4</sub>                      | 0.5                             | 370                | 550       | 570       | 575            |
| <b>5b</b> | 2        | <i>m</i> -cresol,<br>H <sub>2</sub> SO <sub>4</sub> | 2.4                             | 390                | 530       | 570       | 585            |

The PQ **5a** prepared from 1,4-diphenacylbenzene is poorly soluble in H<sub>2</sub>SO<sub>4</sub>, while the PQ **5b** based on 4,4'-diphenacylbiphenyl is soluble in both H<sub>2</sub>SO<sub>4</sub> and *m*-cresol. Polyquinolines **5a,b** have high glass-transition and melting temperatures; their initial thermal and thermooxidative decomposition temperatures are also high.<sup>74</sup>

Insufficient solubilities and high glass-transition temperatures of rigid-rod polyquinolines **4a–f** and **5a,b** made their processing problematic. Therefore, a search for approaches to the enhancement of the working characteristics of PQ was undertaken. Thus rigid-rod PQ **6a–c** containing extended arylene oxide fragments in the side chains were prepared by the condensation of 3,3'-diaroylbenzidines with 4,4'-diacetylbiphenyl.<sup>75</sup>



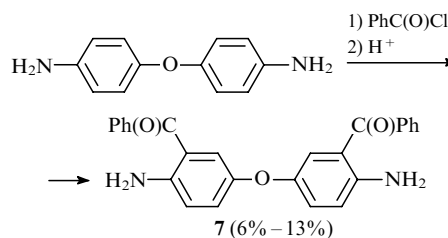
(a) *m*-cresyl phosphate, *m*-cresol, 136–138 °C, 48 h.

The glass-transition temperatures of polymers **6a–c** are in the interval 307–342 °C, while their melting temperatures are in the interval 416–505 °C. The solubilities of these phenyl PQ are similar to those of rigid-rod PQ containing lateral phenyl groups.<sup>65</sup>

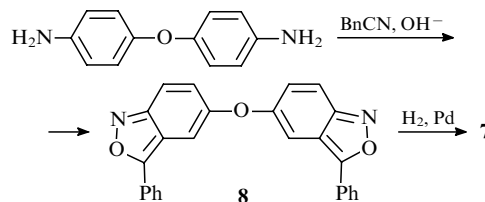
### b. Poly(ether quinolines)

The introduction of ether bonds into macromolecules of PQ, *i.e.*, the synthesis of poly(ether quinolines) (PEQ) has significantly improved their solubilities. Such polymers are formed by the above-considered polycondensation of diphenacylarylenes with bis(*o*-aminocarbonyl) compounds where 4,4'-diamino-3,3'-dibenzoylbiphenyl was replaced by 4,4'-diamino-3,3'-dibenzoyldiphenyl ether (**7**).

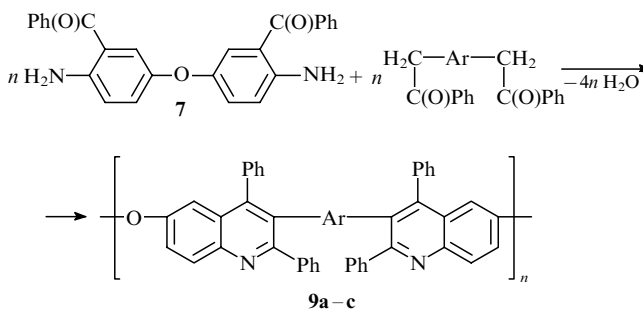
The oxide (**7**) was synthesised by two methods.<sup>51</sup> One of them included direct benzylation of 4,4'-diaminodiphenyl ether under drastic conditions to give compound **7**, which was difficult to purify (yields 6%–13%).



The second approach consisted of the reaction of 4,4'-diaminodiphenyl ether with phenylacetonitrile and subsequent reduction of the 5,5'-oxybis(3-phenyl-2,1-benzisoxazole) (**8**) formed, resulting in the monomer **7** (yield 85%).<sup>51</sup>



The synthesis of poly(ether 3,6-quinolines) **9a–c** from 4,4'-diamino-3,3'-dibenzoyldiphenyl ether (**7**) has been described.<sup>74</sup>



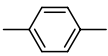
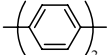
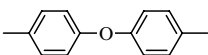
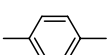
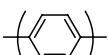
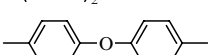
| Polymer   | Ar | Solubility        | $[\eta]$<br>/dl g <sup>-1</sup> | $T_g$ /°C<br>(DSC) | $T_m$ /°C | $T_d$ /°C |                |
|-----------|----|-------------------|---------------------------------|--------------------|-----------|-----------|----------------|
|           |    |                   |                                 |                    |           | air       | N <sub>2</sub> |
| <b>9a</b> |    | CHCl <sub>3</sub> | 0.7                             | 312                | —         | 535       | 570            |
| <b>9b</b> |    | TCE               | 3.6                             | 325                | —         | 530       | 550            |
| <b>9c</b> |    | CHCl <sub>3</sub> | 1.2                             | 255                | —         | 530       | 575            |

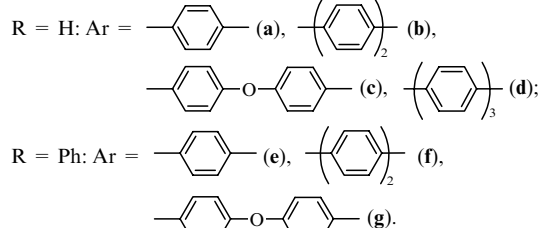
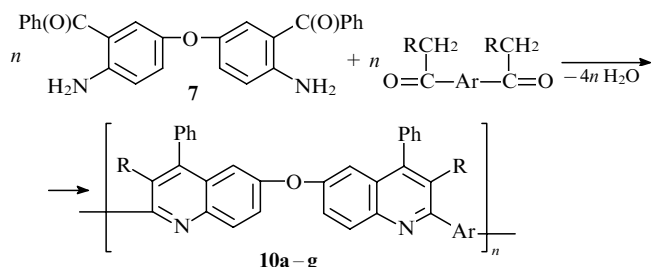
Poly(ether quinolines) **9a–c** were soluble not only in H<sub>2</sub>SO<sub>4</sub> and *m*-cresol, but also in chloroform and tetrachloroethane (TCE). Their glass-transition temperatures were in the range 255–325 °C; their melting temperatures could not be determined, presumably due to the lower crystallinities of these flexible-chain polymers in comparison with the rigid-rod polymers.<sup>76</sup> Solutions of PEQ in *m*-cresol, chloroform and tetrachloroethane were used for the preparation of strong transparent films by casting.

The reaction of 4,4'-diamino-3,3'-dibenzoyldiphenyl ether (**7**) with diacylarylenes in *m*-cresol–PPA and *m*-cresol–P<sub>2</sub>O<sub>5</sub> mixtures was used for the synthesis of phenyl-substituted poly(ether 2,6-quinolines) **10a–g**.<sup>77,78</sup> The reaction conditions and the main characteristics of some of these compounds are listed in Table 3.

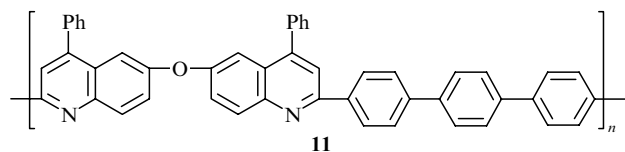


**Table 3.** Conditions of the synthesis and some characteristics of phenyl-substituted poly(ether 2,6-quinolines) **10**.<sup>78</sup>

| Polymer    | Ar                                                                                | R  | Conditions |        | Solubility        | $[\eta]$ /dl g <sup>-1</sup> | $T_g$ /°C | $T_m$ /°C | $T_d$ /°C |
|------------|-----------------------------------------------------------------------------------|----|------------|--------|-------------------|------------------------------|-----------|-----------|-----------|
|            |                                                                                   |    | $T$ /°C    | $t$ /h |                   |                              |           |           |           |
| <b>10a</b> |  | H  | 135        | 122    | CHCl <sub>3</sub> | 0.6                          | 300       | 455       | 540       |
|            |                                                                                   |    | 130        | 48     | CHCl <sub>3</sub> | 1.0                          |           |           |           |
| <b>10b</b> |  | H  | 130        | 41     | <i>m</i> -cresol  | 2.0                          | 308       | 480       | 530       |
|            |                                                                                   |    | 130        | 48     | <i>m</i> -cresol  | 3.1                          |           |           |           |
| <b>10c</b> |  | H  | 135        | 49     | CHCl <sub>3</sub> | 1.0                          | 266       | 448       | 545       |
|            |                                                                                   |    | 130        | 48     | CHCl <sub>3</sub> | 1.6                          |           |           |           |
| <b>10e</b> |  | Ph | 130        | 21     | <i>m</i> -cresol  | 3.4                          | 345       | 475       | 535       |
| <b>10f</b> |  | Ph | 130        | 21     | <i>m</i> -cresol  | 4.1                          | 351       | 480       | 540       |
| <b>10g</b> |  | Ph | 130        | 24     | CHCl <sub>3</sub> | 2.0                          | 305       | 476       | 530       |

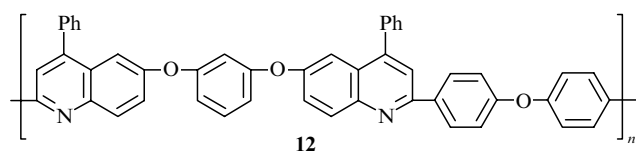


These polymers were soluble in chloroform and *m*-cresol. Even PEQ **11** was soluble in both sulfuric and formic acids and *m*-cresol.<sup>78</sup>

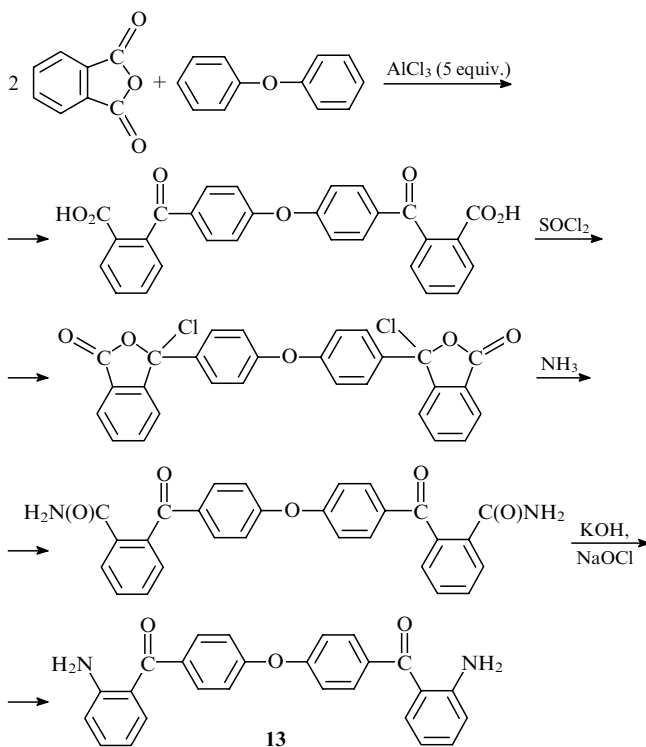


It was shown that the solubilities of phenyl-substituted PEQ were lower than those of the analogues devoid of the phenyl groups, which is in contrast with the data for other classes of rigid-rod polymers.<sup>31–33, 79, 80</sup> This can be attributed to the higher proneness of the former to aggregation due to hindered rotation of the quinoline rings.

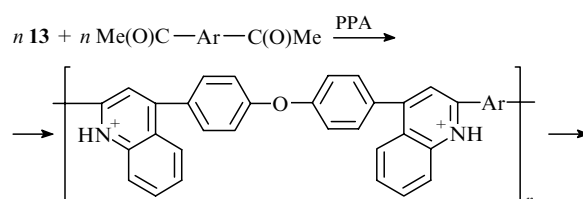
Further increase in the number of ether bonds in the main chains of PEQ was achieved using resorcinol bis(4-amino-3-benzoylphenyl) ether as a monomer. Its condensation afforded PEQ **12**, which is soluble not only in formic acid and chloroform, but also in *N*-methyl-2-pyrrolidone (*N*-MP).<sup>81</sup> The softening temperature of PEQ **12** is 135 °C.

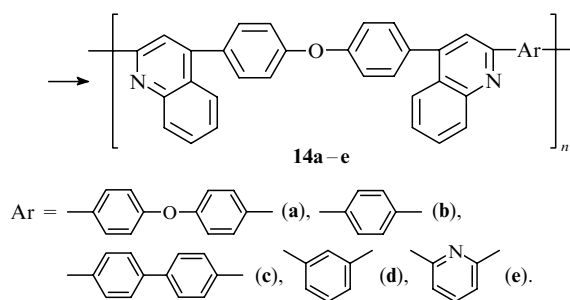


A method for the synthesis of 4,4'-bis(2-aminobenzoyl)di-phenyl ether (**13**) was developed by Norris and Stille.<sup>51</sup>



Its reaction with diacetylenes yielded the polymers **14a–e** containing 2,4-substituted quinoline fragments.<sup>48–50</sup>





This reaction proceeds especially smoothly in mixtures of *m*-cresol with PPA or P<sub>2</sub>O<sub>5</sub>; the formation of a protonated form of PEQ in these media is an essential feature as a result of which the polymer remains in the solution up to the end of the reaction. The reaction conditions and some characteristics of the PEQ synthesised are listed in Table 4.

**Table 4.** Conditions of the synthesis and some characteristics of PEQ **14a,c–e**.<sup>50</sup>

| Polymer    | Conditions |        | $[\eta]^a$<br>/dl g <sup>−1</sup> | $T_g$<br>/°C | $T_m$<br>/°C     | $T_d$<br>/°C |
|------------|------------|--------|-----------------------------------|--------------|------------------|--------------|
|            | $T$ /°C    | $t$ /h |                                   |              |                  |              |
| <b>14a</b> | 125        | 50     | 0.62                              | 251          | 483              | 510          |
|            | 130        | 13     |                                   |              |                  |              |
| <b>14c</b> | 110        | 5      | 0.38                              | 326          | 475              | 575          |
|            | 120        | 12     |                                   |              |                  |              |
|            | 150        | 24     |                                   |              |                  |              |
| <b>14d</b> | 100        | 16     | 0.36                              | 268          | see <sup>b</sup> | 520          |
|            | 130        | 45     |                                   |              |                  |              |
| <b>14e</b> | 100        | 18     | 0.08                              | —            | —                | —            |
|            | 135        | 48     |                                   |              |                  |              |

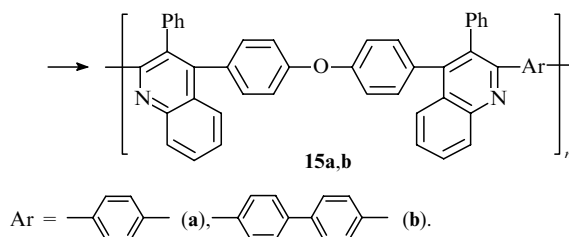
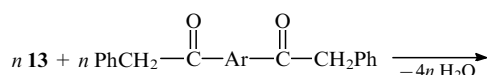
<sup>a</sup> The intrinsic viscosity was measured in *m*-cresol.

<sup>b</sup> An amorphous polymer.

The polyquinolines **14a–e** have amorphous structures and are easily soluble in *m*-cresol and chloroform. Their softening temperatures are much lower than those of rigid-rod PEQ.

Properties of the PEQ polymer **14a** have been studied in much more detail.<sup>48–50</sup> The relatively high molecular mass (~50 000) and its good solubility in *m*-cresol and chloroform made it possible to use it as a starting material for the preparation of strong elastic films and fibres; subsequent orientation of the latter noticeably increased their crystallinities.<sup>50,77</sup> The polymer **14a** possessed high thermal stability upon dynamic and isothermal TGA. Thus dynamic TGA (air,  $\Delta T = 5^\circ\text{C min}^{-1}$ ) revealed that its initial decomposition temperature was 510 °C; a 10% mass loss in nitrogen occurred at 800 °C. According to data from isothermal TGA, the polymer retained its stability upon heating at 300 °C in circulating air over 100 h. It decomposed at 360 °C, the mass loss after 21 h being 10%. Complete decomposition of the polymer occurred after 39 h.

The reaction of 4,4'-bis(2-aminobenzoyl)diphenyl ether (**13**) with 1,4-diphenylacetylbenzene and 4,4'-diphenylacetyl biphenyl afforded phenyl-substituted poly(2,4-quinolines) **15a,b**.<sup>48–50, 69</sup>



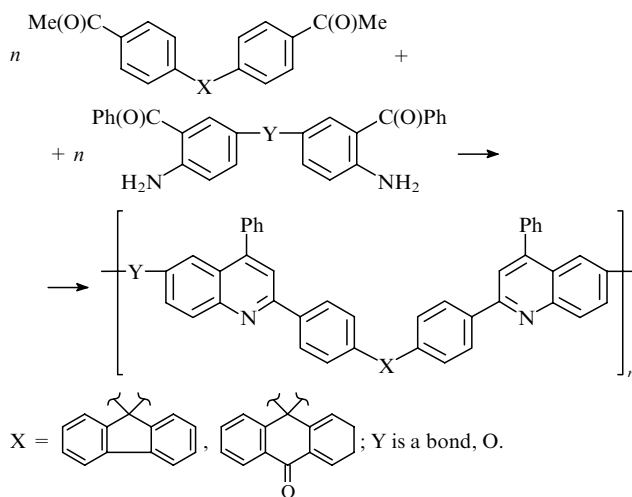
The polymers **15a,b** are soluble in *m*-cresol; their intrinsic viscosities are 0.26 and 0.57 dl g<sup>−1</sup>, respectively. The polymer **15a** was not obtained in a crystalline state; its glass-transition temperature was 273 °C; the glass-transition and melting temperatures of the polymer **15b** were 345 and 500 °C, respectively.<sup>68</sup> Strong elastic films could be prepared from 15%–25% solutions of these PEQ in CHCl<sub>3</sub> or a (3 : 1) TCE–*m*-cresol mixture, which became opaque upon slow evaporation of the solvents due to partial (~20%) crystallisation.

According to dynamic TGA ( $\Delta T = 5^\circ\text{C min}^{-1}$ ) the decomposition of the polymer **15a** in air and in nitrogen began at 530–545 °C and at 530–570 °C, respectively. In nitrogen, the mass loss of the polymer at 800 °C was only 15%–26%. According to the data from isothermal TGA, no mass loss of the polymer **15b** in circulating air occurred over 100 h at 300 °C; over the same time at 371 °C, the mass loss was 48%.

### c. Polyquinolines containing cardo, tetraphenylsilyl and perfluorotetramethylene groups

A series of cardo polymers<sup>82,83</sup> and PQ containing tetraphenylsilyl<sup>84</sup> and perfluorotetramethylene groups have been synthesised in order to improve the processibility of high-molecular-weight PQ.<sup>85,86</sup>

9,9-Bis(4-acetylphenyl)fluorene and 9,9-bis(4-acetylphenyl)-10-anthrone<sup>82</sup> were synthesised aimed at the preparation of cardo PQ. These were further introduced into reactions with bis(*o*-aminobenzophenones).<sup>82</sup>

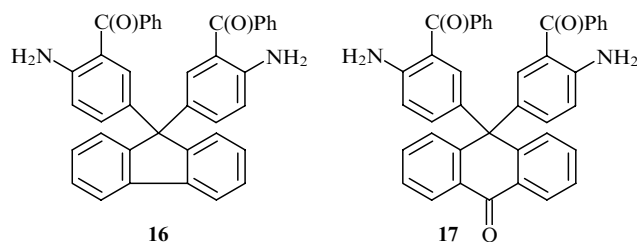


The majority of the cardo PQ thus prepared were soluble not only in *m*-cresol, but also in chloroform and TCE.

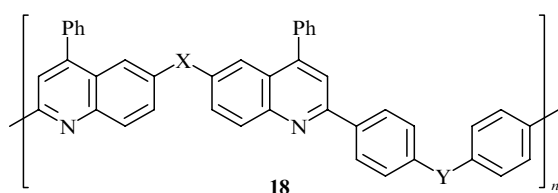
The introduction of cardo groups has made it possible to increase the glass-transition temperatures of PQ by 40–70 °C in comparison with PEQ. The PQ based on cardo diacetyl derivatives are characterised by extremely high thermostabilities; their decomposition began at the temperatures above 550 °C. The decomposition temperatures of anthronyl-containing PQ are 30–50 °C lower than those of fluorene-containing PQ.

By virtue of their high molecular masses (up to  $5.25 \times 10^5$  Da), some of these polymers<sup>83</sup> were successfully used for the preparation of strong films.

Polyquinolines prepared from cardo bis(*o*-amino ketones), viz., 9,9-bis(4-amino-3-benzoylphenyl)fluorene (**16**) and 9,9-bis(4-amino-3-benzoylphenyl)-10-anthrone (**17**),<sup>82</sup> were soluble in chlorinated hydrocarbons and thermostable (up to 520–580 °C). Their glass-transition temperatures were 310–420 °C.

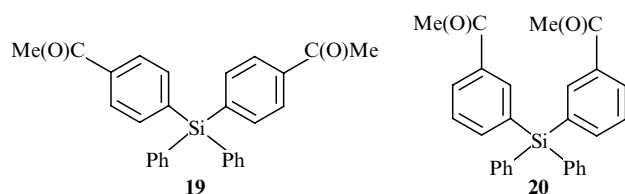


The use of comonomers each containing cardo groups for the synthesis of PQ has led to the polymers **18** which are soluble in chlorinated solvents (CHCl<sub>3</sub>, TCE). Some properties of the cardo PQ **18** are listed in Table 5.



Studies of rigid-rod cardo PQ by dynamic TGA revealed that the polymers containing one cardo and one 4,4'-biphenyl group in the repeating unit of the polymer possessed better mechanical properties than the flexible-chain polymers containing one cardo and one 4,4'-diphenylene oxide group or two cardo groups in the polymer unit.

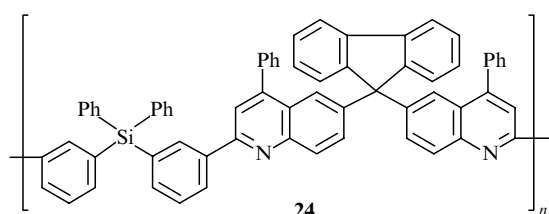
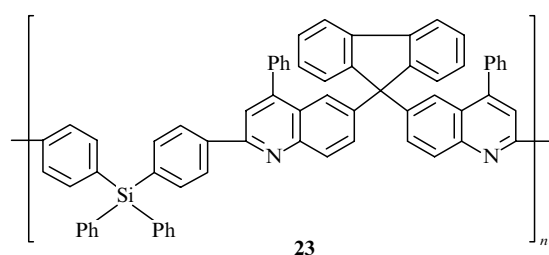
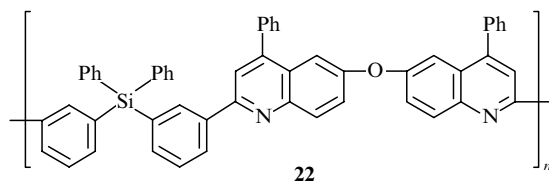
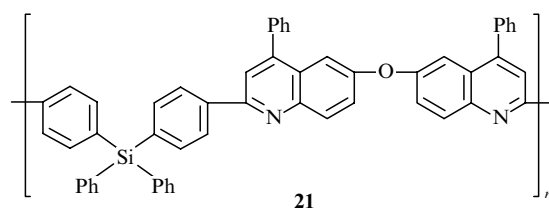
The silicon-containing diacetyl monomers **19** and **20** were synthesised<sup>84</sup> and introduced into the acid-catalysed polycyclocondensation with bis(*o*-aminobenzophenones) **7** and **16**



resulting in PQ **21–24**.

**Table 5.** Some characteristics of cardo PQ **18**.<sup>82</sup>

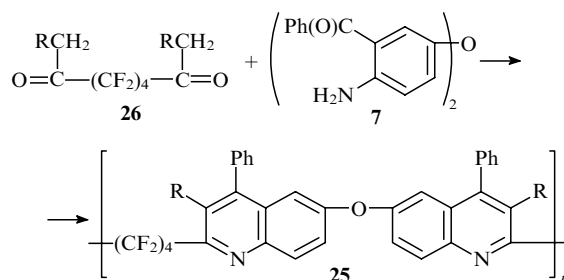
| X | Y | $[\eta]$ / dl g <sup>-1</sup> | $T_g$ / °C | $T_d$ / °C |
|---|---|-------------------------------|------------|------------|
|   |   | 0.58                          | 390        | 580        |
|   |   | 0.70                          | 385        | 530        |
|   |   | 1.30                          | 405        | 540        |
|   |   | 0.53                          | 390        | 520        |



Both homo- and block-copolymers with fluorene-containing cardo blocks were prepared by condensation of equimolar amounts of compounds **7** and **16** with the diacetyl monomers **19** and **20** in *m*-cresol–di-*m*-cresyl phosphate at 140 °C.

The solubilities of the polymers **21–24** exceed those of the majority of PQ.<sup>1–5</sup> In addition, these compounds swell strongly in many solvents, such as *m*-cresol, chloroform, dichloromethane, *N*-MP, DMF, benzene and chlorobenzene.

Easily processable polyquinolines **25** ( $T_g$  = 142–183 °C) were prepared from comonomers **26** containing perfluorotetramethylene groups.<sup>85, 86</sup>



Polymers **21–25** were used for the preparation of high-quality films<sup>50, 69, 77, 79</sup> and fibres<sup>50, 69, 77, 87</sup> some of which manifest high thermal characteristics.<sup>50, 69, 77, 87, 88</sup>

However, introduction of ether bonds or perfluoroalkylene groups aimed at improving the processability of PQ results in a decrease in the glass-transition or softening temperatures and, consequently, their operating temperatures. These can be increased by crystallisation of amorphous polymers. However, its practical realisation is rather a difficult task; therefore, an alternative approach, viz., post-moulding curing of amorphous polymers, has been developed.

#### d. Reactive oligo- and polyquinolines

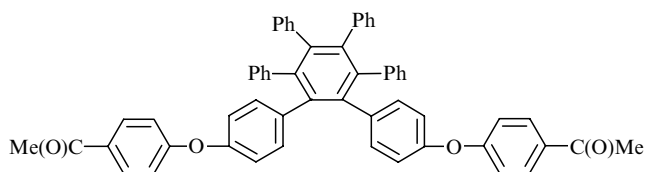
Reactive oligo- and polyquinolines can be prepared by several methods. These include

(1) introduction of terminal arylcyanate groups into PQ with subsequent cyclotrimerisation resulting in internodal *sym*-triazine fragments (Scheme 2);<sup>89</sup>

(2) introduction of biphenylene fragments,<sup>52,90–94</sup> which undergo ring-opening at 350–400 °C to generate biradicals that further recombine into dimers and/or polymers;<sup>90–96</sup>

(3) introduction of terminal biphenylene groups and triple C–C bonds into the main chains of PQ.<sup>94</sup> This enables cross-linking of the polymers, if the reactions are carried out at high temperatures<sup>95</sup> or in the presence of nickel catalysts;<sup>97</sup>

(4) introduction of hexaarylbenzene fragments into macromolecules of PQ<sup>98</sup> using 1,2-bis[4-(acetylphenoxy)phenyl]-3,4,5,6-tetraphenylbenzene as a comonomer for PQ synthesis.



These hexaarylbenzene fragments are effective cross-linking agents, which enable preparation of polymers with enhanced thermal and mechanical properties, especially at temperatures exceeding the glass-transition temperatures of the original PQ;<sup>99</sup>

(5) introduction of terminal [2.2]paracyclophane groups<sup>100</sup> with subsequent curing of reactive PQ obtained due to the opening of the [2.2]paracyclophane rings.

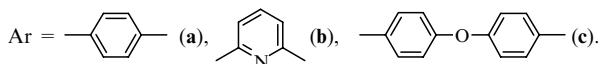
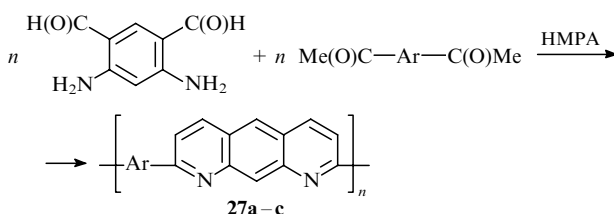
All these approaches seem to hold much promise with regard to the design of novel composites with enhanced thermal and mechanical characteristics.<sup>94</sup>

In addition to thermal and mechanical properties, considerable attention of investigators is given to the electrophysical characteristics of PQ.<sup>98,101</sup> Thus materials with conductivities of

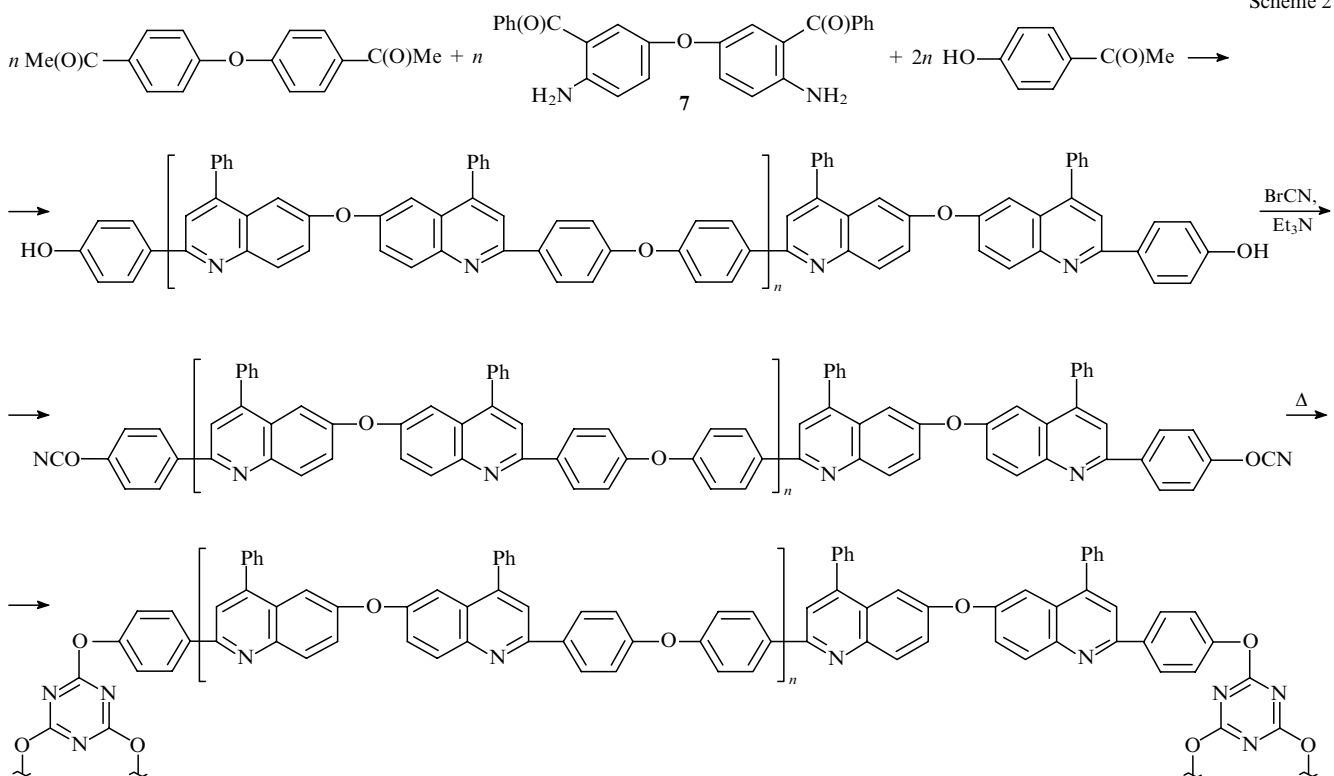
11  $\Omega\text{ cm}^{-1}$  could be prepared by doping PQ devoid of bridging groups with AsF<sub>5</sub>, iodine, sodium naphthalenide and anthracenide.<sup>98,101–107</sup> Among those, rigid-rod PQ prepared by doping with sodium anthracenide manifested the highest conductivities. However, PQ containing bridging groups possessed low permittivities ( $\epsilon \sim 2.8$ )<sup>108</sup> comparable to those of the best fluorine-free PHA.<sup>109</sup>

#### e. Polyanthrazolines

The Friedlander reaction was successfully employed in the synthesis of polymers containing both substituted and non-substituted anthrazoline or isoanthrazoline rings in the main chains. Thus the reaction of 4,6-diaminoisophthalaldehyde with diacetylarenes in hexamethyl phosphorotriamide (HMPA)<sup>110,111</sup> yielded the polymers **27a–c**.

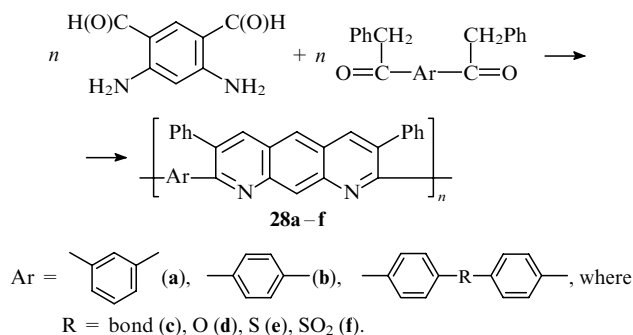


The polyanthrazolines thus prepared possessed high thermostabilities: according to dynamic TGA ( $\Delta T = 10\text{ }^\circ\text{C min}^{-1}$ ), the mass loss in air began at 450 °C, whereas in an inert atmosphere the 5% mass loss was observed at 600–650 °C. However, these polymers were soluble only in sulfuric acid. They sedimented from reaction solutions, which prevented the formation of high molecular mass products; the inherent viscosities of their solutions in sulfuric acid did not exceed 0.26 dl g<sup>–1</sup>. Polyanthrazolines prepared from dibenzoylphenylenediamines instead of dialdehydodiamines as

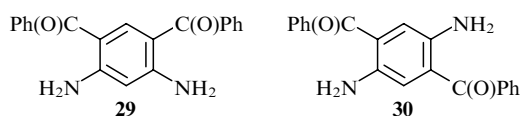


$n = 4, 10, 11$ .

Acid- or base-catalysed reactions of 4,6-diaminoisophthalaldehyde with bis(phenylacetyl)arenes gave the phenyl-substituted PAZ **28a–f**,<sup>113</sup> which manifested better solubilities than their analogues bearing no phenyl groups.



Therefore, phenylated PAZ prepared from 4,6-dibenzoyl-1,3-phenylenediamine (**29**) and 2,5-dibenzoyl-1,4-phenylenediamine (**30**) as monomers in the presence of acid catalysts were used in further studies.<sup>113</sup>



ClC(=O)c1cc([N+](=O)[O-])cc([N+](=O)[O-])c1C(=O)Cl
 $\xrightarrow{\text{PhH, AlCl}_3}$ 
ClC(=O)c1cc([N+](=O)[O-])cc([N+](=O)[O-])c1C(=O)Ph
 $\xrightarrow{[\text{H}]}$ 
Nc1cc(N)cc(C(=O)Ph)c1C(=O)Ph
**29** (76%)

The scheme illustrates the synthesis of 2,6-bis(aminocarbonyl)-4,4'-biphenyl (29) and 2,6-bis(aminocarbonyl)-4,4'-biphenyl (30) from phthalic anhydride derivatives.

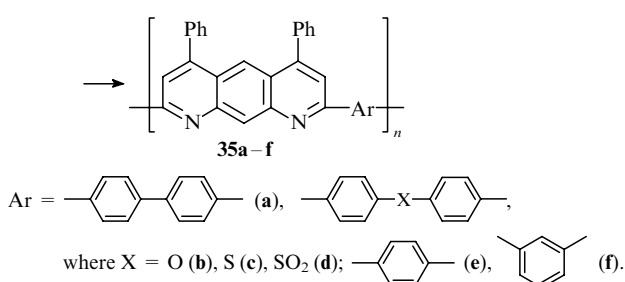
1. Phthalic anhydride reacts with PhH and AlCl<sub>3</sub> to form 2,6-bis(benzoyloxycarbonyl)phthalic acid (31) and 2,6-bis(benzoyloxycarbonyl)phthalic acid (32).

2. 31 reacts with SOCl<sub>2</sub> to form 2,6-bis(benzoyloxycarbonyl)-4,4'-biphenyl-2,6-dicarboxylic acid (33).

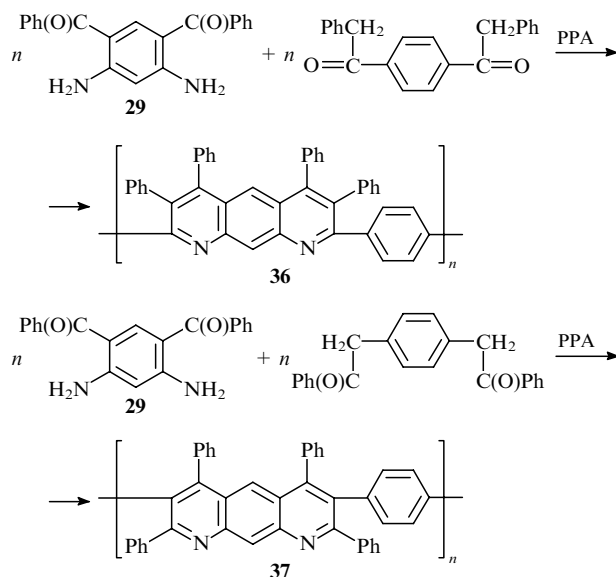
3. 33 reacts with NH<sub>3</sub> to form 2,6-bis(benzoyloxycarbonyl)-4,4'-biphenyl-2,6-diamine (29) (86% yield).

4. 32 reacts with SOCl<sub>2</sub> to form 2,6-bis(benzoyloxycarbonyl)-4,4'-biphenyl-2,6-dicarboxylic acid (34).

5. 34 reacts with NH<sub>3</sub> to form 2,6-bis(benzoyloxycarbonyl)-4,4'-biphenyl-2,6-diamine (30) (72% yield).

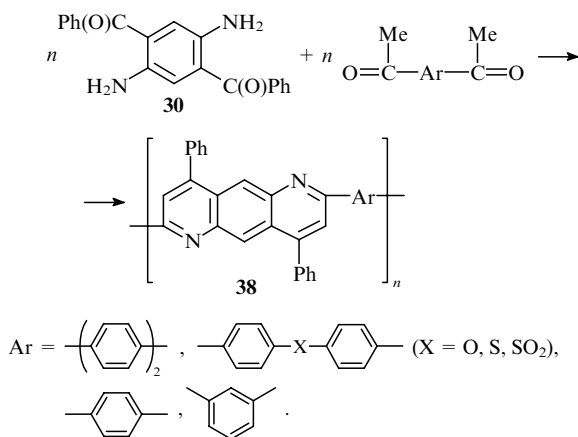
$$n \text{ Ph(O)C-C}_6\text{H}_2\text{(NH}_2\text{)}_2\text{-C(O)Ph} + n \text{ Me-C(=O)-Ar-C(=O)-Me} \xrightarrow{\text{Cat}}$$


Isomeric PAZ **36** and **37** containing four phenyl substituents in each polymeric fragment were prepared by the reaction of diamine **29** with 1,4-bis(phenylacetyl)benzene and 1,4-diphenylbenzene.<sup>1,2,111,113</sup>



The main characteristics of these polymers differ only insignificantly from those of the aforementioned phenylated PAZ **35a–f**.

The substitution of 2,5-dibenzoyl-1,4-phenylenediamine (**30**) for 4,6-dibenzoyl-1,3-phenylenediamine (**29**) gave polyisoanthrazolines **38**,<sup>1,113</sup> due to their greater symmetries, they possessed lower solubilities than those of the isomeric PAZ. The thermal characteristics of polymers **30** are similar to those of other PAZ.

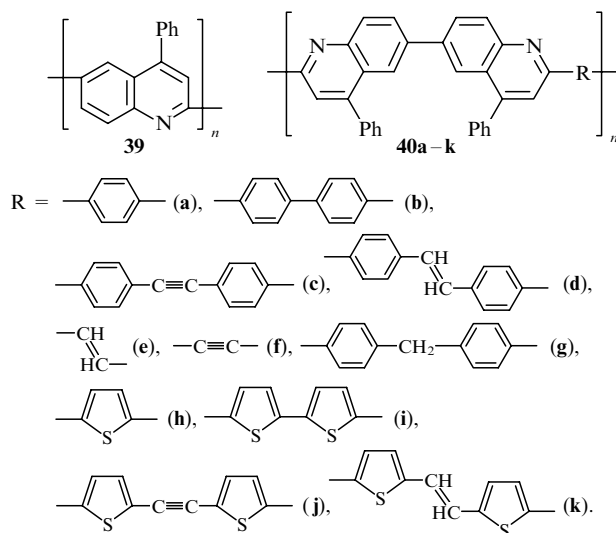


### III. Polyquinolines possessing electroluminescent properties

Polymers possessing electroluminescent properties attracted attention as materials for electrooptics, for the preparation of light-emitting diodes (LED), in particular.<sup>115–124</sup>

Considering that the majority of conjugated electroluminescent polymers form and transport 'holes' much more efficiently than electrons,<sup>125–127</sup> the construction of polymers with enhanced electron-transport properties is a topical task. It was found that polyquinolines with different structures possess remarkable electron-transport properties<sup>8,9,128,129</sup> and can be used for the preparation of electron-transport layers for LED.

The polymers **39** and **40a–k** were the subject of investigation in one of the first systematic studies of PQ and PAZ possessing high photoluminescent properties.<sup>8,9,130</sup>

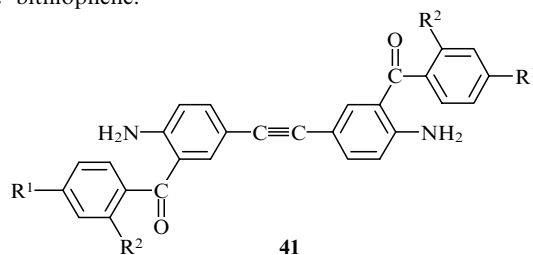


In-depth studies of these polymers, which differ in the lengths of their conjugation chains, have shown that the widths of their optical forbidden bands differed by 1.0 eV. Thus the width of the optical forbidden band ( $E_g$ ) of PQ **40b** containing a biphenyldiyl fragment was equal to 2.81 eV, while that of PAZ **40j** containing a dithienylvinylene fragment was 2.0 eV. Substitution of the thiophene groups for the phenylene groups caused a noticeable long-wavelength shift of the absorption maximum ( $\lambda_{\text{max}}$ ) (by 64–106 nm) with concomitant narrowing of the forbidden band by 0.3–0.5 eV. Some characteristics of these PQ are presented in Table 6.

Table 6. Optical characteristics of conjugated PQ.<sup>9</sup>

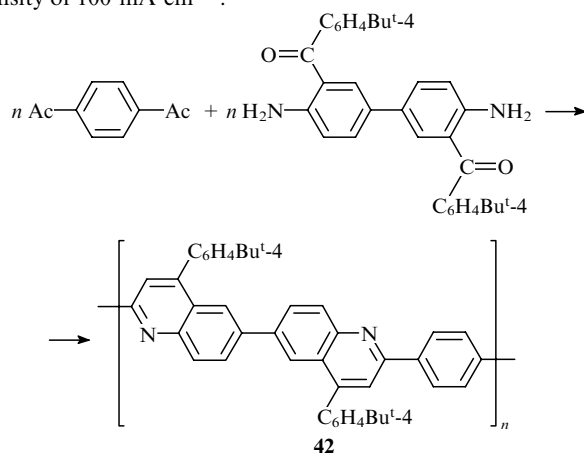
| Polymer    | $\lambda_{\text{max}}$ (film) | $\lambda_{\text{max}}$ (solution) | $E_g$ | $\log \epsilon$ |
|------------|-------------------------------|-----------------------------------|-------|-----------------|
| <b>39</b>  | 410                           | 389                               | 2.65  | 4.16            |
| <b>40a</b> | 398                           | 405                               | 2.78  | 4.63            |
| <b>40b</b> | 394                           | 429                               | 2.81  | 4.83            |
| <b>40c</b> | 399                           | 436                               | 2.72  | 4.86            |
| <b>40d</b> | 408                           | 467                               | 2.65  | 4.88            |
| <b>40g</b> | 370                           | 389                               | 3.01  | 4.68            |
| <b>40h</b> | 441                           | 493                               | 2.49  | 4.78            |
| <b>40i</b> | 468                           | 546                               | 2.33  | 5.06            |
| <b>40j</b> | 469                           | 567                               | 2.26  | —               |
| <b>40k</b> | 484                           | 578                               | 2.23  | 5.00            |

The monomers **41** were synthesised, and a novel procedure for the introduction of the acetylenic fragments into PQ was proposed, which consisted of polycondensation with 5,5'-diacetyl-2,2'-bithiophene.<sup>131</sup>

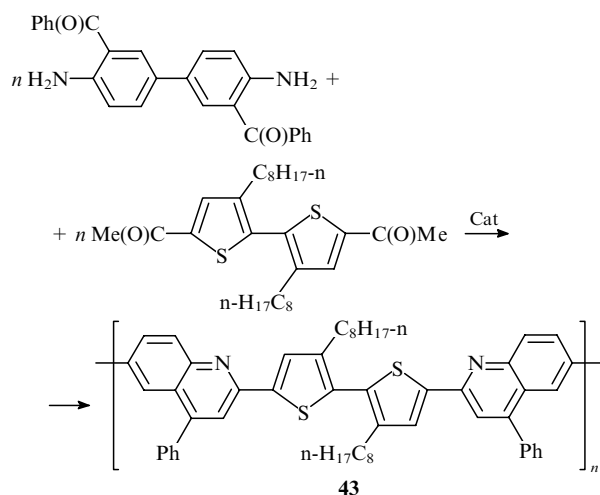


$R^1 = R^2 = \text{H}$ ;  $R^1 = \text{OMe}$ ,  $R^2 = \text{H}$ ;  $R^1 = \text{H}$ ,  $R^2 = \text{F}$ .

An attempt has been made to overcome the limited solubilities of rigid-rod conjugated PQ by modifying them through introduction of alkyl substituents.<sup>132–139</sup> However, no enhanced solubility was observed for PQ **42** containing *tert*-butyl substituents in the *para*-position of the phenyl rings.<sup>133, 134</sup> Notwithstanding, this PQ was used for the preparation of electroluminescent films with a light-yellow emission ( $\lambda_{\text{max}} = 554$  nm), proton/electron quantum efficiency of 0.26% and a brightness of 280 cd m<sup>-2</sup> at a current density of 100 mA cm<sup>-2</sup>.



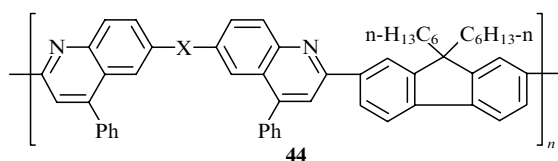
The increase in the solubility of PQ is better achieved by introducing higher alkyl (*e.g.*, octyl) substituents.<sup>135</sup>



The polymer **43** thus prepared was soluble in formic acid and other protic solvents as well as in THF, toluene and CHCl<sub>3</sub>. The absorption maximum of a solution of PQ **43** was 414 nm. Green emission ( $\lambda_{\text{max}} = 510$  and 530 nm) was observed for a solution and a thin polymeric film, respectively.

Considerable attention has also been given to PQ that contained fluorene groups with alkyl substituents.<sup>136–138</sup>

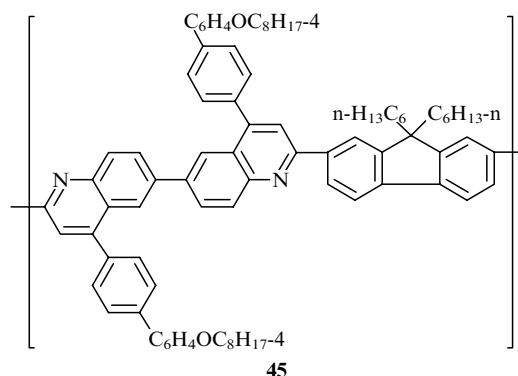
Polyquinolines with the general formula **44** containing 9,9-di(*n*-hexyl)fluorene fragments were prepared by the reaction of 2,7-diacetyl-9,9-di(*n*-hexyl)fluorene with diaminobenzoyl compounds.<sup>136, 137</sup>



X is a bond, O, S, CH = CH.

The PQ formed are soluble in CHCl<sub>3</sub>, THF and chlorobenzene; their glass-transition temperatures lie in the range 195–243 °C. The electroluminescence spectra of PQ are charac-

terised by blue emission (432 nm). The use of [4,4'-diamino-3,3'-bis(4'-octyloxybiphenyl-4-yl)carbonyl]biphenyl as a monomer allowed introduction of additional 4-octyloxybiphenyl groups into PQ **45**, which is soluble in CHCl<sub>3</sub>, THF and dimethylacetamide.<sup>138</sup>



The electroluminescence maximum of PQ **45** lies around 530 nm (green emission). Mixing of this PQ with polyvinylcarbazole results in a blue shift of the maximum due to the dilution effect.<sup>139</sup>

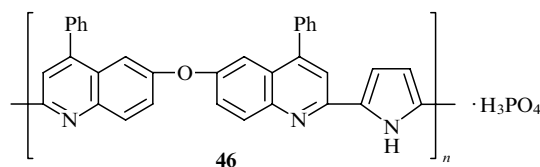
The effectiveness of formation of polymeric mixtures for the enhancement of the electroluminescent properties of the target materials has been reported.<sup>140, 141</sup>

## IV. Conclusion

The data considered in the present review illustrate the indisputable progress in the area of the synthesis of PQ and PAZ and their use in the preparation of unique materials, *e.g.*, fibres, films, composite materials and electroluminescent systems.

Novel promising areas for the application of PQ have recently been outlined. In the first place, these include the construction of second<sup>142–145</sup> and third<sup>146–148</sup> generations of materials for non-linear optics.

Of considerable interest are the data related to the use of pyrrole-containing PQ for complex formation with strong acids.<sup>149</sup> Such complexes were used for the preparation of proton-exchange membranes,<sup>149</sup> which represent the most important components of fuel cells relevant to the key technologies of the 21st century.<sup>150–154</sup> Thus a proton-exchange membrane based on complex **46** manifests enhanced proton conductivity ( $1.5 \times 10^{-5}$  Ω cm<sup>-1</sup> at 157 °C),<sup>149</sup> which surpasses that of the known polybenzimidazole–H<sub>3</sub>PO<sub>4</sub> complexes ( $7 \times 10^{-5}$  Ω cm<sup>-1</sup> at 150 °C).<sup>155</sup>



The remarkably high thermal conductivity of PQ·H<sub>3</sub>PO<sub>4</sub> membranes opens up promising opportunities for their wide applications.

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# Physicochemical aspects of the action of volatile metal corrosion inhibitors

N N Andreev, Yu I Kuznetsov

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**Abstract.** The state-of-the-art of investigations into the development and perfection of volatile corrosion inhibitors is analysed. The characteristic features of metal protection by these compounds and the effects of their chemical structures on the properties are discussed. The problems of adsorption and protective post-effect of volatile corrosion inhibitors are considered. The bibliography includes 133 references.

## I. Introduction

Atmospheric corrosion, which occurs not only under thick (phase-type) films but also under thin (adsorption-type) water films, is the most common type of corrosion.<sup>1–6</sup> The use of volatile corrosion inhibitors (VCIs) for metal protection from atmospheric corrosion started in the 1940s when Shell Co. patented the use of amine nitrites for this purpose.<sup>1</sup>

Volatility is the main distinctive feature of VCIs in comparison with traditional metal corrosion inhibitors in aqueous solutions.<sup>7–12</sup> The ability of VCIs to propagate, upon evaporation, throughout a system to be protected predetermines their major advantage: it is unnecessary to apply such inhibitors on metal surfaces and no special measures are needed to remove them.<sup>1</sup> The latter feature is of importance where VCIs are used to protect military equipment during long-term storage, since this can quickly be put into operation as required.<sup>13, 14</sup>

In the storage and transportation of articles (the so-called temporary protection) or operation of bulky extended constructions and pipelines that contact corrosive vapours and gases, VCIs that spontaneously enter various crevices and interstices are adsorbed on metal surfaces from the vapour phase and create there thin protective films. It is important that the VCI vapour can saturate a corrosive liquid that is often condensed in hardly accessible places, thus ensuring the required protection in the liquid phase as well. It is due to this feature that VCIs are used in power engineering<sup>†</sup> and for the protection of inner surfaces of pipelines.

Depending on the structure that determines the saturated vapour pressure ( $p^0$ ) together with other characteristics, VCIs form adsorption layers of different thicknesses on the surface to be protected. In the corrosion protection of high-precision metal articles (for example, bearings, electrical or radio equipment and particularly electronic equipment that usually operates in moderately-corrosive environments), certain classes of VCIs form nano-sized protective layers upon adsorption, which is the most attractive feature. These VCIs can be used to protect ‘clean’ metallic surfaces where paint coatings are unacceptable. It was also reported<sup>15</sup> that in some cases VCIs improve the efficiency of organic coatings as well.

The majority of complex articles consist of various metals and alloys; for this reason, the so-called versatile VCIs have been developed. Both individual chemical compounds, such as hexamethyleneimine *m*-nitrobenzoate, benzimidazole and certain thiazoles as well as mixtures, *e.g.*, of 1,2,3-benzotriazole (BTA) which is an efficient corrosion inhibitor of many non-ferrous metals with VCIs that reliably protect only ferrous metals (amines, amine nitrites, *etc.*), became popular.<sup>1, 2, 16, 17</sup> However, the majority of these VCIs have low volatility, which limits their scope. In view of this, functionalised alkylamines were studied as VCIs and it was proved that incorporation of an additional functional group into an alkylamine molecule increases the protective ability of VCIs with respect to a wide range of metals and alloys and also makes it possible to optimise their volatility. As a result of these studies, versatile new-generation VCIs have been elaborated: dialkylamino ketones,<sup>1, 18</sup> dialkylamino nitriles,<sup>19</sup> *etc.*<sup>15</sup>

The scope of VCIs has expanded considerably over recent years. In addition to the traditional packing papers and porous carriers,<sup>1, 2, 20</sup> polymeric films containing volatile inhibitors as additives find general use.<sup>21–25</sup> The advantages of such materials over paper are obvious, though the introduction of a VCI into a polymer has some specific features, and not every inhibitor maintains its highly protective properties upon thermal treatment during the film preparation. Water-soluble VCIs were also recommended for modifying acrylate or alkyd films that have been suggested instead of preservative oils or paint coatings applied from organic solvents.<sup>26, 27</sup> Modified thin coatings ( $\delta \leq 25 \mu\text{m}$ ) can be used for the protection of metal articles during sea transportation or storage in air. Such coatings are advantageous due to their environmental safety, as regards both their application and removal, which is effected by aqueous washing solutions.

N N Andreev, Yu I Kuznetsov A N Frumkin Institute of Physical Chemistry and Electrochemistry, Russian Academy of Sciences, Leninsky prosp. 31, 119991 Moscow, Russian Federation. Fax (7-095) 334 85 90, tel. (7-095) 330 11 56, e-mail: nandreev@ipc.rssi.ru (N N Andreev), tel. (7-095) 334 85 90, e-mail: kuznetsov@ipc.rssi.ru (Yu I Kuznetsov)

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<sup>†</sup> The use of ammonia and volatile amines for the anti-corrosion protection of inner surfaces of steam-power plants and tubes started back in the 1920s.<sup>6</sup>

Volatile corrosion inhibitors are often used in combination with usual (contact-type) inhibitors to protect pipelines and equipment of water-supply systems. They are used to slow down corrosion not only in liquids but also in vapours.<sup>28,29</sup> Such protection becomes necessary where tanks or pipes are partially filled with water or where they are operated intermittently, for example, in seasonal operation. Sometimes, during shutdowns of boilers, turbines and other equipment, they are dried with air saturated with VCI vapour; this is more efficient in terms of corrosion protection than ordinary drying.<sup>30</sup> We have found that compounds that form azeotropic mixtures with water can be employed as VCIs,<sup>31</sup> which should help broaden the scope of VCIs. Under certain conditions, such VCIs ensure the metal protection even under heavy condensation of water vapour. In closed systems, aqueous solutions of these VCIs that protect the metal surface without deliberate drying will be convenient for hydrotesting, for example, of power equipment and other types of bulky equipment.

Increasing interest in VCIs is also being felt in the gas industry where they are used to protect the inner surfaces of steel pipelines, both as such and as part of film-forming blends.<sup>32–39</sup> It is important that VCIs are applicable for steel protection from hydrogen sulfide corrosion and from the quite peculiar carbon dioxide corrosion. An efficient method was described<sup>40</sup> for the use of VCIs for protecting the outside surface of an oil pipeline where it crossed a roadway. Mechanical damage is avoided in such cases by mounting a special duct around the pipeline; a VCI is introduced into the annular space in-between.

Volatile corrosion inhibitors were used as the basis for development of a novel type of anticorrosion agents, *viz.*, migrating corrosion inhibitors (MCIs).<sup>41–45</sup> These have been developed for the protection of steel reinforcement in concrete against corrosion, which is a pressing scientific and technical problem of current city- and bridge-building. For example, according to data from Ref. 43, ~200 million dollars is spent annually in the USA to repair bridges where chloride-induced destruction of reinforced concrete has occurred. The first MICs contained volatile amine carboxylates or alkanolamine carboxylates as the most important components that diffused through concrete pores (including vapour diffusion), reached the surfaces of reinforcing steel and inhibited its corrosion. Such inhibitors should not only possess high self-diffusion coefficients, be poorly adsorbed on cement stone and be well adsorbed on steel, but should also be competitive in these parameters with chlorides, which induce most often the corrosive destruction of reinforcing steel in concrete. It should be remembered that reinforcing steel could be corroded initially and that corrosion stimulation that often occurs due to its localisation is unacceptable in reinforced-steel structures, particularly in strained ones.

To date, the mechanism of action of MCIs has been studied insufficiently and its discussion is beyond the scope of this review. However, there is no doubt that this mechanism has much in common with that of VCIs. Obviously, the development of more efficient VCIs would also favour progress in the protection of reinforced-steel structures.

The requirements for corrosion protection have increased during the last decade, especially in terms of environmental safety. This certainly gives impetus to the development of new efficient and environmentally safe compositions and protective agents and favours the development of the theoretical basis of the VCI action. This provides prospects for rapid progress in this field.

## II. Specific features of vapour-phase metal protection by inhibitors

If the space to be protected can be sealed, at least partially, this is a direct indication for the use of VCIs. Depending on the conditions, VCI vapour fills the entire volume by diffusion or with a gas stream. It is the diffusability of the inhibitor vapour that determines the advantages of VCIs over other types of inhibitors

and governs some of their specific parameters, such as the protection radius ( $l_{pr}$ ), passivation time, *etc.*<sup>46–50</sup>

The kinetics of VCI vapour diffusion plays an important role in anti-corrosion protection from the onset of its contact with the metal. Volatile corrosion inhibitors are often used to preserve complex items that may fail due to even minor damage.<sup>25,51</sup> Therefore, it is a prerequisite of protection that an inhibitor be accumulated on a metal surface in an amount sufficient to suppress corrosion before the first corrosion sites appear on the surface. It should be noted that, though the mathematical tools for the description of diffusion processes have been developed to a considerable extent, the first attempts to simulate this condition were undertaken from the late 1980s to the early 1990s.<sup>46–50</sup> A series of studies<sup>47–50</sup> on quasi-steady evaporation of a VCI droplet inside a metallic sphere coated with a water film were the most successful. This model assumed that the surface electrolyte contained an inhibitor in a minimum protective concentration ( $C_{pr}$ ) to prevent metal corrosion.

The analytical solution for the problem has the form

$$l_{pr} = \lambda \sqrt{\frac{Dp^0}{C_{sat} \ln(1 - C_{pr}/C_{sat})}} \quad (1)$$

and defines the relationship between the VCI efficiency expressed as a function of  $l_{pr}$ , the diffusion coefficient ( $D$ ) of VCI vapour in air, the saturation pressure  $p^0$ , the solubility ( $C_{sat}$ ) and the  $C_{pr}$  value under conditions affecting the coefficient  $l$  (temperature, thickness of the moisture film on the metal, *etc.*). Analysis of the possible variation ranges of these parameters<sup>52</sup> showed that  $D$  affects the protection efficiency the least.

This model provides a fairly good description of the trend of the effects of the base parameters on the protective properties of VCIs provided heat exchange and mass exchange with the environment can be neglected, *e.g.*, in the conservation of metal articles under atmospheric conditions. Generally,<sup>1,53</sup> after the article and a VCI source are sealed, the system is kept for some time at a constant temperature in order to allow the inhibitor vapour to reach the surface. Thus  $l_{pr}$  can be regarded as the main criterion of the VCI efficiency, and approaches to enhance protection that follow from Eqn (1) (an increase in the inhibitors'  $p^0$  and their protective capability in thin electrolyte films, uniform spatial distribution of VCI sources, *etc.*) prove to be efficient.

On the other hand, sealed systems where protection is only determined by the initial period of contact of a metal with a VCI are rather rare in real technics. The role of heat transfer and mass transfer processes in initiating corrosion of real systems protected by VCIs consists of violation of the protection conditions ( $C_{inh} > C_{pr}$ ) due to a decrease of the inhibitor concentration in the surface electrolyte ( $C_{inh}$ ) or an increase in  $C_{pr}$  with time.<sup>31,54</sup>

Evaporation of VCI from the space that is protected through a permeable packing is a reason for a decrease in  $C_{inh}$ . Hence, inhibitors with  $p^0 > 13.3$  Pa cannot normally ensure long-term vapour-phase protection.<sup>1</sup> However, corrosion can also be initiated in an unsealed system due to the ingress of aggressive atmospheric components, including water, into such a system.

The introduction of VCIs into a space that is protected is accompanied by their interaction with water contained in the internal environment, formation of solutions, and a decrease in the humidity of the gas phase. These processes usually affect only slightly the corrosivity of the environment<sup>55</sup> but they favour the diffusion of water into the system. Obviously, if the relative humidity of the environment exceeds that above a VCI solution with a concentration of  $C_{pr}$ , gradual dilution of the latter with atmospheric moisture will result in the initiation of corrosion even if the inhibitor is not removed from the space that is protected.

Analysis of basic models has shown that the rate of water diffusion into a space that is protected can appreciably exceed the rate of VCI evaporation and determine the kinetics of its dilution in a system and the protection period. In fact, mass exchange of a quasi-equilibrium system containing a VCI that is miscible with

water in all proportions, with a water-saturated external atmosphere is described<sup>54</sup> by the following equation

$$\frac{N_{\text{H}_2\text{O}}}{N_{\text{inh}}} = \frac{D_{\text{H}_2\text{O}} p_{\text{H}_2\text{O}}^0}{D_{\text{inh}} p_{\text{inh}}^0}, \quad (2)$$

where  $N$  is the number of moles of the inhibitor or water, respectively (depending on the subscript) that diffuse through the barrier material per unit time. An approximate calculation showed that in the case of mass transfer through open pores and violated integrity of the barrier material, the  $N_{\text{H}_2\text{O}}/N_{\text{inh}}$  ratio can reach  $10^5$ . The success in the combined use of VCIs and desiccants for metal protection shows that diffusion of water contributes the most to the rate of a decrease in the  $C_{\text{inh}}$ , at least for VCIs with comparatively small  $p^0$  values.<sup>30</sup>

If the ingress of water into the system decreases  $C_{\text{inh}}$ , the diffusion of acid gases ( $\text{SO}_2$ ,  $\text{NO}_2$ ,  $\text{CO}_2$ ,  $\text{H}_2\text{S}$ , etc.) into it increases the corrosivity of the medium and hence increases  $C_{\text{pr}}$ . This can also result in the corrosion initiation. Binding of such gases by inhibitors, many of which are organic bases (or contain them as components), favours their diffusion into the space that is protected.<sup>1, 16, 52, 56</sup>

Metal protection by a volatile inhibitor can also be violated by heat exchange between the system and the environment. It is well known that abundant condensation of water vapour due to temperature fluctuations is very unfavourable for vapour-phase protection.<sup>18, 57</sup> However, the majority of researchers had previously limited themselves merely to the statement of this fact and simulation of such conditions in VCI efficiency preliminary tests.<sup>16, 51, 56</sup>

The analysis of mechanisms of corrosion initiation by heat exchange that we have carried out<sup>31</sup> has shown that the temperature gradient on a metal results in a redistribution of water and a VCI in the surface electrolyte, similar to that occurring during distillation of solutions. The evaporation is intensified on heated areas and the vapour phase is enriched in the more volatile component of the mixture and its surface concentration decreases. If  $p_{\text{inh}}^0 > p_{\text{H}_2\text{O}}^0$ , a decrease in  $C_{\text{inh}}$  below  $C_{\text{pr}}$  can stimulate corrosion. On the other hand, on cooled surfaces where vapour condenses the surface electrolyte becomes enriched in the volatile component. This may result in the violation of vapour-phase protection if  $p_{\text{inh}}^0 < p_{\text{H}_2\text{O}}^0$ .

There are a number of ways to prevent corrosion that appears by this mechanism. One of them involves the use of VCIs that are irreversibly adsorbed on the metal and have a protective post-effect. If the temperature difference on the metal occurs occasionally and afterwards the system comes to a near-equilibrium state, such a post-effect can protect the article. However, this does not guarantee that the article will remain preserved. No matter what the VCI post-effect, possible heat-exchange can initiate corrosion.

Yet another possibility for vapour-phase metal protection under heat-exchange conditions is the use of VCIs with  $p^0$  and vaporisation enthalpy ( $\Delta H_v$ ) values similar to those of water. In this case, the composition of the surface electrolyte is identical to that of the vapour above it. Evaporation and condensation can neither change  $C_{\text{inh}}$  nor cause corrosion. However, perfect ideal matching of  $p^0$  and  $\Delta H_v$  is only realised for optical isomers and it is practically impossible to select a VCI that satisfies this condition.

The third way, new in principle, for metal protection by volatile corrosion inhibitors under heat exchange conditions is the above-mentioned one, *viz.*, the use of inhibitors that form azeotropic mixtures with water. If the content of these VCIs allows their equilibrium concentrations in the surface electrolyte to exceed the concentrations of the azeotropic mixtures ( $C_{\text{az}}$ ) and  $C_{\text{az}} > C_{\text{pr}}$ , no heat-exchange mode initiating corrosion can be attained in the entire possible temperature range of the environment. In fact, irrespective of whether the azeotropic mixture is characterised by a maximum or minimum in the composition–pressure diagram, the surface electrolyte that meets the condition

$$C_{\text{inh}} > C_{\text{az}} > C_{\text{pr}}, \quad (3)$$

can be distilled to give pure VCI and its solution with a concentration of  $C_{\text{az}}$ . If  $C_{\text{az}} > C_{\text{pr}}$ , the vapour-phase protection cannot be violated by heat exchange. The specific features of metal protection by such inhibitors have been little studied to date, but the prospects associated with them make these studies of high priority.

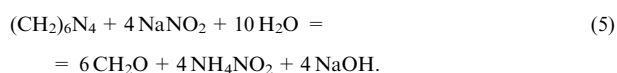
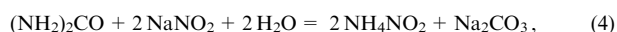
### III. The effect of chemical structures of volatile corrosion inhibitors on their protective properties

In practice, systems protected by VCIs are as a rule subject to a complex of external effects that alter the metal storage life. However, an analysis of the mechanisms of violation of vapour-phase protection described above allowed us to mark the most important characteristics that determine the VCI efficiency, *viz.*, evaporability; inhibitory properties in the surface electrolyte, including the anticorrosion post-effect; solubility in water and ability to form azeotropic mixtures. These characteristics are determined by the chemical structure of VCIs.

An analysis of structure–property relationships plays an important role in the development of efficient corrosion inhibitors for various media.<sup>7, 11, 20, 37, 58, 59</sup> Since the characteristic features of a VCI include its volatility and ability to form protective layers on the metal from the vapour phase, the assessment of the effect of the inhibitor's chemical structure on  $p^0$  is of particular importance in the case of vapour-phase protection.

#### 1. Vaporisation of volatile corrosion inhibitors and dependence of their volatility on the chemical structure

The ability to form vapours (due to evaporation or sublimation), which is often (not quite correctly) called volatility, is a characteristic property of VCIs.<sup>1, 10, 16</sup> Volatility is quantitatively expressed as  $p^0$ . The volatility required for the vapour-phase protection ( $p^0 > 1.3 \times 10^{-3}$  Pa, or  $1.3 \times 10^{-4}$  Pa according to other data)<sup>1, 16</sup> can come from the compound itself or from its hydrolysis products. For example, nitrite–carbamide or nitrite–hexamethylenetetramine mixtures owe their ability to provide vapour-phase protection to the formation of volatile ammonium nitrite in reactions with water:<sup>16, 20</sup>



Vaporisation of individual organic compounds devoid of ionic bonds usually consists of the transfer of their molecules to the gas phase.

Sublimation of salt-type VCIs is associated with their dissociation. The vapours of onium salts consist of non-associated acids and bases;<sup>16, 59</sup> partial pressures of the vapours of these compounds can differ by several orders of magnitude. For example, the vapour of ammonium benzoate consists almost completely of ammonia for which the vapour pressure is  $p = 22.7$  Pa. The value of  $p$  for benzoic acid ( $2.67 \times 10^{-6}$  Pa) is negligibly small. A similar situation characterises hexamethylenonium and diethylammonium *m*-nitrobenzoates. Conversely, vapours of cyclohexylammonium benzoate and octanoate and monoethanolammonium benzoate are enriched in the respective acids.

Several experimental methods have been developed for measuring  $p^0$  that depend on the nature of the compound and on the temperature. Unfortunately, they are rather laborious, require special instruments, and are not always accurate. Therefore, semiempirical computational methods are used to assess the volatility of organic compounds. They are mainly based on measurements of boiling points ( $T_b$ ) of compounds.<sup>60–64</sup>

The effect of temperature on  $p^0$  obeys the Clausius–Clapeyron equation

$$\ln p^0 = -\frac{\Delta H_v^\circ}{RT} + \frac{\Delta S_v^\circ}{R} = -\frac{\Delta G_v^\circ}{RT}, \quad (6)$$

where  $\Delta H_v^\circ$ ,  $\Delta S_v^\circ$ ,  $\Delta G_v^\circ$  are the standard enthalpy, entropy and free energy of vaporisation (evaporation or sublimation), respectively. The equation is fairly well approximated by linear relationships  $\ln p^0 - 1/T$ . The linearity results from weak temperature dependences of  $\Delta H_v^\circ$  and  $\Delta S_v^\circ$ ; it is observed in a wide temperature range above or below compounds' melting points. In accordance with Trouton's rule of the approximate constancy of the boiling entropies for different chemical compounds, it is possible to assess  $\ln p^0$  roughly, based on  $T_b$ .<sup>63</sup>

A greater accuracy is achieved by methods that take into account the specific features of compounds (*e.g.*, chemical similarity method and simulation methods).<sup>60–65</sup> Models implemented as equations, nomograms or special software products<sup>64</sup> facilitate considerably the search for efficient VCIs. However, one cannot use these methods to predict the expediency of synthesising new compounds for creating VCIs. This can be done provided one has knowledge of the regularities relating the chemical structure of an organic compound to its volatility.

In recent years, quantitative structure–activity relationships (QSAR) have been used rather extensively to assess the volatility of organic compounds. These relationships are commonly obtained using quantum mechanical calculations,<sup>64,66</sup> structural topological and/or topochemical analysis.<sup>64,67–72</sup>

The prediction of  $p^0$  makes use of the principle of additivity of the contributions of molecular structural fragments to the thermodynamic characteristics<sup>73–76</sup> that determine the volatility of organic compounds. However, this postulate has recently been called into question, at least with respect to the free energy of vaporisation. In fact, it has been shown<sup>77,78</sup> that variation of substituents in different classes of liquid organic compounds results not in equal but rather in proportional changes of this parameter and the related  $p^0$  value, *i.e.*, linearity of the free energy (LFE) of evaporation.

There is a series of papers<sup>77–80</sup> dealing with the development of methods for the quantitative assessment of  $p^0$  values for organic VCIs based on the LFE principle. A new scale of structural characteristics of substituents, *viz.*, the scale of volatility constants  $\xi_R$ , has been introduced. The  $\xi_R$  values were computed using  $p^0$  data at 293 K for liquid monosubstituted benzenes chosen as the standard series

$$\xi_R = \log p^{0,R} - \log p^{0,H}, \quad (7)$$

where indices R and H refer to substituted and non-substituted compounds, respectively. This approach made it possible to assess  $p^0$  values for liquid organic VCIs from their formulae and data required for calculating correlations of the type

$$\log p^{0,R} = \alpha + \kappa \xi_R, \quad (8)$$

where

$$\alpha = \log p^{0,H},$$

and  $\kappa$  is a constant characterising the series in question. It is important that the  $\xi_R$  scale that has been elaborated is versatile and can be used for both aromatic and aliphatic/alicyclic compounds, including polysubstituted ones. The contributions of spatially separated substituents ( $R^1$  and  $R^2$ ) in such compounds are independent and additive

$$\log p^{0,R^1,R^2} = \alpha + \kappa \sum \xi_R. \quad (9)$$

Adjacent substituents can partially shield each other from intermolecular interactions, affecting  $\alpha$  and  $\kappa$  values and sometimes impairing the accuracy of data description. However, in most cases, the accuracy is sufficient for predicting the volatility of VCIs. This statement is demonstrated in Fig. 1.

Studies in this field resulted in the creation of an advanced system for the prediction and directed modification of the

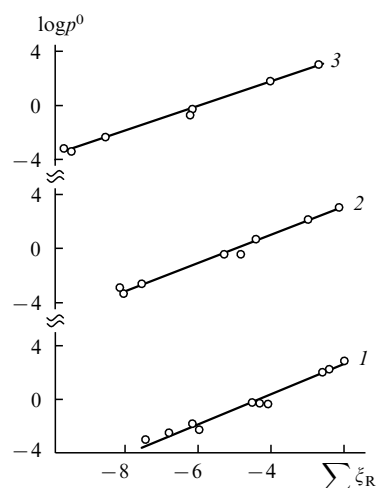


**Figure 1.** Dependences of  $\log p^0$  on  $\sum \xi_R$  for primary (1), secondary (2) and tertiary amines (3).

volatility of liquid organic corrosion inhibitors.<sup>77–80</sup> It was shown that the fulfilment of the LFE principle for the evaporation process results from the isoentropicity, that is, constancy of the standard entropy for a series of related compounds. This allowed a quantitative *a priori* assessment of the volatility of organic compounds in a broad temperature range above the boiling points by correlation methods,

$$\log p_{(T)}^{0,R} = A_1 + \frac{B_1}{T} + C_1 \xi_R + \frac{D_1 \xi_R}{T}, \quad (10)$$

where  $A_1$ ,  $B_1$ ,  $C_1$  and  $D_1$  are constants. It is important that this type of correlation relationship can be derived from data on boiling points of organic compounds under vacuum distillation conditions.

The approach elaborated for the prediction of  $p^0$ , together with the methods for reconstructing relationships of types (8)–(10) in the absence of data allowing one to determine them directly, often makes it possible to reject non-promising VCIs before synthesising them.

However, this system is unsuitable for salts of organic acids and bases that are perhaps the most promising class of volatile inhibitors of atmospheric corrosion. The results of a recent study (Ref. 59) provide possibilities for the quantitative assessment of their volatility. An analysis of a system 'salt of a weak acid and a weak base—its saturated aqueous solution—vapour' has led to the conclusion that it is possible to compute the pressure and composition of the saturated vapour of salt-type VCIs that do not undergo irreversible reactions with water. Computation is based on the solubilities of the salt and its constituent acid and base, as well as their  $p^0$  and  $pK_a$  values.

## 2. Effects of basicity and hydrophobicity on the functional properties of volatile corrosion inhibitors

Obviously, by no means every volatile compound can provide vapour-phase protection of a metal. An inhibitor should possess properties required for slowing down (or suppressing) surface reactions that cause metal corrosion. No matter for what purpose and in what form a VCI is used, other conditions being equal, it will protect the metal the more reliably the more strongly it inhibits corrosion in the surface (phase- or adsorption-type) moisture. Therefore, studies on the effect of the chemical structures of organic compounds on their inhibitory properties are of primary importance for developing new VCIs.

Diverse semiempirical QSAR approaches to this problem exist. They have been analysed in relation to metal corrosion inhibitors in aqueous and aqueous–organic solutions in a number of papers.<sup>7,11,57,58,81</sup> One can distinguish two main directions of

these studies. One of these, which has been developing intensely over the past decade, is based on the use of quantum chemical methods.<sup>81–87</sup> However, these methods are not yet used to create VCIs. Yet another direction, which has been developed more thoroughly, is based on Pearson's concept of hard and soft acids and bases and on the LFE principle.<sup>7, 11, 57, 58, 83, 88–90</sup>

The effect of the chemical structure of a VCI on its inhibitory properties depends considerably on the metal that is protected and on corrosion conditions. Perhaps, the relationship between the protective properties of organic compounds and their  $pK_a$  values is deduced most often; in the majority of cases, the efficiency of inhibitors similar in chemical nature increases with an increase in the basicity of compounds.

For ammonia and lower amines, which constitute the most common class of VCIs, corrosion protection of metals is to some extent associated with the ability of VCIs to alkalinise aqueous solutions.<sup>1, 6, 10, 17, 91</sup> A moderate increase in pH of surface moisture films decreases the corrosivity of the medium with respect to both steel and other materials. In this case, corrosion problems appear only for aluminium and only under conditions of abundant condensation of water. The alkalification factor is important not only in the protection against atmospheric corrosion, but also in the protection of steel equipment from carbon dioxide-induced corrosion in steam-condensate systems, refinery units, and oil-and-gas pipelines.<sup>92–95</sup>

One should not underestimate the possibility of pH control of the protective properties of salt-type VCIs as well. It is not incidental that hydrolysis of the majority of them produces alkaline medium; their anions are often oxidants that alkalinise the near-surface layer upon reduction.

On the other hand, it has long been known<sup>1, 17, 18</sup> that the effect of  $pK_a$  on the protective properties, even for individual amines, is not reduced to an increase in pH by these compounds. Following adsorption on the metal surface, they ensure metal protection at lower pH values than an alkali.<sup>96, 97</sup> It should be noted that the increase in the protective effect of volatile amines with an increase in their  $pK_a$  often remains high in electrolytes with the same pH.<sup>96</sup> This can be explained by an increase in the amine adsorptivity with an increase in the electron density on the nitrogen atom, as can be measured by the ability of the compound to bind a proton. In this case, the beneficial effect of the amine basicity on the steel protection by these compounds is observed not only in solutions, but also in a humid atmosphere.<sup>52</sup>

The importance of the VCI adsorption itself has been demonstrated<sup>38, 39, 97</sup> in the protection of steel from carbon dioxide-induced corrosion, *i.e.*, under conditions where pH control was traditionally considered to play the major role.<sup>92</sup> It turned out that the order of steel protection efficiency of amines in the vapour phase differs from the basicity series. For instance, dibutylamine ( $pK_a = 11.25$ ) is the best VCI among butylamine derivatives, whereas tributylamine ( $pK_a = 11.04$ ) is the worst, and its protection efficiency is even lower than that of butylamine ( $pK_a = 10.78$ ).<sup>97</sup> It is of note that VCIs that are efficient in a carbon dioxide atmosphere include not only amines but also some carboxylic acids that cannot decrease the acidity of the medium but are readily adsorbed on steel, such as lauric acid.<sup>38, 98</sup> This suggests that basicity is not always the dominant parameter of the inhibitory action of VCIs. This conclusion is not unexpected. It is well known that the reactivity of organic compounds cannot be described by basicity alone.<sup>99–101</sup>

Therefore, different characteristics of substituents were considered in studies on organic inhibitors. In particular, correlations between the efficiency of metal corrosion inhibition and electronic  $\sigma$ -constants of substituents have repeatedly been established.<sup>7, 37, 57, 58, 102</sup> The type of constants that describe such relationships and the character of their effect change depending on the charge-transfer effects occurring in the compounds, the nature of adsorption bonds and the specific features of inhibitors' protective action. It is unlikely that VCIs are different from other organic inhibitors in this respect, and it is not by chance that both

salts of substituted benzoic acids<sup>7</sup> and volatile Schiff bases<sup>11, 102</sup> are among the compounds studied in most detail.

On the other hand, the use of  $\sigma$ -constants of substituents for the description of the protective properties of inhibitors by LFE methods is not always sufficient. One of the reasons is that adsorption of an inhibitor from an aqueous solution can be accompanied by partial dehydration of its molecules or ions, hence the affinity of an inhibitor for water is very important for metal protection.<sup>7, 11</sup> In order to take these factors into account, hydrophobicity constants derived from the distribution ratios of substituted organic compounds in the biphasic system octanol–water<sup>101</sup> are often used in addition to electronic parameters of substituents. This approach allows one to improve the accuracy of quantitative 'structure–protective effect' relationships, *e.g.*, in the case of salts of substituted aromatic acids.<sup>7</sup> An increase in Hansch's hydrophobicity of substituents also increases the ability of inhibitors to stabilise oxide films on metals, including those formed in air.

The hydrophilic–hydrophobic balance of VCIs becomes particularly important in the case of vapour-phase protection. The ability of inhibitors adsorbed from the vapour phase to hydrophobise a metal surface is considered to be an additional protection factor. While it is sufficient to use the  $pK_a$  values of volatile amines for describing their inhibitory effect with respect to steel in chloride solutions,<sup>96</sup> the role of hydrophobicity may become considerable in the case of vapour-phase protection.

The reasons for the beneficial effect of the VCI hydrophobicity on the efficiency of steel protection in humid atmospheres are clear.<sup>103</sup> It is known that the physical adsorption on non-porous adsorbents is enhanced with an increase in the length of the alkyl substituent. The non-specific interaction of VCIs with a metal surface increases in parallel with the hydrophobicity, since introduction of a hydrophobic hydrocarbon fragment into an organic molecule increases its polarisability and attraction to the adsorbate caused by electron density fluctuations.<sup>104</sup> Furthermore, an increase in hydrophobicity increases the ability of VCIs to displace adsorbed water from the metal surface and impart water-repellent properties to it. However, the contribution of the hydrophobising action of VCIs should not be overestimated. If organofluorine and organosilicon compounds that are not widely used as VCIs are excluded from consideration, this is not a major contributing factor in metal-protection processes.

The basicity and hydrophobicity also affect the solubility of VCIs in surface water films and in condensed phases, which affects the kinetics of VCI propagation in the space that is protected,<sup>47–50, 52</sup> mass exchange with the environment,<sup>54</sup> interphase distribution of the inhibitor, and eventually protection efficiency. The effect of VCI solubility on vapour-phase metal protection is complex and depends on specific conditions. However, it is obvious that a VCI should be soluble in aqueous electrolyte solutions in order to provide fast and efficient corrosion inhibition.

The solubility of VCIs, many of which are weak electrolytes, also depends on their ability to undergo ionisation in water. However, the solubilities of compounds belonging to the same reaction series and possessing similar  $pK_a$  values, often differ considerably. For example, an increase in the length of the hydrocarbon substituent in primary amines, starting from propylamine, almost does not affect their basicities but decreases the solubility. According to Abramzon,<sup>105</sup> changes in the hydrophilic–hydrophobic balance of monofunctional aliphatic compounds upon increase in the number of C–H bonds by one result in the increase in the standard free energy of dissolution ( $\Delta G_{\text{sol}}^\circ$ ) by  $\sim 1.76 \times 10^6 \text{ kJ mol}^{-1}$ . Accordingly, the saturation concentration ( $C_{\text{sat}}$ ) for compounds rather poorly soluble in water, which is described by Eqn (11)

$$\ln C_{\text{sat}} = -\frac{\Delta G_{\text{sol}}^\circ}{RT}, \quad (11)$$

also changes. From the structural formula and solubility of one member of the series one can assess  $C_{\text{sat}}$ . Unfortunately, this approach does not allow one to predict the solubility changes when heteroatoms are introduced in a molecule and is of little use for aromatic compounds.

In the latter case, it is reasonable to use correlations based on the LFE principle. It has been shown<sup>106</sup> that the change in  $C_{\text{sat}}$  due to structure variation for liquid aromatic compounds that are not ionised in water is described by the Hansch equation

$$\ln C_{\text{sat}} = a + b\pi_R, \quad (12)$$

where  $a$  and  $b$  are constants for a given series,  $b < 0$ ; and  $\pi_R$  is the substituent's hydrophobicity.

Combination of the methods described makes it possible to optimise the properties of VCIs in a certain range (which is currently rather narrow) by modifying their chemical structures. It should be taken into account here that a decrease in the inhibitor's solubility with an increase in hydrophobicity may result in the loss of protective properties. This situation is particularly characteristic of corrosive media where the  $C_{\text{pr}}$  values of inhibitors are high. However, it was noted<sup>96</sup> that complete protection of steel in 0.005 M aqueous solution of NaCl, e.g., by tributylamine, was impossible, due to the low  $C_{\text{sat}}$  value. A similar situation has been reported in vapour-phase protection.<sup>103</sup> Steel corrosion was not suppressed in the vapour phase even above saturated solutions of *n*-nonylamine and *n*-decylamine, whereas butylamine which is more hydrophilic and has a similar basicity prevents corrosion at a concentration as low as 0.14 mol litre<sup>-1</sup>.

It is impossible to optimise the chemical structure of organic compounds for creating more efficient VCIs without revealing the specific features of their adsorption on metals that are protected. Furthermore, it has become clear in recent years that VCIs can have a rather prolonged protective post-effect. This opens new prospects for their application and calls for studies of VCI desorption from the surface of metals and oxides.

#### IV. Adsorption and desorption of volatile corrosion inhibitors

From the very first years of investigations into VCIs, their adsorption was studied by both direct and indirect methods, among which electrochemical methods, including those applied to processes occurring under thin moisture films,<sup>1</sup> were of considerable importance. It has been shown that, first, it takes a long time (hours or even days) to form protective films on metals placed in a VCI atmosphere and, second, once such films have been formed, corrosion on these samples begins, following removal of VCI vapour, later than on metals that have not been subjected to pre-treatment with the VCI. Unfortunately, the advantages of employment of this phenomenon in the practice of vapour-phase anti-corrosion protection were underestimated for a long time.

Obviously, the reason for the VCIs' post-effect is determined by the character of their adsorption on metals. If we take into account that this effect is much more pronounced on iron and steels than on zinc and aluminium, it is reasonable to assume that chemisorption of the VCIs on the surface occurs. However, not only chemisorption prevents desorption of VCIs.

In fact, the adsorption of *N,N*-diethylaminoethanol vapour (in the range of  $p/p^0$  from 0.1 to 0.9) on the surface of naturally oxidised iron powder results virtually in a monolayer but increases 4–5-fold at  $p/p^0 = 1.0$  (Fig. 2).<sup>107</sup> This is close to the ellipsometric estimate of its adsorption on an iron surface in air.

Evacuation of the inhibitor vapour resulted in its total desorption, which suggests the reversibility of adsorption, at least in the absence of an access of air and in a relatively short-term experiment (~5 days). On the other hand, adsorption of water on an iron powder that has preliminarily adsorbed no more than a monolayer of this VCI occurs in a different way than on its clean surface. Despite VCI desorption, the maximum mass gain is ~5 times smaller than that upon water adsorption by a surface

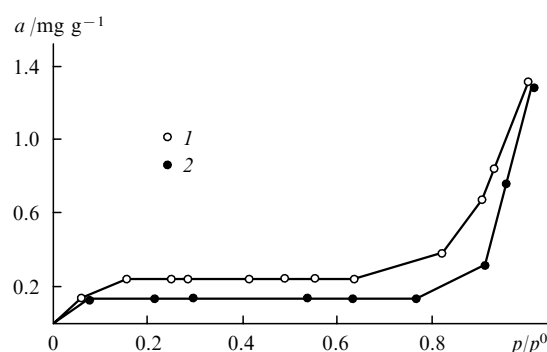


**Figure 2.** Adsorption isotherms of *N,N*-diethylaminoethanol on the surface of naturally oxidised iron powder at 13 (1) and 22 °C (2).<sup>107</sup>

free from the inhibitor (Fig. 3). Evacuation results in a 'zero' mass for a given experiment, that is, the mass of the sample that has already adsorbed the VCI (0.14 mg g<sup>-1</sup>). Hence, the VCI studied decreases the limiting adsorption of water even at low inhibitor coverage, which may be explained by the adsorption of water molecules on the same surface-active centres as the VCI. This property of VCIs is of key importance, since it is known that a considerable increase in the corrosion rate of a metal in water vapour occurs after at least 2–4 monolayers of adsorbed water have been formed on the metal surface.

If iron powder has first adsorbed 0.26 mg g<sup>-1</sup> of the VCI, which corresponds to the plateau on the adsorption isotherm of *N,N*-diethylaminoethanol at 13 °C (see Fig. 2), evacuation of the vapour does not restore the original mass of the sample. This suggests that either partially irreversible VCI adsorption occurs under the effect of water vapour or that additional oxidation of iron with water stimulated by traces of the VCI takes place. Obviously, under real conditions of anticorrosion protection, the adsorption of VCIs is complicated by the presence of oxygen and other gases in the atmosphere. A volatile corrosion inhibitor can react with them, while the surface can catalyse the process.

In fact, the results of studies on the adsorption–desorption kinetics of various VCIs on the surface of naturally oxidised iron (Fig. 4) by ellipsometric methods confirm that the formation of adsorption layers takes rather a long time (several days are required even for fairly volatile compounds). Furthermore, these results suggest the polymolecular adsorption of amine-type VCIs and adsorption irreversibility to a considerable degree for many well-known VCIs. Attention should be paid to the fact that the

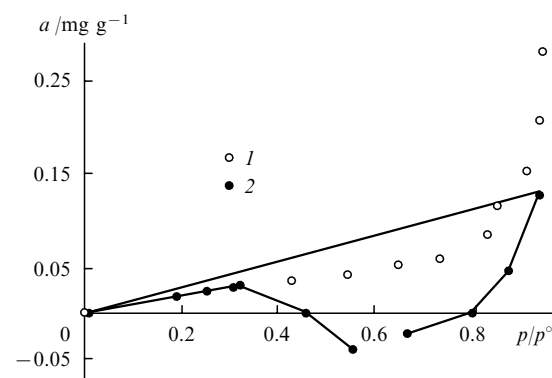


**Figure 3.** Adsorption isotherms of water vapour on the original sample of iron powder (1) and on a sample with preliminary adsorption of *N,N*-diethylaminoethanol (2).<sup>107</sup>

For convenience in the comparison of isotherms, the changes in the sample mass refer to the zero coordinate corresponding to the original mass of the sample that has adsorbed the VCI (0.14 mg g<sup>-1</sup>).

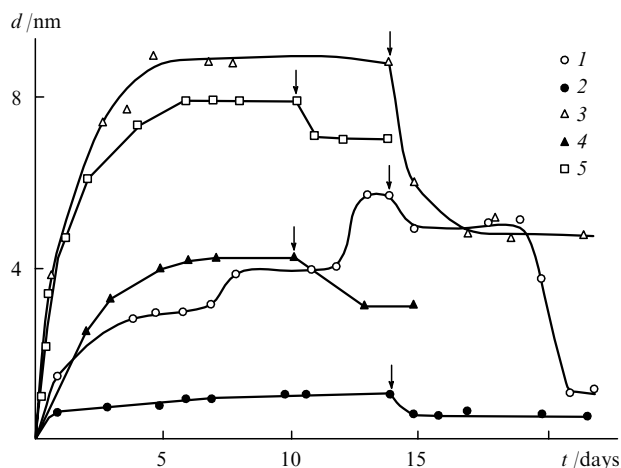


**Figure 4.** Kinetics of VCI adsorption–desorption on iron surface under atmospheric conditions.<sup>107</sup>

(1) 2-Aminoethanol, (2) *N*-ethyldiethanolamine, (3) *N,N*-diethylaminoethanol, (4) *N,N*-diethylaminopropionitrile, (5) 4-diethylamino-3-methylbutan-2-one. The variations in ellipsometric angle  $\Delta$  have been converted to the thickness of adsorption layers  $d$  using Drude's approximation:  $d = -\alpha(\Delta - \Delta_0) = -\alpha\delta\Delta$ .

irreversibility of *N,N*-diethylaminoethanol adsorption was clearly higher than that measured in the above adsorption measurements *in vacuo*. In this case, longer exposure of a sample in VCI vapour favours not only the chemisorption of the amine, but also increases the probability of formation of a structured polymolecular adsorption film by the inhibitor. This follows from the results of studies on the mechanism of action of yet another well-known amine-type VCI, *viz.*, *N,N*-diethylaminopropionitrile.<sup>19</sup>

The interaction of *N,N*-diethylaminopropionitrile with an iron surface was studied by XPS and ellipsometry.<sup>108</sup> In addition, IR spectra of a  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> powder impregnated with the VCI were measured immediately after drying following exposure in air for different periods of time. These studies resulted in the conclusion that a film consisting of a chemisorbed and a physically adsorbed layer is formed on the oxidised iron. The formation of the first layer is due to hydrolysis of *N,N*-diethylaminopropionitrile; as a result, compounds that are less volatile than the original compound but have a higher protective effect in aqueous solutions, that is, diethylaminopropionamide and possibly the diethylaminopropionate anion, are adsorbed on the surface. This chemisorbed layer is formed in 1.5–2 days; it does not undergo desorption *in vacuo* and it is not removed upon washing with ethanol or upon prolonged (up to 8 months) exposure to a dry atmosphere.

The physically adsorbed layer is also non-uniform. Taking into account the ability of the CN group in *N,N*-diethylaminopropionitrile to add another VCI molecule due to the formation of both a donor–acceptor bond with the nitrogen atom of the amino group and a 'paired dipole bond' with the CN group oriented antiparallel, it was assumed that associates with increased viscosity are formed atop the chemisorbed layer. They are soluble in ethanol but almost cannot be removed *in vacuo*. This layer should provide good screening of the metal surface preventing the penetration of a corrosive medium. On the other hand, *N,N*-diethylaminopropionitrile remains partly unbound and, being rather volatile, is desorbed from the surface not only *in vacuo*, but also on storage in air.

A study on the formation of adsorption layers in *N,N*-diethylaminopropionitrile vapour<sup>109</sup> showed that the characteristic electron binding energies in the spectra of an iron surface are almost the same irrespective of whether the VCI is adsorbed from the liquid or vapour phase. However, the spectra of O1s electrons change as the exposure time increases. As in the case of VCI

application by the contact technique, the intensity of lines in the high-energy region of the spectrum ( $E_b = 532–534$  eV) increases, which is explained by the adsorption of oxygen-containing hydrolysis products on iron. The spectra of rinsed and non-rinsed samples were identical after exposure for 30 h. After exposure for 300 h, the high-energy region of the spectrum becomes predominant. However, unlike the case of VCI adsorption from the liquid phase, the low-energy region of the spectrum corresponding to iron oxides is retained.

After adsorption of *N,N*-diethylaminopropionitrile vapour on iron, as upon contact application of the inhibitor, the Fe2p<sub>3/2</sub> spectrum contains both the lines corresponding to the original iron sample ( $E_b = 707$  and 711.5 eV) and, when exposed for periods from 10 min to 300 h, 'shoulders' in the region of 708–710 eV due to the appearance of nucleophilic species on the iron surface. For samples washed with ethanol, the intensities of lines in the spectrum of Fe2p<sub>3/2</sub> electrons remain virtually unchanged for all exposure times. For non-washed samples, the spectrum of Fe2p<sub>3/2</sub> electrons after the first 30 h of exposure differs only slightly from the corresponding spectrum for the washed samples. After exposure for 48 hours, the content of iron in the layer in question on non-washed samples quickly decreases and then remains unchanged (Fig. 5). The maximum in the spectrum ( $E_b = 711.5$  eV) also persists after exposure for 300 h. This makes it different from the spectra obtained upon contact application of the VCI. In the latter case, a low-energy shift of the maximum was observed as early as after 36 h of exposure. Furthermore, the high-energy region of the spectrum corresponding to oxides was retained after exposure of iron in the vapour phase.

The kinetic regularities of variations in the relative content of the elements analysed are the same as for adsorption of this VCI from the liquid phase. Starting from the first minutes of exposure, the concentrations of nitrogen, oxygen and carbon (the curves for carbon are not shown in Fig. 5), measured on the surfaces washed with a solvent, increase abruptly, whereas the content of iron decreases. After ~30 h, these parameters level off. After the first 30 h of adsorption, the curves for washed and non-washed samples almost do not differ from each other, but for non-washed samples the relative concentrations of the elements stabilise after a longer period, as a rule, after 2 days.

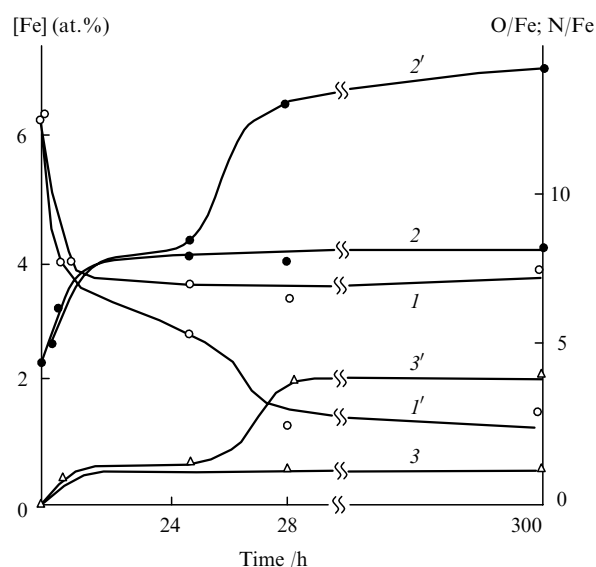


**Figure 5.** Variation in the concentration of iron (1, 1') and the relative content of oxygen (2, 2') and nitrogen (3, 3') on an iron surface exposed to *N,N*-diethylaminopropionitrile vapour. (1–3) After washing with ethanol (1'–3') without washing.



A comparative analysis of the effect of the VCI from the liquid and vapour phases on iron showed that the mechanism of formation and growth of protective layers does not depend on the way the inhibitor was applied on the surface. However, it affects the ratio of the chemisorbed and physically adsorbed VCI. In fact, chemisorption of the inhibitor after a 300-hour exposure is higher if the film is formed from the vapour phase, whereas the physically adsorbed VCI layer is thicker upon contact application. This is probably due to the fact that, unlike the case of gradual adsorption of *N,N*-diethylaminopropionitrile vapour, the contact application of the inhibitor favours the association of VCI molecules. In the latter case, the thickness of the physically adsorbed layer prevents the access of water from the atmosphere followed by hydrolysis of the VCI. This can explain the smaller concentration of chemisorbed species.

The results of ellipsometric measurements (Fig. 4) showed that, once a polymolecular film of *N,N*-diethylaminopropionitrile has been formed from the vapour phase, its desorption does not exceed 28% and occurs most intensively during the first three days. The remaining film is strongly bound to the surface of the iron sample.

We also observed an important contribution of chemical transformations to the protective effect of VCIs for one of the most efficient versatile inhibitors of atmospheric corrosion, *viz.*, 4-diethylamino-3-methylbutan-2-one.<sup>110</sup> The adsorption of this VCI on iron also results in a polymolecular protective film. The adsorption is largely irreversible (see Fig. 4) due to oxidation, dimerisation, condensation and perhaps more profound chemical transformations of unsaturated ketones formed upon the dissociative adsorption of the VCI. It is no wonder that this inhibitor has a long post-treatment effect (Table 1).

It was previously assumed that lower amines are prone to desorption. Hence, metal protection requires that they are always present in the corrosive medium, whereas their higher homologues can provide metal protection due to the post-treatment effect, *i.e.*

by irreversibly adsorbed molecules.<sup>111</sup> Most often, this is actually the case. For example, allylamine ( $pK_a = 9.42$ ) does not show any protective post-treatment effect and even stimulates copper corrosion. However, diallylamine ( $pK_a = 9.29$ ) or *n*-heptylamine, which possess higher hydrophobicities, show post-treatment effects not only on steel but also on zinc. *n*-Octylamine protects steel even more efficiently. In fact, a steel sample exposed for 12 days in *n*-octylamine vapour did not undergo corrosion for over 30 days in a VCI-free atmosphere with a 100% relative humidity.<sup>110</sup>

Such a strong adsorption of amines on the surface of oxidised steel depends on their nature and agrees well with our concepts about interactions of a hard base with a hard acid; the role of the latter, unlike iron itself, is played by its oxidised surface.<sup>103</sup> The energy characteristics of such an interaction have not yet been studied in sufficient detail. So, its calorimetric estimate based on the integral heat of adsorption of both liquid amines (heat of immersion) and their vapours deserves attention. It has been shown<sup>112</sup> that the amino group in *n*-octylamine provides the major contribution to the heat of adsorption on a naturally oxidised iron powder. The value of this parameter for *n*-octylamine is noticeably higher than those of non-polar *n*-undecane and even polar octanol. Therefore, both the high potential of dispersive interaction with the  $C_8$  hydrocarbon radical and the specific interaction of the amino group with electron-withdrawing surface sites are responsible for the high energy of adsorptive interaction of the alkylamine with the iron powder studied.

Such sites can include coordination-unsaturated ion-atoms of iron with incomplete d-shells, which enter into donor–acceptor interactions with nitrogen atoms of the amino groups. It has been shown that Fe(II) and Fe(III) sites are present on the surface of oxidised finely dispersed iron, *e.g.*, in an IR-spectroscopic study of CO and NO adsorption.<sup>113</sup> Under atmospheric conditions, these centres are blocked with water molecules that cannot be removed by low-temperature evacuation and are desorbed only partially upon evacuation at 100 °C. It should be noted that the collective properties of the surface and adsorbate are strongly affected by the formation of donor–acceptor bonds by these compounds and the ionisation potential of the organic compound.<sup>114</sup>

According to estimates,<sup>112</sup> the total heat of adsorption and condensation of *n*-octylamine is as high as 44 kJ mol<sup>−1</sup>; this can suggest its ability to be chemisorbed on an oxidised iron surface (taking into account partial irreversibility of amine adsorption). Interestingly, the irreversibility of adsorption increases in the series *n*-octylamine < cyclohexylamine < primary aliphatic amines  $C_{10}–C_{13}$ . In these cases, the fractions of strongly adsorbed compounds are 25%, 40% and 60% of their total content, respectively. It was noted that the adsorption energies are virtually the same for amines with different hydrocarbon radicals. Hence, electron-withdrawing sites are arranged rather sparsely on the surface, which allows them to easily interact with the amino groups despite considerable size differences in the ‘landing sites’ that are about 30, 60 and 80–90 Å<sup>2</sup> for cyclohexylamine, *n*-octylamine and aliphatic amines  $C_{10}–C_{13}$ , respectively.

In this case, it was also noted that the adsorption of water on the surface of a powder modified by *n*-octylamine was lower than that on the original adsorbent. It would seem that this difference is attributable to the fact that water cannot totally displace chemisorbed VCI molecules. However, the fact of the partially irreversible adsorption of water implies that its interaction with the surface is more complex. Presumably, the adsorbed VCI facilitates additional oxidation of iron or undergoes protonation to give the octylammonium ion and a surface hydroxy group.

On the other hand, elongation of the alkyl fragment in the molecules decreases the volatility of amines and their solubility in water; therefore, higher amines can only be used at high temperatures, *e.g.*, in the protection of power plants. It is more efficient to use certain heteroalkylated amines as VCIs: under ordinary conditions, even hydrophilic ethylenediamine can provide a long-

**Table 1.** Protective post-effect of VCIs under 100% relative humidity in the absence of forced condensation of moisture on the samples.

| Volatile inhibitor                 | $\tau$ /months | Sample |    |    |
|------------------------------------|----------------|--------|----|----|
|                                    |                | St.3   | Cu | Zn |
| Allylamine                         | 0.5            | —      | —  | —  |
|                                    | 1.0            | —      | —  | —  |
| Diallylamine                       | 0.5            | ++     | —  | ++ |
|                                    | 1.0            | ++     | —  | ++ |
|                                    | 2.0            | +      | —  | —  |
|                                    | 3.0            | +      | —  | —  |
| Heptylamine                        | 1.0            | ++     | —  | +  |
|                                    | 2.0            | +      | —  | +  |
|                                    | 3.0            | —      | —  | +  |
| Ethylenediamine                    | 0.5            | ++     | —  | +  |
|                                    | 1.0            | ++     | —  | ±  |
|                                    | 2.0            | ++     | —  | —  |
|                                    | 3.0            | +      | —  | —  |
| <i>N,N</i> -Diethylaminoethanol    | 0.5            | ++     | ++ | +  |
|                                    | 1.0            | ++     | ++ | —  |
|                                    | 2.0            | ++     | —  | —  |
|                                    | 3.0            | +      | —  | —  |
| 4-Diethylamino-3-methylbutan-2-one | 0.5            | ++     | ++ | ±  |
|                                    | 1.0            | ++     | ++ | ±  |
|                                    | 2.0            | ++     | ++ | —  |
|                                    | 3.0            | +      | ++ | —  |

**Note.** The following notation is used:  $\tau$ , exposure time; two plus signs, absence of corrosion; one plus sign, small corrosion damage; one plus-minus sign, poor metal protection; one minus sign, no protection; two minus signs, corrosion stimulation.

lasting protective post-treatment effect on low-carbon steel (Table 1).

Thus, by creating adsorption layers from a VCI-containing vapour phase, it is possible to provide a prolonged post-treatment metal-protection effect. This refers not only to protection from atmospheric corrosion. Studies on a VCI in a carbon dioxide atmosphere have shown<sup>115</sup> that the irreversibility of VCI adsorption is much higher than in air. In fact, the adsorption of 2-aminoethanol is enhanced according to a power law in both cases, though it is somewhat more slow in a carbon dioxide atmosphere. After the cell has been unsealed and the VCI has been removed from it, 2-aminoethanol is desorbed gradually (Fig. 4). However, in air, desorption is incomplete even after 14 days, though the irreversibility of its adsorption is not high: the desorption coefficient  $K_d$  that expresses the fraction of the desorbed VCI exceeds 80%. The desorption of 2-aminoethanol becomes even less ( $K_d \approx 14\%$ ) if the protective film on the metal surface was formed in a carbon dioxide atmosphere.<sup>115</sup>

This suggests the formation of stronger bonds of the VCI with carbonate compounds that are formed on iron.<sup>116</sup> The results of FTIR studies on the reaction of  $\text{CO}_2$  with 2-aminoethanol on naturally oxidised iron confirmed that amino alcohol carbonates could be formed on the surface.<sup>115</sup> Presumably, the long-term protective post-treatment effect of some other VCIs in the carbon dioxide atmosphere is due to similar reasons. For example, after exposure of low-carbon steel electrodes to vapour of aliphatic amine 'A' ( $K_d \approx 7\%$ ), the corrosion current in the corrosive aqueous solution containing (per litre) 0.25 g  $\text{AcOH}$  + 5 g  $\text{NaCl}$  + 0.04 g  $\text{Na}_2\text{S}$  ( $p_{\text{CO}_2} = 1 \text{ atm}$ ) changes only slightly during the first 200 hours, whereas it increases almost threefold for the electrodes that have not been treated with the inhibitor.<sup>39</sup> Subsequently, the corrosion current gradually increases due to the inhibitor desorption, but even after 350 h, it is still 1.5-fold smaller than that for the untreated metal. Similar results that prove the possibility of the long-term post-treatment effect of VCIs were obtained in a study<sup>117</sup> where protective films were obtained using comparatively concentrated aqueous solutions ( $4 \text{ g litre}^{-1}$ ) of the same VCIs. The data obtained are still insufficient for drawing the conclusion that it is preferable to create protective VCI layers from the vapour phase, but the prospects of using 'self-organisation' effects for this purpose deserve attention. In recent years, these effects have attracted the particular attention of scientists in various fields of chemistry,<sup>118</sup> including those who deal with the anti-corrosion protection of metals.<sup>119–124</sup>

In this respect, the formation of protective layers on metals by benzotriazole (BTA), which is one of the most famous copper alloy corrosion inhibitors,<sup>7,10,11</sup> commonly used for corrosion prevention in aqueous solutions, is of interest. For this reason, the interaction of its solutions with copper is usually studied. However, despite its relatively low volatility ( $p_s \approx 1.3 \cdot 10^{-3} \text{ Pa}$  at  $25^\circ\text{C}$ ), it is an excellent VCI and is used to suppress the corrosion of copper, zinc and their alloys.<sup>1,16</sup> The protective properties of BTA have long been attributed to the formation of a polymeric film of its complex with metal cations. Numerous justifications for this point of view have been considered in reviews.<sup>125–128</sup> However, the opinions regarding the structure of the resulting film remained controversial, which was partially due to differences in the conditions of film formation and the impossibility of detailed determination of their composition and morphology by *in situ* methods.

The adsorption of BTA was studied<sup>128,129</sup> from the vapour phase on the 110 face of a copper single crystal in an ultrahigh vacuum directly in the chamber of an instrument that makes it possible to analyse the surface by a scanning tunnel microscope, as well as by slow-electron diffraction and UV photoemission methods. It was shown that in  $\sim 85 \text{ min}$  a monolayer was formed on copper where the BTA molecules were arranged parallel to the metal surface ('planar adsorption'). After that, slow changes in the spectra were observed during 125 min of exposure; the changes became noticeable between 120 and 185 min due to the formation

of a second layer where two BTA molecules are arranged on one BTA molecule of the first layer binding with it through nitrogen atoms. It is believed that this kind of polymerisation of the adsorbate changes the orientation of its molecules on the surface and favours  $\pi$ -bonding of the molecules with the surface, while the ligand's electrons are transferred to the lowest unoccupied d-orbitals of copper.

It is of note that, as shown by X-ray photoelectron spectroscopy (XPS),<sup>130,131</sup> certain azoles that are less volatile but more hydrophobic than BTA, e.g., 3,5-diphenyl-4*H*-1,2,4-triazole or 2,5-bis(2-pyridyl)-1,3,4-oxadiazole, can also be chemisorbed on a steel surface.

Of sulfur-containing volatile compounds, thiophene ( $p^0 = 2.3 \text{ Pa}$ ) has long been known as a steel corrosion inhibitor; its adsorption from the vapour phase on the faces of single-crystal iron was studied<sup>132</sup> by several methods in an ultrahigh vacuum chamber. This compound, when chemisorbed on an iron surface through S–Fe bonds, first loses hydrogen  $\alpha$ -atoms and then  $\beta$ -atoms.  $\alpha$ -Dehydrogenation results in polymeric chain structures where the thiophene rings are oriented horizontally or vertically, depending on the temperature.

Although adsorption studies from the vapour phase in an ultra-high vacuum are undoubtedly valuable, it should be noted that the results obtained do not always allow one to draw conclusions on the nature and character of a bond between a VCI and an oxide-coated hydroxylated metal surface under atmospheric conditions. If water is present in the gas phase, the situation can be different as well. An obvious example is the adsorption of silanes on hydroxylated iron from the vapour phase which is not accompanied by chemisorption even at elevated temperatures (up to  $80^\circ\text{C}$ ).<sup>133</sup> In the case of joint adsorption of silanes and water vapour, the former are hydrolysed to give silanols  $\text{R}_4\text{--}_n\text{Si(OH)}_n$  that undergo condensation with the hydroxylated surface followed by polymerisation.

\* \* \*

The scope of VCI application has been rapidly expanding over recent years. However, this is hindered by the insufficient development of the theory of vapour-phase protection. Many physicochemical aspects of mechanisms of action of VCIs are still understood only roughly. Therefore, it should be acknowledged that total algorithmisation of designing optimal molecular structures of VCIs for solving particular practical problems remains a task for tomorrow. In the authors' opinion, the current priority tasks include the development of methods for predicting the formation of azeotropes of organic compounds with water, mathematical description and experimental simulation of conditions of vapour-phase metal protection, development of the theory of the mutual influence of components of mixed inhibitors and studies on the VCI adsorption and mechanisms of the post-treatment effect.

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<sup>a</sup> — *Protect. Met. (Engl. Transl.)*

<sup>b</sup> — *Russ. J. Appl. Chem. (Engl. Transl.)*

<sup>c</sup> — *Russ. J. Phys. Chem. (Engl. Transl.)*

<sup>d</sup> — *Electrochemistry (Engl. Transl.)*

# Phase equilibria, phases and compounds in the V–C system

V N Lipatnikov

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**Abstract.** The review summarises the results of experimental and theoretical investigations dealing with phase equilibria and the synthesis and prediction of new compounds and phases in the vanadium–carbon system. The generalised thermodynamic characteristics of disordered cubic vanadium monocarbide  $VC_y$  and lower hexagonal vanadium subcarbide  $V_2C_{y'}$ , which are the most important compounds in the V–C system, are surveyed. The crystal structures of all known and possible compounds formed by vanadium and carbon, including the  $V_8C_{12}$  molecular cluster, are discussed in detail. The phase diagrams for the V–C system taking into account ordering of nonstoichiometric vanadium carbide  $VC_y$  are considered. The bibliography includes 149 references.

## I. Introduction

Group IV and V d-transition metal carbides are strongly non-stoichiometric interstitial compounds.<sup>1–4</sup> Cubic (with the B1-type structure) vanadium carbide  $VC_y$  is one of the most interesting compounds of this type. This compound not only has wide practical application but also has been extensively studied by both experimental and theoretical methods.

In 1830, N Selfström isolated a black powder from metallurgical slags from Swedish blast furnaces. This powder contained an unknown element, which was later called vanadium. More recently, this powder was demonstrated to be  $V_2O_5$ . In pure form, vanadium was isolated by H Roscoe in 1869. In the early 20th century, it was found that doping of steels with vanadium (in an amount from 0.2 mass % to 0.5 mass %) increases their hardness, toughness, shock strength and resistance to abrasion and wear. Hence, vanadium-containing steels have found wide application in defence technology and engine building, in particular, in the manufacture of air engines and car motors. Detailed investigations demonstrated that the hardness properties of steels are improved because vanadium reacts with carbon dissolved in steels

and forms grains of hard and refractory vanadium carbide. Initially, it was speculated that such carbide phases as  $V_2C_3$ ,  $V_4C_3$  and  $V_5C_4$  were formed.<sup>5–7</sup> However, more recent studies revealed the formation of vanadium carbides, which have basic structures of lower hexagonal carbide  $V_2C_{y'}$  or higher cubic carbide  $VC_y$ . Vanadium carbides are poorly soluble in iron, which hinders the growth of large crystals. This is favourable for the formation of a homogeneous fine-grained structure in steels.

Cubic vanadium carbide  $VC_y$ , like most other transition metal carbides, was synthesised for the first time by H Moissan<sup>8</sup> in 1893 by heating  $V_2O_5$  with coal in the absence of air. It was believed that the composition of the carbide synthesised was close to  $VC_{1.0}$ . However, more recent studies demonstrated that vanadium carbide prepared by carbothermal reduction contains a large amount of oxygen.

The history of investigations of vanadium carbides and the V–C system can be arbitrarily divided into three periods.

In the first period, from the late 19th century up to 1940, vanadium carbide, like carbides and nitrides of other transition metals (titanium, zirconium, hafnium, niobium and tantalum), was considered as a usual chemical compound with constant composition. At that time, most studies were concerned with the determination of crystal structures and unit cell parameters of vanadium carbide samples prepared by one method or another. It was believed that vanadium carbide had the stoichiometric VC composition.

At the end of the first period (1930–1940), researchers started studies of the thermodynamic and various physical properties of carbides and nitrides and revealed numerous discrepancies in the results of investigations of the properties of vanadium carbide. These discrepancies could not be accounted for by experimental errors, the use of various experimental approaches or the presence of impurities in the samples under investigation. Detailed crystal-chemical studies demonstrated that the observed discrepancies were associated with the difference in the carbon content of carbides. It appeared that the composition of vanadium carbide (as well as of all Group IV and V transition metal carbides and nitrides) can vary over a wide range with retention of the crystal structure. The lower boundary of the homogeneity region of cubic vanadium carbide  $VC_y$  was long thought to be  $VC_{0.75}$ . Based on this fact, the authors of the early studies<sup>7,9</sup> suggested the existence of the  $V_4C_3$  phase. Nowadays, it is known that the  $VC_{0.65}$  composition corresponds to the lower boundary of the homogeneity region of cubic vanadium carbide. The precise position of the upper boundary has long remained unknown, but it was hypoth-

V N Lipatnikov Institute of Solid State Chemistry, Urals Branch of the Russian Academy of Sciences, ul. Pervomaiskaya 91, 620219 Ekaterinburg, Russian Federation. Fax (7-343) 374 44 95, tel. (7-343) 374 73 06, e-mail: lipatnikov@ihim.uran.ru

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esised that this boundary is most likely close to the stoichiometric composition  $VC_{1.0}$ .

In the second period (1940–1970), investigations of strongly nonstoichiometric carbides were almost completely concerned with composition–property relationships. Interest in carbides quickened in 1960s, when the influence of the composition on the crystal-chemical, thermodynamic, thermophysical, electrical, magnetic, optical, mechanical and other properties of these compounds were extensively studied. At the same time, the main qualitative views of the nature of chemical bonding in nonstoichiometric carbides were formulated. At the end of the second period, many researchers mistakenly believed that nonstoichiometric carbides had been completely studied. In 1962, the first version of the phase diagram for the V–C system was published.<sup>10, 11</sup> In this diagram, the regions of existence of cubic  $VC_y$  and hexagonal  $V_2C_{y'}$  ( $\beta$ - $V_2C$ ) vanadium carbides were shown (Fig. 1). This diagram has remained virtually unchanged for more than two decades.

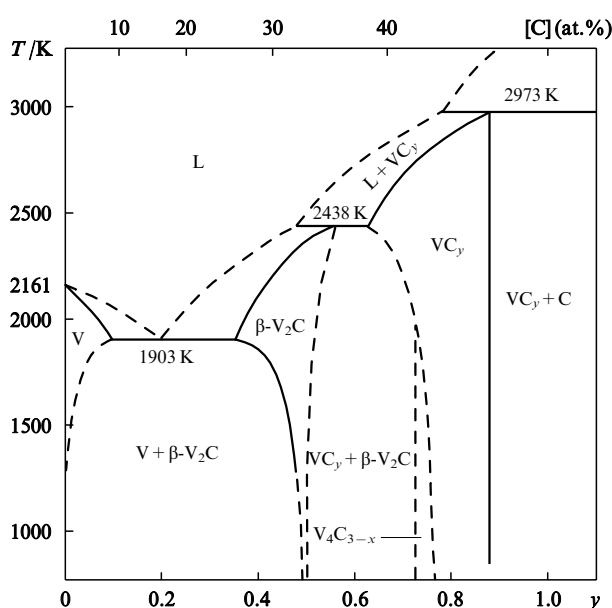


**Figure 1.** Phase diagram of the V–C system at temperatures higher than 800 K, which was constructed without considering ordered phases.<sup>10</sup>

Once wide homogeneity regions had been found for nonstoichiometric carbides, it was long thought that carbon atoms and structural vacancies (vacant interstitial sites in the metal sublattice) are randomly distributed in the lattice. However, crystallographic studies published in the late 1960s and onward demonstrated that, under particular conditions, interstitial atoms and vacancies can be redistributed over sites of the crystal lattice and form different types of ordered structures. It is nonstoichiometric vanadium carbide in which the first ordered carbide phase, *viz.*,  $V_8C_7$ , was discovered in 1966.<sup>12</sup> More recently (in 1968), the ordered  $V_6C_5$  phase was found.<sup>13</sup> These studies marked the beginning of the third period of investigations of nonstoichiometric carbides dealing with ordering and its influence on the properties of nonstoichiometric compounds. Nowadays, it is evident that, at temperatures lower than 1000 K, an ordered state of nonstoichiometric carbides is in thermodynamic equilibrium, whereas a disordered state is metastable in this temperature range.

Studies of the properties of nonstoichiometric carbides depending on the distribution of carbon atoms and vacancies demonstrated that the changes in the properties upon ordering are comparable in magnitude with the changes in these properties associated with variations in the composition of nonstoichiometric carbide within the homogeneity region of an ordered phase.

Therefore, the change in the composition of carbides, on the one hand, and redistribution of atoms and vacancies in the crystal lattice of carbides, on the other hand, are two equally probable ways of controlling the properties of these substances. However, the characteristic feature of ordering as a way of providing fine control over the properties of nonstoichiometric carbides is that it changes the properties of carbides, while the chemical composition remains unchanged.

In the last decade of the 20th century, a large number of ordered phases of nonstoichiometric carbides, which have been found experimentally, and the development of methods of calculations of phase equilibria made it possible to construct the phase diagrams for the M–C systems ( $M = \text{Ti, Zr, Hf, V, Nb or Ta}$ ),<sup>1–4, 14–34</sup> which take into account not only the presence of strongly nonstoichiometric carbides  $MC_y$  ( $MC_y \square_{1-y}$ , where  $\square$  is a structural vacancy) but also their ordering at temperatures lower than 1200–1300 K.

In 1992, a new class of molecular metal carbon nanoclusters  $M_8C_{12}$  was discovered (see Refs 35 and 36) and the stable molecular cluster  $V_8C_{12}$  was detected in vaporisation products of the V–C system.

Therefore, considerable information on phase equilibria and compounds in the V–C system had been accumulated by the turn of the 20th century. The phase diagram for this system appeared to be much richer and more complex than had been assumed earlier. The aim of the present review is to generalise experimental and theoretical data on compounds and phases in the V–C system published in the last 15 years with consideration for the earlier results. Emphasis is given to the phase equilibria and crystal structures of phases and compounds consisting of vanadium and carbon.

## II. Phase diagrams for the V–C system at temperatures higher than 1000 K and thermodynamic properties of disordered carbides $VC_y$ and $V_2C_{y'}$

### 1. Phase diagrams

The V–C system is among the best-studied systems formed by transition metals and carbon. The first version of the phase diagram for the V–C system (see Fig. 1), which takes into consideration the presence of the cubic and hexagonal carbide phases  $VC_y$  and  $V_2C_{y'}$  ( $\beta$ - $V_2C$ ) characterised by homogeneity regions, was proposed in the study.<sup>10</sup> Later on, phase equilibria in this system were considered in the studies,<sup>37–39</sup> where 17 samples with different vanadium and carbon contents, their phase compositions and structures were studied by X-ray diffraction, differential thermal analysis and the metallographic method. The phase equilibria in the V–C system were analysed in the study.<sup>40</sup>

The melting point of vanadium metal determined in different studies is  $2161 \pm 10$ ,<sup>10</sup>  $2199 \pm 6$  (see Refs 37–39) or 2183 K.<sup>40</sup> The addition of carbon to vanadium leads to a decrease in the melting point to the eutectic temperature [ $1923 \pm 7$ ,<sup>37–39</sup> 1921 (see Ref. 40) or 1923 K (see Ref. 41)]. The  $L \rightleftharpoons V + V_2C_y$  eutectic mixture contains  $\sim 15$  at.% carbon.<sup>37, 38, 40, 41</sup> An increase in the carbon content leads to an increase in the melting point from the eutectic temperature to the temperature of the peritectoid transformation  $L + VC_y \rightleftharpoons V_2C_{y'}$ , which was evaluated at 2438 (see Ref. 10) or  $2460 \pm 10$  K.<sup>37–39</sup> Congruently melting carbide  $VC_{0.74-0.77}$ ,<sup>37, 38</sup>  $VC_{0.81}$  (see Ref. 40) or  $VC_{0.83}$  (see Ref. 41) has the highest melting point [ $2921 \pm 12$ ,<sup>37–39</sup> 2929 (see Ref. 40) or 3073 K,<sup>41</sup> respectively]. The temperature of the eutectic  $L \rightleftharpoons VC_y + C$  containing  $49.5 \pm 0.5$  at.% or 53.5 at.% carbon is  $2898 \pm 12$  (see Refs 37 and 38) or 2943 K,<sup>40</sup> respectively.

The phase diagrams for the V–C system, which were proposed in the studies<sup>41, 42</sup> with consideration for possible ordered vanadium carbide phases, are presented in Figs 2 and 3. The first attempt to construct a region of the phase diagram for the V–C system corresponding to the co-existence of the ordered  $V_6C_5$  and

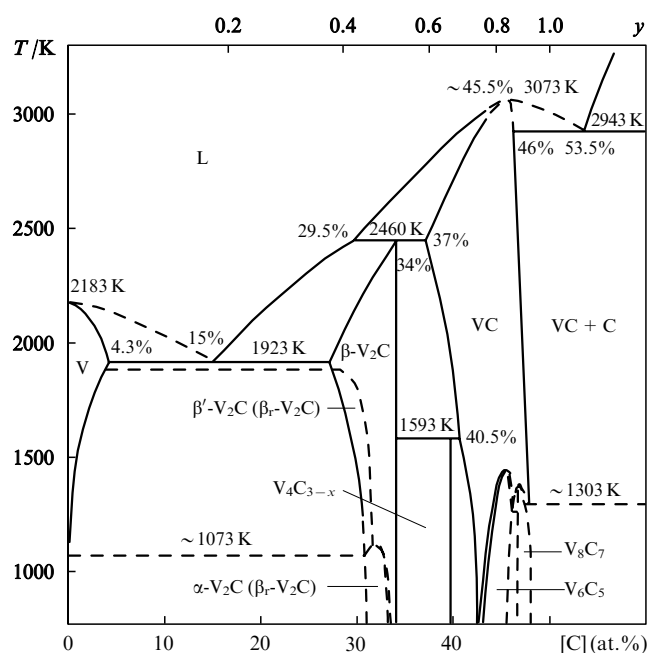


**Figure 2.** Phase diagram of the V–C system at temperatures higher than 800 K.<sup>41</sup>

$\alpha$ -V<sub>2</sub>C ( $\beta'$ -V<sub>2</sub>C) and  $\beta'$ -V<sub>2</sub>C ( $\beta_h$ -V<sub>2</sub>C) are the low-temperature orthorhombic and high-temperature hexagonal ordered phases, respectively, of lower hexagonal disordered carbide V<sub>2</sub>C<sub>y</sub>' ( $\beta$ -V<sub>2</sub>C); V<sub>6</sub>C<sub>5</sub> and V<sub>8</sub>C<sub>7</sub> are the ordered phases of nonstoichiometric cubic carbide VC<sub>y</sub>; V<sub>4</sub>C<sub>3-x</sub> ( $x = 0.2-0.5$ ) is an individual compound belonging to the rhombohedral (trigonal) system, which presumably has the composition VC<sub>0.67</sub>; the composition and the temperature range of existence of the V<sub>4</sub>C<sub>3-x</sub> compound presented in the figure are inconsistent with the most reliable experimental data.

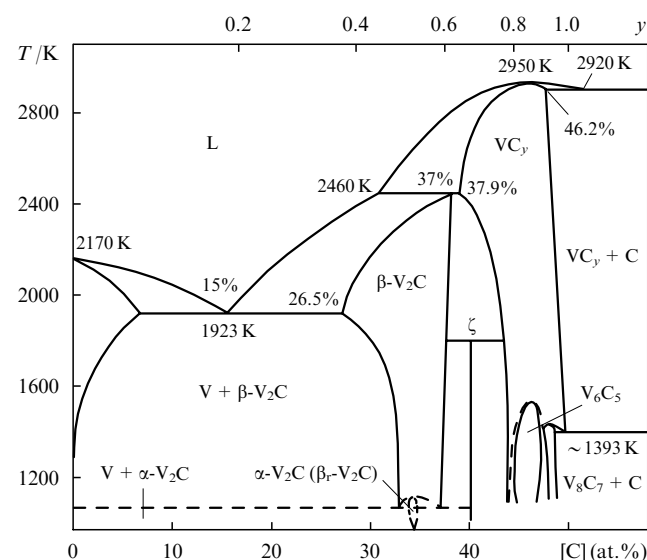


**Figure 3.** Phase diagram of the V–C system at temperatures higher than 1000 K.<sup>42</sup>

$\alpha$ -V<sub>2</sub>C ( $\beta'$ -V<sub>2</sub>C) is the orthorhombic ordered phase of lower hexagonal carbide V<sub>2</sub>C<sub>y</sub>' ( $\beta$ -V<sub>2</sub>C); V<sub>6</sub>C<sub>5</sub> and V<sub>8</sub>C<sub>7</sub> are the ordered phases of nonstoichiometric cubic carbide VC<sub>y</sub>;  $\zeta$  is the rhombohedral (trigonal) phase  $\zeta$ -V<sub>4</sub>C<sub>3-x</sub> ( $x = 0.2-0.5$ ), whose composition corresponds to V<sub>3</sub>C<sub>2</sub> (VC<sub>0.67</sub>); the position of the  $\zeta$ -V<sub>4</sub>C<sub>3-x</sub> phase presented in the figure is inconsistent in the composition and temperature range with experimental data.

V<sub>8</sub>C<sub>7</sub> phases was made in the study.<sup>43</sup> In the publication,<sup>41</sup> an ordered region was hypothesized to exist in the phase diagram, and this region was identical to that reported in the study.<sup>43</sup> In the review,<sup>40</sup> the ordering was not discussed at all and was not reflected in the phase diagram of the V–C system.

Analysis of the phase diagram presented in Fig. 2 shows that hexagonal lower carbide V<sub>2</sub>C<sub>y</sub>' ( $\beta$ -V<sub>2</sub>C) has a rather extended homogeneity region from VC<sub>0.45-0.46</sub> to VC<sub>0.52-0.56</sub> at 1200 K. The homogeneity region of V<sub>2</sub>C<sub>y</sub>' is expanded with increasing temperature. At 1923 K (the temperature of the eutectic  $L \rightleftharpoons V + V_2C_{y'}$ ), hexagonal carbides VC<sub>0.36-0.37</sub> and VC<sub>0.52-0.58</sub> correspond to the lower and upper boundaries of the homogeneity region, respectively. A decrease in the temperature can be accompanied by ordering of lower hexagonal carbide V<sub>2</sub>C<sub>y</sub>' giving rise to the orthorhombic ordered  $\alpha$ -V<sub>2</sub>C ( $\beta'$ -V<sub>2</sub>C) phase.<sup>44</sup> The precise temperature of the disorder–order phase transition V<sub>2</sub>C<sub>y</sub>'  $\rightleftharpoons$   $\alpha$ -V<sub>2</sub>C ( $\beta'$ -V<sub>2</sub>C) is unknown. According to the results of different studies, this temperature varies from 1100 to 1600 K. Data on the crystal structures of the  $\beta'$ -V<sub>2</sub>C ( $\beta_h$ -V<sub>2</sub>C) and  $\beta$ -V<sub>2</sub>C (V<sub>2</sub>C<sub>y</sub>') phases are also available in the literature. Both phases have a hexagonal metal sublattice, but differ in the distribution of carbon atoms. The former phase is an  $\epsilon$ -Fe<sub>2</sub>N-type ordered hexagonal phase, and the latter phase is a disordered hexagonal phase with the L'3 (W<sub>2</sub>C) structure. From this fact it follows that the  $\beta'$ -V<sub>2</sub>C ( $\beta_h$ -V<sub>2</sub>C)  $\rightleftharpoons$   $\beta$ -V<sub>2</sub>C (V<sub>2</sub>C<sub>y</sub>') transformation can occur. These hypothetical phase equilibria are shown in Fig. 2 by dashed lines.

Cubic carbide VC<sub>y</sub> has a wide homogeneity region from VC<sub>0.72</sub> to VC<sub>0.88</sub> at 1500 K and from VC<sub>0.60</sub> to VC<sub>0.87</sub> at  $\sim 2450$  K. This is the only compound among strongly nonstoichiometric carbides, which is characterised by the upper boundary of the homogeneity region most remote from the stoichiometric composition MC<sub>1.0</sub>. At temperatures lower than 1500 K, the homogeneity region of nonstoichiometric cubic carbide VC<sub>y</sub> has two ordered phases, viz., V<sub>6</sub>C<sub>5</sub> with monoclinic<sup>43,45</sup> or trigonal<sup>13</sup> symmetry and the cubic V<sub>8</sub>C<sub>7</sub> phase.<sup>12,46-49</sup> The ordered V<sub>6</sub>C<sub>5</sub> phases are characterised by a rather extended homogeneity region, whereas the homogeneity region of the V<sub>8</sub>C<sub>7</sub> phase is small.

The phase diagrams (see Figs 2 and 3) show also the  $\zeta$ -V<sub>4</sub>C<sub>3-x</sub> phase consistent with the VC<sub>0.67</sub> composition (V<sub>3</sub>C<sub>2</sub>). This phase has a rhombohedral (trigonal) structure and is an individual compound of the V–C system, although it is sometimes erroneously called (see, for example, Ref. 42) the ordered carbide phase VC<sub>y</sub>. The  $\zeta$ -V<sub>4</sub>C<sub>3-x</sub> phase does not belong to ordered phases of cubic carbide, because its metal sublattice has trigonal rather than cubic symmetry. According to the results of the study,<sup>10</sup>  $\zeta$ -V<sub>4</sub>C<sub>3-x</sub> exists only at temperatures lower than 1617 K and decomposes through a peritectoid reaction at  $T \geq 1617$  K. However, the  $\zeta$ -V<sub>4</sub>C<sub>3-x</sub> phase was observed at higher temperatures (up to 1870 K) in the studies.<sup>38,50,51</sup> According to the latest and most reliable experimental data,<sup>52</sup> the  $\zeta$ -V<sub>4</sub>C<sub>3-x</sub> phase contains 37.9 at.% C and has a very narrow ( $\sim 0.4$  at.% C) homogeneity region from VC<sub>0.605</sub> to VC<sub>0.615</sub>. The minimum temperature, at which this phase was detected after 78-hour annealing, is 1540 K. The temperature of peritectoid decomposition of the  $\zeta$ -phase during heating is 2150 K.<sup>52</sup> Therefore, the composition and the temperature range of existence of the  $\zeta$ -V<sub>4</sub>C<sub>3-x</sub> phase in the diagrams of the V–C system (see Figs 2 and 3) are not quite correct. Data on the crystal structures of the phases in the V–C system and the special points in its phase diagram at  $T > 1000$  K are given in Tables 1 and 2.

The phase equilibria associated with ordering of nonstoichiometric vanadium carbide VC<sub>y</sub> and occurring at temperatures lower than 1300–1400 K have been described in detail<sup>1,3,4,15,19,28,47,48,53,54</sup> and will be considered below.

**Table 1.** Crystal structures of the phases existing in the V–C system at temperatures higher than 1000 K.

| Phase                                                          | [C] (at. %) | Space group             | Pearson symbol | Lattice type                                          |
|----------------------------------------------------------------|-------------|-------------------------|----------------|-------------------------------------------------------|
| V                                                              | 0–4.3       | $Im\bar{3}m (O_h^9)$    | $cI2$          | A2 (W)                                                |
| $\alpha$ -V <sub>2</sub> C<br>( $\beta_F$ -V <sub>2</sub> C)   | ~31.0–33.0  | $Pbcn (D_{2h}^{14})$    | $oP12$         | $\zeta$ -Fe <sub>2</sub> N                            |
| $\beta$ -V <sub>2</sub> C<br>(V <sub>2</sub> C <sub>y'</sub> ) | ~27.0–34.0  | $P6_3/mmc (D_{6h}^4)$   | $hP3$          | L'3 (W <sub>2</sub> C)                                |
| $\beta'$ -V <sub>2</sub> C<br>( $\beta_h$ -V <sub>2</sub> C)   | ~27.5–31.5  | $P\bar{3}m1 (D_{3d}^3)$ | $hP9$          | Ni <sub>3</sub> N<br>( $\epsilon$ -Fe <sub>2</sub> N) |
| $\zeta$ -V <sub>4</sub> C <sub>3–x</sub>                       | ~37.6–40.1  | $R\bar{3}m (D_{3d}^5)$  | $hR20$         | —                                                     |
| VC <sub>y</sub>                                                | ~37.0–48.0  | $Fm\bar{3}m (O_h^5)$    | $cF8$          | B1 (NaCl)                                             |
| V <sub>6</sub> C <sub>5</sub>                                  | ~43.0–46.0  | $C2 (C_2^3)$            | $mC44$         | —                                                     |
| V <sub>6</sub> C <sub>5</sub>                                  | ~43.0–46.0  | $P3_1 (C_3^2)$          | $hP33$         | —                                                     |
| V <sub>8</sub> C <sub>7</sub>                                  | ~46.0–47.0  | $P4_332 (O^6)$          | $cP60$         | —                                                     |
| C                                                              | 100         | $P6_3/mmc (D_{6h}^4)$   | $hP4$          | A9 (graphite)                                         |

**Table 2.** Parameters of the special points in the phase diagram of the V–C system at temperatures higher than 1000 K.

| Reaction                                                                                                                                 | Compositions of phases involved in the reaction (at. % C) |      |      | T /K      | Reaction type     |
|------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|------|------|-----------|-------------------|
| $L \rightleftharpoons V + V_2C_{y'}$<br>( $\beta$ -V <sub>2</sub> C)                                                                     | 15.0                                                      | 4.3  | 27.0 | 1923 ± 7  | eutectic          |
| $L + VC_{y'} \rightleftharpoons V_2C_{y'}$<br>( $\beta$ -V <sub>2</sub> C)                                                               | 29.5                                                      | 37.0 | 34.0 | 2460 ± 10 | peritectic        |
| $L \rightleftharpoons VC_{y'}$                                                                                                           | —                                                         | 45.5 | —    | 3073 ± 10 | congruent melting |
| $L \rightleftharpoons VC_{y'} + C$                                                                                                       | 53.5                                                      | 46.0 | ~100 | 2943 ± 3  | eutectic          |
| $V_2C_{y'} (\beta$ -V <sub>2</sub> C) + VC <sub>y</sub> $\rightleftharpoons$ $\rightleftharpoons \zeta$ -V <sub>4</sub> C <sub>3–x</sub> | 35.1                                                      | 39.5 | 37.9 | 2150      | peritectoid       |
| $L \rightleftharpoons V$                                                                                                                 | —                                                         | 0    | —    | 2183 ± 3  | melting           |
| $VC_{y'} \rightleftharpoons V_6C_5$                                                                                                      | —                                                         | 45.5 | —    | ~1500     | ordering          |
| $VC_{y'} \rightleftharpoons V_8C_7$                                                                                                      | —                                                         | 46.6 | —    | ~1400     | "                 |

**2. Structures and thermodynamic properties of disordered vanadium carbides**

**a. Structures**

Cubic (*B1* structure type) disordered vanadium monocarbide VC<sub>y</sub> is the most important compound existing in the V–C system at temperatures higher than 1000 K (Table 3). The width of the homogeneity region of VC<sub>y</sub> depends on the temperature. The solid-state synthesis of vanadium monocarbide is generally carried out at ~2000 K followed by quenching to room temperature, which makes it possible to retain cubic carbide VC<sub>y</sub> in the disordered state. At 2000 K, disordered cubic vanadium carbide has a homogeneity region from VC<sub>0.65</sub> to VC<sub>0.88</sub>. This region ( $0.65 \leq y \leq 0.88$ ) was reported in most of the published data. The unit cell of VC<sub>y</sub> can be described as two face-centred (metal and non-metal) sublattices, which are shifted with respect to each other by one-half of the lattice period (Fig. 4). In the metal

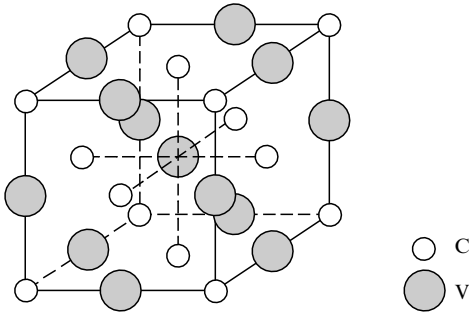


**Figure 4.** The unit cell of cubic disordered nonstoichiometric vanadium monocarbide VC<sub>y</sub> [the *B1* structure type (NaCl)]. All sites of the metal sublattices are occupied by vanadium atoms, the sites of the non-metal sublattice are randomly (with probability *y*) occupied by carbon atoms.

sublattice, all sites are occupied by vanadium atoms. In the non-metal (carbon) sublattice, the number of sites is larger than the number of interstitial atoms. In the disordered state (which is thermodynamically at equilibrium only at  $T > 1300$ –1400 K, whereas it is retained as a quenched metastable state at lower temperatures), the carbon atoms are randomly distributed over the sites, and all sites of the non-metal sublattice are occupied with the same probability equal to *y* (the relative carbon content of VC<sub>y</sub>). This provides retention of cubic symmetry of the disordered non-metal sublattice and signifies that all sites of the carbon sublattice in disordered VC<sub>y</sub> are crystallographically equivalent. The typical X-ray diffraction pattern of homogeneous cubic vanadium carbide is shown in Fig. 5. A high degree of homogeneity of carbide VC<sub>0.83</sub> is evidenced by splitting of the  $K_{\alpha 1}$  and  $K_{\alpha 2}$  doublets observed already for the (311)<sub>B1</sub> reflection. The crystal

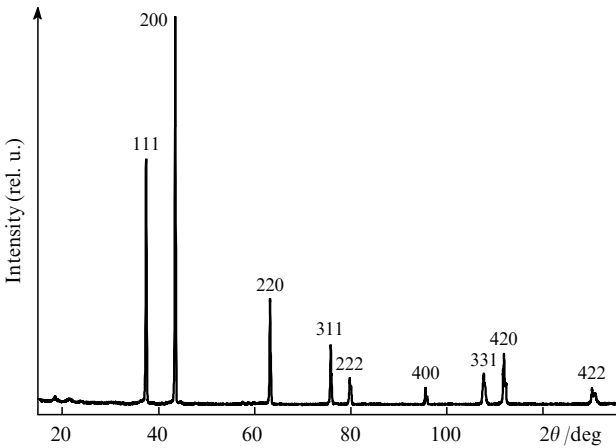


**Figure 5.** X-Ray diffraction pattern of disordered homogeneous carbide VC<sub>0.83</sub> with a *B1*-type cubic structure (Cu  $K\alpha_{1,2}$  radiation).  $a_{B1} = 0.41596$  nm.<sup>25</sup>

**Table 3.** Characteristics of cubic and hexagonal disordered nonstoichiometric vanadium carbides.

| Phase                          | Symmetry  | Space group           | Lattice type                   | Atom | Position and multiplicity | Atomic coordinates |          |          | Probability of occupancy |
|--------------------------------|-----------|-----------------------|--------------------------------|------|---------------------------|--------------------|----------|----------|--------------------------|
|                                |           |                       |                                |      |                           | <i>x</i>           | <i>y</i> | <i>z</i> |                          |
| VC <sub>y</sub>                | cubic     | $Fm\bar{3}m (O_h^5)$  | <i>B1</i> (NaCl)               | V    | 4( <i>a</i> )             | 0                  | 0        | 0        | 1                        |
|                                |           |                       |                                | C    | 4( <i>b</i> )             | 1/2                | 1/2      | 1/2      | <i>y</i>                 |
| V <sub>2</sub> C <sub>y'</sub> | hexagonal | $P6_3/mmc (D_{6h}^4)$ | <i>L'</i> 3 (W <sub>2</sub> C) | V    | 2( <i>a</i> )             | 0                  | 0        | 0        | 1                        |
|                                |           |                       |                                | C    | 2( <i>c</i> )             | 1/3                | 2/3      | 1/4      | <i>y'</i> /2             |



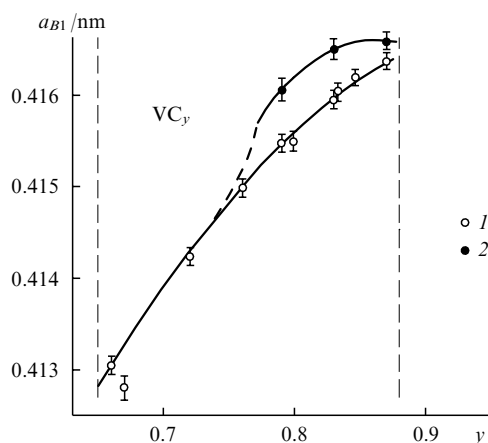


**Figure 6.** Plot of the parameter  $a_{B1}$  of the basic cubic crystal lattice vs. the composition of carbide  $VC_y$  in quenched disordered (1) and annealed ordered (2) states.<sup>25</sup> The boundaries of the homogeneity region of carbide  $VC_y$  are shown by vertical bars.

lattice period of both disordered and ordered  $VC_y$  increases with increasing carbon content (Fig. 6).

Lower vanadium carbide  $V_2C_{y'}$  ( $\beta$ - $V_2C$ ), which is also called semicarbide or subcarbide, has a hexagonal structure of the  $L/3$  ( $W_2C$ ) type. In this structure, carbon atoms randomly occupy no more than one-half of all octahedral interstitial sites in the metal sublattice (Fig. 7). Since it cannot be unambiguously determined which sites of the non-metal sublattice are occupied by carbon atoms, and which sites are, on the contrary, vacant, the probability of finding a carbon atom in each site of the non-metal sublattice of lower vanadium carbide  $V_2C_{y'}$  is  $y'/2$  (see Table 3). The width of the homogeneity region of disordered lower vanadium carbide quenched to high temperatures is small, from  $VC_{0.42}$ – $0.45$  to  $VC_{0.50}$ . The volume of its unit cell enriched in carbon slightly increases. The unit cell parameters of the carbide of stoichiometric composition  $V_2C$  ( $VC_{0.50}$ ) are larger than those of  $V_2C_{0.94}$  ( $VC_{0.47}$ ) ( $a = 0.2902$  and  $c = 0.4577$  nm as opposed to  $a = 0.2885$  and  $c = 0.4571$  nm). The X-ray diffraction pattern of disordered lower vanadium carbide  $V_2C$  ( $VC_{0.50}$ ) with a hexagonal lattice of the  $L/3$  ( $W_2C$ ) type is shown in Fig. 8.

The thermodynamic properties of nonstoichiometric vanadium carbides vary substantially within their homogeneity regions. Hence, investigations, in which the measured thermody-

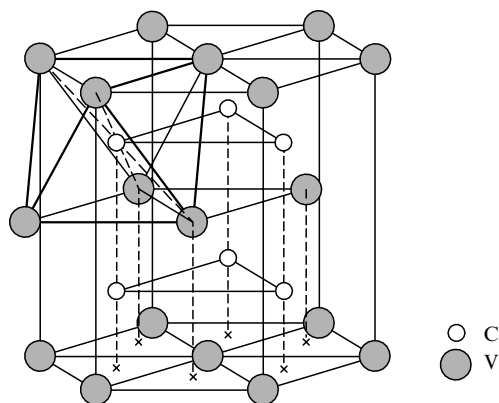


**Figure 7.** Hexagonal (space group  $P6_3/mmc$ ) structure of the  $L/3$  ( $W_2C$ ) type of lower vanadium carbide  $V_2C_{y'}$ . Metal atoms form a hexagonal close-packed lattice, in which one-half or less than one-half of octahedral interstitial sites are randomly occupied by carbon atoms.

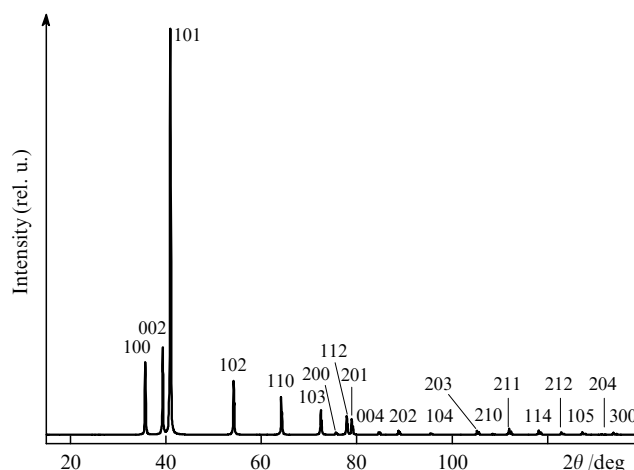


**Figure 8.** X-Ray diffraction pattern of disordered homogeneous lower vanadium carbide  $V_2C$  ( $VC_{0.50}$ ) with a  $L/3$ -type hexagonal structure (Cu  $K\alpha_{1,2}$  radiation).  $a = 0.2902$  nm,  $c = 0.4577$  nm.

amic characteristics were assigned to a particular composition of carbide in the known structural (disordered or ordered) state, are of great interest. The temperature and concentration dependences of the thermodynamic characteristics of disordered carbides allow the quantitative description of high-temperature phase equilibria involving  $VC_y$  and  $V_2C_{y'}$ . Besides, disorder–order phase transformations and transitions between ordered phases can be directly studied with the use of these data. However, available results of experimental thermodynamic investigations of nonstoichiometric vanadium carbides, whose compositions and crystal structures were well characterised, are scarce.

## b. Enthalpy of formation

The enthalpies of formation of cubic carbide  $VC_y$  with different carbon contents were determined<sup>55,56</sup> by calorimetry from the thermal effects of combustion in oxygen:

| Carbide     | $\Delta H_{f, 298}^\circ / \text{kJ mol}^{-1}$ | Carbide     | $\Delta H_{f, 298}^\circ / \text{kJ mol}^{-1}$ |
|-------------|------------------------------------------------|-------------|------------------------------------------------|
| $VC_{0.72}$ | $-90.5 \pm 5.6$                                | $VC_{0.82}$ | $-111.7 \pm 4.1$                               |
| $VC_{0.76}$ | $-108.2 \pm 7.0$                               | $VC_{0.84}$ | $-98.9 \pm 4.2$                                |
| $VC_{0.77}$ | $-101.6 \pm 5.4$                               | $VC_{0.88}$ | $-100.3 \pm 5.9$ (see Ref. 55)                 |
| $VC_{0.80}$ | $-96.7 \pm 12.0$                               | $VC_{0.88}$ | $-112.2 \pm 4.7$ (see Ref. 56)                 |

The empirical dependence of the enthalpy of formation on the composition of cubic carbide  $VC_y$  for the range  $0.72 \leq y \leq 0.88$  was described<sup>56</sup> by a linear function

$$\Delta H_{f, 298}^\circ(y) = -48.3 - 66.3y \pm 6.7 \text{ (kJ mol}^{-1}\text{)}.$$

In the study,<sup>57</sup> the enthalpy of formation of carbide  $VC_{0.88}$  was estimated at  $-100.9 \pm 2.9 \text{ kJ mol}^{-1}$ .

However, analysis of the experimental results<sup>55–57</sup> taking into account experimental errors demonstrated<sup>58</sup> that the enthalpy of formation of cubic  $VC_y$  is square function of the carbon content and, for the range  $0.70 \leq y \leq 0.88$ , takes the form

$$\Delta H_{f, 298}^\circ(y) = 104.78 - 437.73y + 224.02y^2 \text{ (kJ mol}^{-1}\text{)}. \quad (1)$$

As mentioned above, the characteristic feature of cubic carbide  $VC_y$  is that the upper boundary of its homogeneity region corresponds to  $VC_{0.875}$  and is far from the equiatomic composition  $VC_{1.0}$ . All attempts to synthesise stoichiometric carbide  $VC_{1.0}$  failed. However, the thermodynamic characteristics were theoretically estimated. The enthalpy of formation of hypothetical carbide  $VC_{1.0}$  was evaluated<sup>59</sup> at  $-117.2 \pm 41.9 \text{ kJ mol}^{-1}$ . In the study,<sup>60</sup> the energy of formation of structural vacancies in cubic carbide  $VC_y$  was calculated from the experimental data<sup>56</sup> and the

standard enthalpy of formation  $\Delta H_{f,298}^\circ$  of the stoichiometric compound  $\text{VC}_{1.0}$  was estimated at  $-105.9 \pm 2.9 \text{ kJ mol}^{-1}$ . According to the results of the study,<sup>60</sup> the enthalpy of formation linearly depends on the composition of cubic carbide  $\text{VC}_y$  in the composition region from  $\text{VC}_{0.65}$  to  $\text{VC}_{1.0}$ .

$$\Delta H_{f,298}^\circ(y) = -91.4 - 14.5y \text{ (kJ mol}^{-1}\text{)}. \quad (2)$$

It should be noted that the enthalpy difference between carbide  $\text{VC}_{0.88}$  and hypothetical  $\text{VC}_{1.0}$  calculated by Eqns (1) and (2) is small (2.0 and 1.7  $\text{kJ mol}^{-1}$ , respectively). The small enthalpy difference corresponds to the small difference in the free energy of formation of these compounds, which can be compensated by the contribution of the configurational entropy of non-stoichiometric carbide. As a result, carbide  $\text{VC}_{0.88}$  can have a lower free energy than stoichiometric carbide  $\text{VC}_{1.0}$ , due to which imperfect carbide  $\text{VC}_{0.88}$  rather than stoichiometric carbide  $\text{VC}_{1.0}$  exists in equilibrium with carbon. This situation cannot occur, for example, in the case of carbide  $\text{TiC}_y$ , because its free energy depends more strongly on the composition compared to vanadium carbide. This is evident from the enthalpy differences. For titanium carbides  $\text{TiC}_{0.88}$  and  $\text{TiC}_{1.0}$ , this difference is  $16.5 \text{ kJ mol}^{-1}$ ,<sup>28</sup> i.e., it is 7–8 times larger than that for carbides  $\text{VC}_{0.88}$  and  $\text{VC}_{1.0}$ .

The dependence of the enthalpy of formation (in  $\text{kJ mol}^{-1}$ ) on the composition of lower carbide  $\text{V}_2\text{C}_{y'} \equiv \text{VC}_y$  ( $y \leq 0.5$ ) determined in the study<sup>61</sup> can be described by the following function:

$$\Delta H_{f,298}^\circ(y) = -42.2 - 53.7y \pm 2.6,$$

according to which the enthalpy of formation of carbide  $\text{V}_2\text{C}$  ( $\text{VC}_{0.5}$ ) is

$$\Delta H_{f,298}^\circ \text{V}_2\text{C} = 2 \Delta H_{f,298}^\circ \text{VC}_{0.5} = -138.1 \text{ kJ mol}^{-1}.$$

Apparently, this value is underestimated in magnitude. In the study,<sup>57</sup> the enthalpy of formation of  $\text{V}_2\text{C}$  was estimated at  $-147.4 \pm 21.0 \text{ kJ mol}^{-1}$ , which is more realistic.

### c. Enthalpy (heat content)

The enthalpies ( $H_T^\circ - H_{298}^\circ$ ) of cubic  $\text{VC}_y$  with different carbon contents were measured at 500–1500,<sup>62</sup> 1300–2500 (see Ref. 63) and 400–1100 K (see Ref. 64) and approximated by the polynomials

$$H_T^\circ - H_{298}^\circ = A + BT + CT^2 + DT^{-1}. \quad (2a)$$

In the study,<sup>62</sup> the enthalpies of several samples of lower vanadium carbide  $\text{V}_2\text{C}_{y'}$  ( $\text{VC}_y$  for  $y \leq 0.5$ ) with different carbon contents were also measured. The measured temperature depend-

ences ( $H_T^\circ - H_{298}^\circ$ ) show a jump increase in the enthalpy at  $\sim 1385 \text{ K}$  associated with the disorder–order transition. The polynomials proposed in this study, can be considered as suitable for the description of the enthalpy in the temperature range from 300 to 1385 K. The polynomials reported in the studies<sup>62,63</sup> do not quite satisfy the evident normalisation condition at  $T = 298 \text{ K}$

$$H_T^\circ - H_{298}^\circ \equiv 0.$$

Hence, in the present review, the preliminary results of measurements<sup>62,63</sup> were processed taking into account this condition. The polynomial coefficients are given in Table 4.

The enthalpies of vanadium carbides containing small amounts of oxygen and nitrogen, for example, of  $\text{V}(\text{C}_{0.995}\text{O}_{0.002}\text{N}_{0.003})_{0.813}$ , were measured in the study.<sup>64</sup> The composition of the latter carbide was written as  $\text{VC}_{0.813}$ . However, the carbon content in this formula is overestimated. Hence, the index for carbon presented in Table 4 is written according to its actual content.

The empirical temperature and concentration dependence of the enthalpy (in  $\text{kJ mol}^{-1}$ ) of disordered cubic carbide was obtained from the data given in Table 4,

$$\begin{aligned} (H_T^\circ - H_{298}^\circ)_{\text{VC}_y} = & (-7.69 + 26.95 \times 10^{-3}T + \\ & + 11.84 \times 10^{-6}T^2 - 416T^{-1}) + \\ & + (0.24 - 18.29 \times 10^{-3}T - 11.75 \times 10^{-6}T^2 + 1864T^{-1})y + \\ & + (-12.66 + 42.47 \times 10^{-3}T)y^2. \end{aligned} \quad (3)$$

This dependence allows one to estimate the enthalpy of  $\text{VC}_y$  for all  $y$  in the temperature range from 300 to 2000 K.

The enthalpy ( $H_T^\circ - H_{298}^\circ$ ) <sub>$\text{V}_2\text{C}$</sub>  (in  $\text{kJ mol}^{-1}$ ) of hexagonal carbide  $\text{V}_2\text{C}$  ( $\beta\text{-V}_2\text{C}$ ) is twice as high as the enthalpy of hexagonal  $\text{VC}_{0.5}$

$$(H_T^\circ - H_{298}^\circ)_{\text{V}_2\text{C}} = 2(H_T^\circ - H_{298}^\circ)_{\text{VC}_{0.5}}.$$

The temperature dependence, which was determined from the results of the study<sup>62</sup> and refined taking into account the normalisation condition ( $H_T^\circ - H_{298}^\circ \equiv 0$  at  $T = 298 \text{ K}$ ), takes the form

$$\begin{aligned} (H_T^\circ - H_{298}^\circ)_{\text{V}_2\text{C}} = & -33.58 + 83.12 \times 10^{-3}T + \\ & + 1.7 \times 10^{-6}T^2 + 2580T^{-1}. \end{aligned} \quad (4)$$

This dependence is valid for the temperature range from 300 to 1600 K.

**Table 4.** Coefficients of the temperature dependence of enthalpy for hexagonal ( $\text{VC}_{0.42}$ ,  $\text{VC}_{0.45}$ ,  $\text{VC}_{0.51}$ ) and cubic vanadium carbides  $\text{VC}_y$  [see Eqn (2a)].

| $\text{VC}_y$                          | $A/\text{kJ mol}^{-1}$ | $10^3 B/\text{kJ mol}^{-1} \text{K}^{-1}$ | $10^6 C/\text{kJ mol}^{-1} \text{K}^{-2}$ | $D/\text{kJ K mol}^{-1}$ | $T/\text{K}$ | Ref. |
|----------------------------------------|------------------------|-------------------------------------------|-------------------------------------------|--------------------------|--------------|------|
| $\text{VC}_{0.42}$                     | -15.283                | 38.573                                    | 0.716                                     | 1109.9                   | 300–1385     | 62   |
| $\text{VC}_{0.45}$                     | -15.883                | 40.017                                    | 0.572                                     | 1164.3                   | 300–1585     | 62   |
| $\text{VC}_{0.51}$                     | -16.790                | 41.562                                    | 0.849                                     | 1290.0                   | 300–1585     | 62   |
| $\text{VC}_{0.70}$                     | -17.589                | 43.702                                    | 1.214                                     | 1328.5                   | 300–1585     | 62   |
| $\text{VC}_{0.72}$                     | -9.397                 | 29.051                                    | 8.366                                     | 0                        | 1300–2000    | 63   |
| $\text{VC}_{0.75}$                     | -9.613                 | 29.470                                    | 9.355                                     | 0                        | 1300–2000    | 63   |
| $\text{VC}_{0.75}$ (see <sup>a</sup> ) | -15.422                | 45.043                                    | 5.091                                     | 460.9                    | 300–1100     | 64   |
| $\text{VC}_{0.76}$                     | -17.591                | 43.756                                    | 1.549                                     | 1315.5                   | 300–1585     | 62   |
| $\text{VC}_{0.81}$ (see <sup>a</sup> ) | -14.778                | 43.132                                    | 6.746                                     | 395.0                    | 300–1100     | 64   |
| $\text{VC}_{0.84}$ (see <sup>a</sup> ) | -17.156                | 47.473                                    | 4.043                                     | 789.8                    | 300–1100     | 64   |
| $\text{VC}_{0.84}$                     | -17.630                | 43.827                                    | 2.093                                     | 1306.3                   | 300–1385     | 62   |
| $\text{VC}_{0.86}$                     | -17.822                | 43.999                                    | 2.412                                     | 1339.8                   | 300–1385     | 62   |
| $\text{VC}_{0.86}$                     | -12.378                | 39.851                                    | 5.656                                     | 0                        | 1300–2000    | 63   |
| $\text{VC}_{0.87}$ (see <sup>a</sup> ) | -18.056                | 50.062                                    | 2.158                                     | 877.8                    | 300–1100     | 64   |
| $\text{VC}_{0.88}$ (see <sup>a</sup> ) | -16.775                | 46.186                                    | 4.064                                     | 789.8                    | 300–1100     | 64   |
| $\text{VC}_{0.88}$                     | -16.908                | 42.324                                    | 2.730                                     | 1207.9                   | 300–1385     | 62   |

<sup>a</sup> The compositions of carbides  $\text{VC}_y$  determined in the study<sup>64</sup> are given in accordance with the real carbon content.

The enthalpies of hexagonal carbide VC<sub>0.46</sub> and cubic carbides VC<sub>0.71</sub>, VC<sub>0.83</sub> and VC<sub>0.86</sub> in the temperature range of 400–1300 K were also experimentally determined in the studies.<sup>65,66</sup> These enthalpies are apparently slightly underestimated.

#### d. Heat capacity and entropy

The heat capacities of hexagonal and cubic vanadium carbides VC<sub>0.46</sub>, VC<sub>0.53</sub>, VC<sub>0.71</sub>, VC<sub>0.83</sub> and VC<sub>0.86</sub> were measured<sup>65,67</sup> in the temperature range from 10 to 300 K by adiabatic calorimetry. The preliminary results of measurements were described in the publication.<sup>67</sup> The tabulated heat capacities, enthalpies and entropies of these carbides (Tables 5 and 6) were published in the study.<sup>65</sup> The experimental error was no higher than 1%.

**Table 5.** Heat capacities  $C_p$  (J g-atom<sup>-1</sup> K<sup>-1</sup>),  $\Delta S_T^\circ = S_T^\circ - S_{10}^\circ$  (J g-atom<sup>-1</sup> K<sup>-1</sup>) and  $H_T^\circ - H_{10}^\circ$  (J g-atom<sup>-1</sup>) for hexagonal carbides VC<sub>0.46</sub> and VC<sub>0.53</sub> in the temperature range of 10–300 K.<sup>65,67</sup>

| T/K | VC <sub>0.46</sub> |                            |                    | VC <sub>0.53</sub> |                            |                    |
|-----|--------------------|----------------------------|--------------------|--------------------|----------------------------|--------------------|
|     | $C_p$              | $H_T^\circ - H_{10}^\circ$ | $\Delta S_T^\circ$ | $C_p$              | $H_T^\circ - H_{10}^\circ$ | $\Delta S_T^\circ$ |
| 10  | 0.008              | —                          | —                  | 0.008              | —                          | —                  |
| 50  | 1.629              | 21.0                       | 0.544              | 1.390              | 17.0                       | 0.461              |
| 100 | 7.360              | 268.8                      | 3.475              | 6.720              | 219.8                      | 3.056              |
| 150 | 11.70              | 753.6                      | 6.783              | 11.02              | 674.1                      | 6.615              |
| 200 | 14.82              | 1419.3                     | 10.59              | 14.28              | 1310.5                     | 10.26              |
| 250 | 17.16              | 2223.2                     | 14.19              | 16.78              | 2089.2                     | 13.73              |
| 273 | 17.99              | 2625.1                     | 15.70              | 17.72              | 2487.0                     | 15.24              |
| 298 | 18.80              | 3085.7                     | 17.33              | 18.54              | 2939.1                     | 16.87              |
| 300 | 18.86              | 3127.5                     | 17.46              | 18.62              | 2976.8                     | 17.00              |

The temperature dependence of the heat capacity (in J mol<sup>-1</sup> K<sup>-1</sup>) of hypothetical stoichiometric vanadium carbide VC<sub>1.0</sub> was calculated.<sup>60</sup>

$$C_p(T) = 38.4 + 0.017T - 1351.5T^{-1}. \quad (5)$$

The heat capacity of this carbide determined at 300 K (39.0 J mol<sup>-1</sup> K<sup>-1</sup>) is, apparently, overestimated. For comparison, the heat capacities of carbides VC<sub>0.71</sub>, VC<sub>0.83</sub> and VC<sub>0.86</sub> were evaluated at 30.50, 31.95 and 32.10 J mol K<sup>-1</sup>, respectively.<sup>65</sup>

The heat capacities of ordered carbides VC<sub>0.79</sub>, VC<sub>0.83</sub> and VC<sub>0.87</sub> were measured<sup>25,26,68,69</sup> in the temperature range from 300 to 1570 K by differential scanning calorimetry. The temperature dependences of the heat capacity at  $T > 1300$  K show peaks characteristic of order–disorder phase transitions.

The heat capacities of VC<sub>0.76</sub>, VC<sub>0.80</sub>, VC<sub>0.85</sub> and VC<sub>0.87</sub> in the temperature range of 1–20 K were measured in the study.<sup>70</sup> At  $T < 5$  K, the heat capacity is described by the dependence

$$C_p(T) = \gamma T + \alpha T^3 + \beta T^5.$$

**Table 6.** Heat capacities  $C_p$  (J g-atom<sup>-1</sup> K<sup>-1</sup>),  $\Delta S_T^\circ = S_T^\circ - S_{10}^\circ$  (J g-atom<sup>-1</sup> K<sup>-1</sup>) and  $H_T^\circ - H_{10}^\circ$  (J g-atom<sup>-1</sup>) for cubic carbides VC<sub>0.71</sub>, VC<sub>0.83</sub> and VC<sub>0.86</sub> in the temperature range of 10–300 K.<sup>65,67</sup>

| T, K | VC <sub>0.71</sub> |                            |                    | VC <sub>0.83</sub> |                            |                    | VC <sub>0.86</sub> |                            |                    |
|------|--------------------|----------------------------|--------------------|--------------------|----------------------------|--------------------|--------------------|----------------------------|--------------------|
|      | $C_p$              | $H_T^\circ - H_{10}^\circ$ | $\Delta S_T^\circ$ | $C_p$              | $H_T^\circ - H_{10}^\circ$ | $\Delta S_T^\circ$ | $C_p$              | $H_T^\circ - H_{10}^\circ$ | $\Delta S_T^\circ$ |
| 10   | 0.008              | —                          | —                  | 0.004              | —                          | —                  | 0.042              | —                          | —                  |
| 50   | 1.005              | 12.0                       | 0.293              | 0.712              | 9.0                        | 0.251              | 0.670              | 8.0                        | 0.209              |
| 100  | 5.610              | 172.0                      | 2.386              | 4.815              | 139.0                      | 1.758              | 4.690              | 135.0                      | 1.675              |
| 150  | 9.839              | 561.0                      | 5.485              | 8.960              | 485.7                      | 4.522              | 8.834              | 473.1                      | 4.396              |
| 200  | 13.15              | 1138.8                     | 8.792              | 12.43              | 1025.8                     | 7.620              | 12.27              | 1004.8                     | 7.453              |
| 250  | 15.78              | 1863.1                     | 12.02              | 15.28              | 1720.8                     | 10.72              | 15.07              | 1691.5                     | 10.47              |
| 273  | 16.79              | 2269.2                     | 13.44              | 16.37              | 2085.0                     | 12.10              | 16.16              | 2051.5                     | 11.85              |
| 298  | 17.75              | 2671.2                     | 14.99              | 17.38              | 2507.9                     | 13.57              | 17.17              | 2466.0                     | 13.31              |
| 300  | 17.84              | 2704.7                     | 15.07              | 17.46              | 2512.1                     | 13.69              | 17.25              | 2503.7                     | 13.40              |

Taking into account the method used for the synthesis, the obtained carbides were, apparently, disordered. Nevertheless, with the reference to optical anisotropy of VC<sub>0.85</sub> observed in reflected white light, the authors of the study<sup>70</sup> hypothesised that this sample can contain the ordered V<sub>6</sub>C<sub>5</sub> phase.

According to the results of the investigation,<sup>65</sup> the entropies  $S_{298}^\circ$  of nonstoichiometric cubic carbides VC<sub>0.71</sub>, VC<sub>0.83</sub> and VC<sub>0.86</sub> are 14.99, 13.57 and 13.31 J g-atom<sup>-1</sup> K<sup>-1</sup> (see Tables 5 and 6) or 25.62, 24.83 and 24.76 J mol<sup>-1</sup> K<sup>-1</sup>, respectively. These values were used to calculate the dependence of the entropy (J mol<sup>-1</sup> K<sup>-1</sup>) on the composition of cubic vanadium carbide

$$S_{298}^\circ(y) = 40.21 - 32.77y + 17.22y^2. \quad (6)$$

The entropy  $S_{298}^\circ$  of hexagonal VC<sub>0.53</sub> is 16.87 J g-atom<sup>-1</sup> K<sup>-1</sup> (see Table 5) or 25.81 J mol<sup>-1</sup> K<sup>-1</sup>. Hence, the entropy of lower carbide V<sub>2</sub>C ( $\beta$ -V<sub>2</sub>C) of stoichiometric composition can be estimated at 51–52 J mol<sup>-1</sup> K<sup>-1</sup>. This entropy of hexagonal carbide  $\beta$ -V<sub>2</sub>C is, apparently, underestimated. In the study,<sup>71</sup> the change in the entropy upon the formation of  $\beta$ -V<sub>2</sub>C was evaluated at  $-4.2$  J mol<sup>-1</sup> K<sup>-1</sup>. Hence it follows that

$$S_{298}^\circ \text{V}_2\text{C} = 2S_{298}^\circ \text{V} + S_{298}^\circ \text{C} + \Delta S_{298}^\circ.$$

Taking into account the entropies of vanadium metal ( $S_{298}^\circ \text{V} = 28.67$  J mol<sup>-1</sup> K<sup>-1</sup>)<sup>72</sup> and carbon ( $S_{298}^\circ \text{C} = 5.39$  J mol<sup>-1</sup> K<sup>-1</sup>),<sup>73</sup>  $S_{298}^\circ \text{V}_2\text{C}$  for lower vanadium carbide is 58.53 J mol<sup>-1</sup> K<sup>-1</sup>.

#### e. Free energy

It was demonstrated<sup>28,74</sup> that the part of the free energy ( $F$ ) of the disordered MX<sub>y</sub> compound, which does not include components accounting for the contribution of the configurational entropy  $S_c(y,0)$ , is

$$F_0(T) + yF_1(T) + y^2F_2(T) = \Delta H_f^\circ(y) + (H_T^\circ - H_{298}^\circ)_{\text{MX}_y} - (7) \\ - T \left[ S_{298}^\circ(y) + \int_{298}^T \frac{1}{T} d(H_T^\circ - H_{298}^\circ)_{\text{MX}_y} \right].$$

The free energy (in kJ mol<sup>-1</sup>) of disordered vanadium carbide can be calculated with the use of dependences (1), (3) and (6) according to Eqn (7). The calculations carried out in the studies<sup>2,25–27</sup> demonstrated that the following dependence is valid for disordered cubic carbide VC<sub>y</sub>:

$$F_0(T) + yF_1(T) + y^2F_2(T) = (97.09 + 145.0 \times 10^{-3}T - 11.84 \times 10^{-6}T^2 - 208T^{-1} - 26.95 \times 10^{-3}T \ln T) + \\ + (-437.49 - 86.23 \times 10^{-3}T + 11.75 \times 10^{-6}T^2 + 932T^{-1} + 18.29 \times 10^{-3}T \ln T)y + \\ + (211.36 + 267.21 \times 10^{-3}T - 42.47 \times 10^{-3}T \ln T)y^2. \quad (8)$$

The energy parameters  $F_0(T)$ ,  $F_1(T)$  and  $F_2(T)$  of the free energy determined for disordered cubic carbide VC<sub>y</sub> are

applicable for the temperature range of 298–2000 K. Analogous calculations performed in these studies for hexagonal carbide  $\beta$ -V<sub>2</sub>C without consideration for its homogeneity region gave the following dependence of the free energy (in kJ mol<sup>-1</sup>) for the temperature range of 298–1600 K

$$F(T)_{V_2C} = -180.96 + 513.67 \times 10^{-3}T - 1.70 \times 10^{-6}T^2 + 1290T^{-1} - 83.12 \times 10^{-3}T \ln T. \quad (9)$$

With a knowledge of the parameters  $F_0(T)$ ,  $F_1(T)$  and  $F_2(T)$  and the free energy  $F(T)_{V_2C}$ , it is possible to perform thermodynamic calculations of phase equilibria involving hexagonal and cubic nonstoichiometric vanadium carbides.

### f. High-temperature vaporisation of vanadium carbide

In studies of the thermodynamic properties of nonstoichiometric carbides, vapour pressure measurements over a vaporising solid compound are used along with adiabatic, differential scanning and bomb calorimetry. From the viewpoint of determining the thermodynamic properties of nonstoichiometric carbides, congruent vaporisation (sublimation), *i.e.*, vaporisation, which occurs in equilibrium conditions without changes in the composition of the solid phase, is of most interest.

According to the kinetic theory of gases, the rate of vaporisation from the surface existing in equilibrium with vapour is equal to the condensation rate proportional to the equilibrium vapour pressure  $p$ . Under non-equilibrium conditions (for example, in the case of vacuum vaporisation from the open surface), the vaporisation rate is independent of the condensation rate but is equal to the equilibrium vaporisation rate at this temperature  $T$ .<sup>75</sup> This is true if the residual pressure in a vacuum chamber is no higher than 10 Pa ( $\sim 0.1$  mmHg). Therefore, the equilibrium parameter, *viz.*, the saturated vapour pressure, can be found from the rate of stationary vacuum vaporisation, after which many thermodynamic characteristics can be calculated. If the transition of the condensed phase into vapour is accompanied by its dissociation, the observed vaporisation rate and the partial pressures are smaller than the equilibrium values. This fact can be taken into account by introducing the vaporisation coefficient  $\alpha \leq 1.0$ .

The kinetic and thermodynamic conditions of congruent vaporisation of disordered nonstoichiometric interstitial compounds have been considered in detail in the monograph.<sup>1</sup> The thermodynamics of congruent vaporisation of nonstoichiometric compounds was investigated also in the studies.<sup>76,77</sup>

The vapour composition over the VC–C system in the temperature range of 2417–2603 K was studied by mass spectrometry.<sup>78</sup> Judging from the X-ray diffraction data and the lattice parameter, the authors used a sample containing carbide VC<sub>0.88</sub> along with free carbon. The vapour pressure was not measured and only data on the V : VC<sub>2</sub> ratio in the gas phase were reported.

The studies<sup>79,80</sup> were concerned with vaporisation of vanadium carbide by the Knudsen effusion method in the temperature range of 2346–2545 K. Taking into account the method of the synthesis, the composition of the resulting carbide is VC<sub>0.99</sub>. Hence, the study was, apparently, performed with the use of carbide VC<sub>0.88</sub> containing a large amount of free carbon. The vaporisation rate was determined from the mass change upon vaporisation. Vaporisation did not lead to a change in the composition of vanadium carbide, and the condensate consisted of pure vanadium. The temperature dependence of the vapour pressure of vanadium  $p_V$  (in atm) over the VC–C system is described by the equation

$$\log p_V = 7.63 - \frac{30\,700}{T}. \quad (10)$$

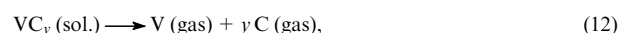
Investigation of the phase equilibria in the V–C system demonstrated<sup>10</sup> that heating of vanadium carbide of any composition *in vacuo* leads to the predominant loss of the metal. Vapor-

isation of vanadium carbide becomes noticeable at temperatures higher than 1800 K.

Storms<sup>11</sup> found the temperature dependence of the vapour pressure of vanadium (in atm) based on the thermochemical characteristics of dissociation of carbide VC<sub>0.88</sub> in equilibrium with carbon

$$\log p_V = 7.56 - \frac{31\,210}{T}. \quad (11)$$

Vaporisation of carbide VC<sub>0.84</sub> in the temperature range from 2073 to 2423 K under vacuum of 0.0013 Pa ( $1 \times 10^{-5}$  mmHg) was investigated<sup>81</sup> by the Langmuir method based on the determination of the vaporisation rate from the open surface of a sample heated *in vacuo*. The total time of vacuum vaporisation varied from 42 h at 2073 K to 12 h at 2423 K. During vaporisation, the crystal lattice parameter on the sample surface slightly increases. Taking into account the changes in the chemical composition and the lattice parameter, the vaporisation rate of vanadium atoms during vacuum heating of carbide VC<sub>0.84</sub> was initially larger than the vaporisation rate of carbon atoms, *i.e.*,  $V_V/V_C > 1/y$ . As a result, the samples were depleted in metal and enriched in carbon, and their compositions became close to the upper boundary of the homogeneity region of cubic carbide (VC<sub>0.88</sub>). Vacuum heating of vanadium carbide leads to vaporisation of not only vanadium but also of carbon, because elimination of free carbon was observed neither on the surface nor in the bulk of the samples. At 2000–2400 K, vaporisation of vanadium carbide occurs according to the reaction<sup>81</sup>



the composition of the congruently vaporising carbide varied from VC<sub>0.85</sub> to VC<sub>0.87</sub> and was shifted to the upper boundary of the homogeneity region with increasing temperature. A similar conclusion about the predominant loss of the metal and the shift of the composition of vanadium carbide to the upper boundary of the homogeneity region as a result of vaporisation has been drawn earlier in the study.<sup>10</sup>

An increase in the temperature from 2073 to 2423 K led to an increase in the total rate of vacuum vaporisation of vanadium carbides by a factor of almost 300, and the mass loss through vaporisation at 2423 K for one hour was 6%–7%. The experimental data on the vaporisation rate of vanadium carbide (in kg m<sup>-2</sup> s<sup>-1</sup>) at 2000–2500 K can be described by the equation<sup>81</sup>

$$\ln V = 25.117 - \frac{80\,900}{T} \pm 0.015. \quad (13)$$

The partial pressures of vanadium and carbon over congruently vaporising vanadium carbides were estimated from the measured vaporisation rate and assuming that the vaporisation coefficient of vanadium is 1.<sup>81</sup> At 2073, 2273 and 2423 K, congruent vaporisation of carbides VC<sub>0.85</sub>, VC<sub>0.86</sub> and VC<sub>0.87</sub>, respectively, was demonstrated to occur. The estimated partial pressures of vanadium and carbon were as follows:  $1.1 \times 10^{-3}$  and  $0.9 \times 10^{-3}$  Pa over carbide VC<sub>0.85</sub> at 2073 K; 0.035 and 0.030 Pa over carbide VC<sub>0.86</sub> at 2273 K; and 0.34 and 0.30 Pa over carbide VC<sub>0.87</sub> at 2423 K, respectively.

Vaporisation in the V–C system was thoroughly investigated<sup>50</sup> by mass spectrometry using a Knudsen effusion cell. The vapour was ionised and the ion current rather than its absolute pressure was measured. Several samples of vanadium metal and 18 samples of vanadium carbides of different compositions were used in measurements. The measurements for the samples of different compositions were carried out in the temperature ranges of 1445–1819, 1740–2226 and 1809–2173 K. The activity of vanadium ( $a_V$ ) was determined as the ratio of the ion currents of vanadium metal and vanadium carbide vaporised under comparable conditions. In these calculations, the heat of vaporisation of vanadium metal (532.1 kJ mol<sup>-1</sup>) was used as the basic value. The plots of  $\log a_V$  vs  $y$  for 1700 and 2000 K were constructed, and the carbon activity  $a_C$  was calculated by numerical integration

according to the Gibbs–Duhem equation. In the investigation,<sup>50</sup> the equation was not given in an explicit form. However, the carbon activity was, apparently, determined by integration of the following equation:

$$d \ln a_C = -\frac{1}{y} d \ln a_V. \quad (14)$$

The partial enthalpies of vaporisation of vanadium and carbon were calculated by the equation

$$\Delta \bar{H}_{V(C)} = \Delta H_{V(C)}^\circ - RT \ln a_{V(C)} \quad (15)$$

using the enthalpies of vaporisation of vanadium and carbon at 1650 K:  $\Delta H_V^\circ = 525.4$  and  $\Delta H_C^\circ = 713.8$  kJ mol<sup>−1</sup>.

The free energies of formation of vanadium carbides VC<sub>y</sub>, with different carbon contents at 1700 K were calculated<sup>50</sup> according to the formula

$$\Delta F_f(y, T) = RT(\ln a_V + y \ln a_C) + RT[y \ln y + (1-y) \ln(1-y)]. \quad (16)$$

At 1700 K,  $\Delta F_f(y, 1700)$  varied from  $-19.9$  for VC<sub>0.74</sub> to  $-21.3$  kJ mol<sup>−1</sup> for VC<sub>0.88</sub>. The enthalpy of formation  $\Delta H_f^\circ$  of carbide VC<sub>0.88</sub> is  $-104.6 \pm 1.8$  J mol<sup>−1</sup>. It should be noted that the results published in the study<sup>50</sup> were obtained for the temperature range higher than the temperature of the order–disorder transition VC<sub>y</sub>–V<sub>8</sub>C<sub>7</sub>, *i.e.*, for the disordered state of vanadium carbide.

### III. Ordered phases of nonstoichiometric vanadium carbides

Cubic vanadium carbide VC<sub>y</sub> is the first transition metal carbide, in which ordering was observed,<sup>12</sup> and is one of a few strongly nonstoichiometric carbides, in which atom–vacancy ordering was studied in detail. Let us consider the main concepts related to this ordering.

Atomic or atom–vacancy ordering is a synonym of a disorder–order structural phase transition (magnetic ordering in the case of magnetic phase transitions). Ordering as a phase transition is a result of atomic redistribution over sites of the crystal lattice of a substitutional solid solution. In the disordered state, components of the solid solution, which can replace each other, are randomly distributed over the sites of the crystal lattice and the probability of occupancy of a particular site by an atom of a particular type is equal to its concentration in solution. A decrease in the temperature leads to ordering, with the result that the crystal lattice sites of a disordered solution are divided into several sublattices. Sublattices of an ordered solution differ from each other in the probability of occupancy of the sites by atoms of a particular type. Ordered phases generated by dividing the lattice of a disordered crystal into several sublattices are called superstructures.

Ordering can also occur in interstitial solid solutions, if the number of interstitial sites is larger than the number of atoms occupying these sites. In the ordering process in interstitial solutions, vacancies and interstitial atoms serve as components of substitutional solutions, whereas solvent atoms form a stationary atomic framework, within which the interstitial atoms and vacancies are redistributed.

In disordered nonstoichiometric compounds, all sites of the non-metal sublattice are crystallographically equivalent. Ordering is accompanied by redistribution of interstitial atoms and structural vacancies over the non-metal sublattice sites. As a result, the crystal lattice sites of the disordered solution become non-equivalent and are divided into at least two sublattices, which differ in the probability of occupancy of the sites by atoms of one and the same type. From the above it is evident that nonstoichiometry is a prerequisite for ordering in imperfect interstitial compounds, because it is responsible for the fact that the number of interstitial

sites is larger than the number of atoms. Hence, the presence of structural vacancies in nonstoichiometric interstitial compounds leads, under certain conditions, to ordering. In the simplest case, ordering in a non-metal sublattice consists in dividing the system formed by octahedral interstitial sites of the metal sublattice into two new sublattices. All sites in the first superstructure sublattice are occupied by interstitial atoms, whereas the sites in the second sublattice are vacant. Hence, it is safe to assume that ordering in nonstoichiometric compounds gives rise to a vacancy sublattice.

Ordering in non-metal sublattices of nonstoichiometric compounds is accompanied by lowering of crystal symmetry. Actually, some symmetry transformations of a disordered non-metal sublattice, which relate the occupied sites to the vacancies, are not involved in the symmetry group of the ordered crystal, because these sites are crystallographically non-equivalent.

Over many years, the positions of interstitial atoms in lattices of nonstoichiometric compounds were determined primarily by X-ray diffraction methods. However, X-ray scattering amplitudes for interstitial atoms are small compared to those for metal atoms, due to which it is not always possible to determine the positions of interstitial atoms by analysing the intensities of diffraction lines. Hence, it is a wide spread opinion that interstitial atoms in non-metal sublattices of nonstoichiometric compounds are always randomly distributed.

The development of experimental techniques and, particularly, the use of neutron diffraction, made it possible to reveal that, under certain conditions, an ordered distribution of interstitial atoms can occur in nonstoichiometric compounds. The neutron diffraction technique is one of the most informative methods for studying nonstoichiometric interstitial compounds, because neutron scattering intensities of transition metal nuclei are comparable with those of light elements. Ordering of interstitial atoms in these compounds was detected also by other diffraction methods, such as electron diffraction, high-resolution X-ray diffraction and various physicochemical methods.

Ordering of interstitial atoms has been experimentally observed in most nonstoichiometric carbides of Group IV and V transition metals.

Vanadium carbides VC<sub>y</sub> and V<sub>2</sub>C<sub>y</sub> are rather convenient to study. Since the X-ray scattering amplitude for the vanadium atom differs not very much (by a factor of  $\sim 5$ ) from that for carbon, superstructure reflections can be observed in X-ray diffraction patterns. The neutron scattering amplitude for the vanadium atom is negative and small in magnitude compared to that for the carbon atom ( $-0.038 \times 10^{-12}$  and  $0.665 \times 10^{-12}$  cm, respectively).<sup>82</sup> For this reason, the ordered non-metal (carbon) sublattice makes the major contribution to neutron diffraction from vanadium carbide, and the most intense superstructure reflections are weaker than the structure reflections (111)<sub>B1</sub> and (200)<sub>B1</sub> by only a factor of 11–20, *i.e.*, these reflections are quite observable. Besides, vanadium carbide can be studied by NMR spectroscopy, because the <sup>51</sup>V nuclei have the nonzero spin  $I = 7/2$ . The structures of ordered phases of nonstoichiometric vanadium carbides VC<sub>y</sub> and V<sub>2</sub>C<sub>y</sub> were studied by X-ray, neutron and electron diffraction, NMR spectroscopy and electron and optical microscopy. However, in spite of the fact that ordering in vanadium carbides was studied more thoroughly compared to other transition metal carbides, many experimental data on the compositions and structures of ordered phases of carbide VC<sub>y</sub> were not confirmed in later studies. These phases are not mentioned in the present review.

#### 1. NMR spectroscopic studies of vanadium carbide

NMR spectroscopy provides information on the mutual arrangement of interstitial atoms and structural vacancies in non-metal sublattices of nonstoichiometric compounds, *i.e.*, information on the short-range order in such compounds. As a rule, no more than three–four types of the nearest environment of metal atoms formed by carbon atoms and vacancies are observed in ordered phases of nonstoichiometric carbides.<sup>3,4</sup> Hence data on the short-

range order in non-metal sublattices of carbides obtained by NMR spectroscopy provide indirect evidence for the presence of a particular ordered phase in samples.

The nearest environment of the vanadium atom in carbide  $VC_y$  with the  $B1$  structure involves three coordination spheres (see Fig. 4). The first coordination sphere is formed by six occupied or partially vacant sites of the non-metal sublattice. The second ordered coordination sphere consists of 12 metal atoms. The third coordination sphere is formed by eight sites of the non-metal sublattice occupying the vertices of the cubic unit cell. It is convenient to describe the environment of the metal atoms with the use of superscripts and subscripts indicating the numbers of vacancies in the first and third non-metal coordination spheres, respectively. For example, the vanadium position  $V_0^0$  signifies that the first coordination sphere of vanadium is complete (contains no vacancies), whereas the second non-metal coordination sphere has two vacancies.

Carbides  $VC_y$  with  $y = 0.66, 0.70, 0.80, 0.84$  and  $0.875$  were studied by NMR spectroscopy throughout the homogeneity region of the cubic phase.<sup>83</sup> The  $^{51}\text{V}$  NMR spectra of carbides  $VC_{0.875}$ ,  $VC_{0.84}$  and  $VC_{0.70}$  show several resonance lines, whose intensities depend on the composition of  $VC_y$ . The intensities of two lines rapidly decrease, whereas the intensity of the third line increases as the carbon content decreases. The spectrum of carbide  $VC_{0.70}$  shows an additional weak line. All observed lines and their satellites in the  $^{51}\text{V}$  NMR spectra of  $VC_y$  were compared with the positions of the vanadium atoms, whose first coordination spheres have different numbers of vacancies:  $V_0$  (without vacancies),  $V_1$  (with one vacancy),  $V_2$  and  $V_3$ . The following expression relating the jump in the Knight shift ( $K$ ) to the number of vacancies ( $n$ ) in the nearest environment of the vanadium atom was derived:

$$K_n - K_{n-1} \approx nK_0, \quad (17)$$

where  $K_0 \approx 0.07\% - 0.09\%$ , *i.e.*, the jump in the Knight shift is proportional to the number of vacancies in the first coordination sphere of the vanadium atom in  $VC_y$ .

To elucidate the character of distribution of vacancies in vanadium carbide, the experimental distribution of probabilities  $P(n)$  of vanadium sites was compared with the random distribution of probabilities calculated by the formula

$$P(n) = C_6^n (1 - y)^n y^{6-n}. \quad (18)$$

For all  $VC_y$  samples under consideration, the experimental distributions differed from the random distribution. For example, a decrease in the carbon content leads to a much more rapid decrease in the probability of existence of the  $V_0$  positions with the complete (without vacancies) environment in the first coordination sphere compared to the random distribution, and the  $V_3$  positions are observed much more rarely. A small number of the  $V_3$  positions and the absence of vanadium atom positions, whose first coordination spheres have four or more vacancies, were attributed to repulsion between the adjacent vacancies. Therefore, according to the results of the study,<sup>82</sup> cubic vanadium carbide has a short-range order.

The  $^{51}\text{V}$  NMR spectrum of carbide  $VC_{0.875}$  differs substantially from the spectra of other vanadium carbides. In particular, the intensity ratio of the lines corresponding to the  $V_0$  and  $V_1$  positions is 1 : 3. Assuming that the relative intensity of each line is proportional to the relative number of the corresponding positions, three-fourths of all vanadium atoms in carbide  $VC_{0.875}$  have one vacancy in the first coordination sphere, whereas the rest of the vanadium atoms have a complete environment. This distribution of vacancies is indicative of the presence of the  $V_8C_7$ -type superstructure with the space group  $P4_332$  or  $P4_132$ .<sup>12</sup> However, the authors of the publication<sup>83</sup> cast doubt that this model of distribution of vacancies is quite consistent with the real lattice. Actually, this superstructure characterised by a helicoidal arrangement of vacancies has only the  $V_0^1$  and  $V_1^1$  positions, whereas analysis of satellites in the NMR spectrum suggested the

existence of three types of positions  $V_1$ , which could not be resolved.

Interesting results were obtained in the study of an annealed single crystal of  $VC_{0.84}$ .<sup>13, 84</sup> The  $^{51}\text{V}$  NMR spectra of this carbide were resolved into lines corresponding to the  $V_0$  and  $V_1$  positions. Investigation of the satellites made it possible to resolve the intense band of  $V_1$  into lines corresponding to the  $V_1^0$ ,  $V_1^1$  and  $V_1^2$  positions which have no vacancies, one vacancy and two vacancies in the second coordination sphere, respectively. In the spectra, the intensity ratio of the  $V_1^1$  and  $V_1^2$  lines is 2 : 1. Hence, it is reasonable to assume that the number of the  $V_1^1$  positions in the carbide under study is twice as large as the number of the  $V_1^2$  positions. Taking into account high intensities of the lines, the corresponding  $V_1^1$  and  $V_1^2$  positions can be considered as positions of an ordered structure of vanadium carbide.

In the study of  $VC_{0.84}$  by electron diffraction,<sup>13</sup> the authors suggested the trigonal symmetry for the ordered phase  $V_6C_5$ . The available NMR data made it possible to describe the distribution of carbon atoms and vacancies in the trigonal unit cell, *i.e.*, to determine the structure of  $V_6C_5$ , taking into account the ratio of the number of the  $V_1^1$  positions to the number of the  $V_1^2$  positions. The trigonal superstructure of  $V_6C_5$  with the space group  $P3_1$  can be represented as helical chains composed of  $V_6C_5$  quasimolecules. The presence of weak lines corresponding to the  $V_0$  and  $V_1^0$  positions was attributed to the deviation of the composition of vanadium carbide  $VC_{0.84}$  from the ideal composition of the ordered phase  $V_6C_5$  ( $VC_{0.83}$ ). It should be noted that the presence of these lines can be associated also with the violation of the long-range order in the sample under investigation.

Attempts to obtain quantitative data on the short-range order in carbide  $VC_y$  by minimisation of the  $^{51}\text{V}$  NMR spectra were made in the studies.<sup>85, 86</sup> The experimental  $^{51}\text{V}$  NMR spectra of carbides  $VC_{0.75}$ ,  $VC_{0.84}$ ,  $VC_{0.85}$ ,  $VC_{0.86}$  and  $VC_{0.87}$  are analogous to the spectra described in the study<sup>83</sup> and have resonance lines corresponding to the  $V_0$ ,  $V_1$  and  $V_2$  vanadium atom positions. Assuming that the lines in the spectra are associated with the fact that the crystals contain nuclei in different local environments (different positions of metal atoms), and the intensity of the line is proportional to the number of positions of a particular type, the theoretical intensity of the line was represented as

$$I_{\text{theor}}(v) = \sum_i \lambda_i P_i I_i(v), \quad (19)$$

where  $P_i$  is the probability of existence of a cluster characterised by the  $i$ th configuration of the nearest environment of the resonating nucleus formed by non-metal atoms,  $\lambda_i$  is the multiplicity of the  $i$ th configuration; and  $I_i(v)$  is the mathematical model of the ideal spectral line for this configuration. (In the study,<sup>85</sup> the lines were described by the Gaussian distribution; the octahedron composed of six sites of the non-metal sublattice containing a metal atom in the centre was chosen as the basic cluster.) The probabilities  $P_i$  were represented as an expansion in series of pair and multi-particle correlation parameters, which were determined by minimisation of the functional  $\sum [I_{\text{theor}}(v) - I_{\text{exp}}(v)]^2$ . The spectra were best described taking into account pair and triple correlations. The consideration of higher-order correlation moments did not lead to a substantial change in the spectra.

According to the results of the studies,<sup>85, 86</sup> the pair correlations  $\varepsilon_{21}$  describing the distribution of carbon atoms (or vacancies) between two adjacent vertices of the octahedron, which are located relative to each other in the first coordination sphere, are negative throughout the homogeneity region of vanadium carbide. This fact indicates that the probability of finding vacancies in the nearest proximity to each other is lower than that in the case of random distribution throughout the homogeneity region of  $VC_y$ . The short-range order parameter  $\alpha_1$  for the first coordination sphere is approximately equal to  $-0.1$ . This parameter slowly increases in magnitude and passes through a minimum in the vicinity of the  $VC_{0.83}$  composition as the deviation from the stoichiometry increases.

The results of calculations<sup>85,86</sup> for the correlations and the short-range order parameter in vanadium carbide are on the whole consistent with the results of the publications.<sup>13,83,84</sup> The latter data provide evidence that there is the short-range order in carbide  $VC_y$  due to repulsions between vacancies. In the monograph,<sup>86</sup> the presence of ordered phases of vanadium carbide was erroneously attributed to a particular short-range order. In the studies,<sup>3,4,19,87,88</sup> it was demonstrated that the long-range order does not necessarily appear in nonstoichiometric compounds with the  $B1$  structure even in the presence of the highest short-range order in the first and second coordination spheres. Hence, the presence of the short-range order in strongly nonstoichiometric carbides is a necessary but not sufficient condition for the presence of the long-range order.

## 2. Diffuse electron scattering

Ordering in nonstoichiometric vanadium carbides was studied also by diffuse electron scattering. The short-order range parameters  $\alpha_{hkl}$  for eight nearest coordination spheres of non-metal sublattices were calculated<sup>89,90</sup> using experimental data<sup>45</sup> on the intensities of diffuse electron scattering by vanadium carbide  $VC_{0.75}$ . The vacancy was chosen as the centre of the coordination spheres. For nonstoichiometric carbide  $MC_y$ , the number of carbon atoms  $n_C$  and the number of vacancies  $n_{\square}$  in the  $j$ th sphere with coordination number  $z_j$  are

$$n_C = z_j(1 - \alpha_j)y, \quad (20)$$

$$n_{\square} = z_j[1 - (1 - \alpha_j)y].$$

With a knowledge of the short-range order parameter (including  $\alpha_j = 0$ ), the number of carbon atoms and the number of vacancies in the corresponding coordination sphere can be calculated by these equations.

The calculated parameters  $\alpha$  and the numbers  $n_C$  and  $n_{\square}$  in each coordination sphere are given in Table 7. For comparison, these values were calculated for the ordered phase  $V_6C_5$  with monoclinic (space group  $C2/m$  or  $C2$ ) or trigonal (space group  $P3_1$ ) superstructures (ideal  $M_6X_5$ -type superstructures do not differ in the short-range order) and disordered carbide  $VC_{0.75}$ .

As can be seen from Table 7, the distribution of carbon atoms and vacancies in the non-metal sublattice of carbide  $VC_{0.75}$  determined in the studies<sup>45,89,90</sup> differs substantially from the random distribution in disordered carbide  $VC_{0.75}$ . In the first two coordination spheres, the numbers of vacancies are much smaller than those observed for the random distribution. The parameter  $\alpha$  oscillates and decreases in magnitude with increasing radius of the coordination sphere. The data on the distribution of carbon atoms and vacancies were interpreted<sup>89,90</sup> as a consequence of mutual repulsion between the vacancies, and it was noted that an analogous short-range order should be observed in niobium and

tantalum carbides. A conclusion about the same type of short-range order in nonstoichiometric Group V transition metal monocarbides was drawn also in the study.<sup>91</sup> The authors of the cited paper believed that it is impossible to prepare completely disordered (without short-range order)  $VC_y$  samples with  $y > 0.78$ .

Diffuse electron scattering was also used to study the short-range order in lower hexagonal carbides  $V_2C_y$  and  $Nb_2C_y$ .<sup>92</sup> It was demonstrated that the short-range order and the long-range order in these carbides are associated with the distribution of carbon atoms and structural vacancies in regular  $C-\square-C-\square-\dots$  rows parallel to the  $c$  axis. A comparison of the experimental and calculated diffuse scattering intensities revealed the possible types of ordering in carbides  $V_2C$  and  $Nb_2C$ .

## 3. Crystal structures of ordered phases of nonstoichiometric vanadium carbides

Most precise and detailed information on the crystal structures of ordered phases of nonstoichiometric compounds can be obtained by diffraction methods. Principal structural characteristics of both experimentally observed and calculated ordered phases of nonstoichiometric lower hexagonal  $V_2C_y$  and cubic  $VC_y$  vanadium carbides are given in Table 8.

In disordered lower vanadium carbide  $V_2C_y$  ( $\beta$ - $V_2C$ ) with a hexagonal structure of the  $L'3$  ( $W_2C$ ) type, the hexagonal  $\varepsilon$ - $Fe_2N$ -type ordered phase  $\beta'$ - $V_2C$  ( $\beta_h$ - $V_2C$ ) initially appears due to ordering caused by lowering of the temperature. At temperatures lower than 1100 K, the orthorhombic  $\zeta$ - $Fe_2N$ -type ordered phase  $\beta_r$ - $V_2C$  ( $\alpha$ - $V_2C$ ) is formed. The existence of the hexagonal ordered phase  $\beta'$ - $V_2C$  ( $\beta_h$ - $V_2C$ ) was documented.<sup>37,44,47,93,94,105–109</sup> The orthorhombic ordered phase  $\beta_r$ - $V_2C$  ( $\alpha$ - $V_2C$ ) was found in the studies.<sup>44,46,93,94,105,108–113</sup> However, the refined data on the structures and crystal lattice parameters, the conditions of formation, concentrations and temperature ranges of existence of these phases obtained by different (and sometimes the same) research groups are not quite consistent with each other. Instability of the hexagonal  $\varepsilon$ - $Fe_2N$ -type ordered phase  $\beta'$ - $V_2C$  ( $\beta_r$ - $V_2C$ ) was noted in the investigation.<sup>107</sup> This high-temperature ordered phase was not observed in quenched samples of lower vanadium carbide.<sup>92,113</sup> However, the results of experimental studies<sup>108,109</sup> performed by high-temperature neutron diffraction demonstrated that the orthorhombic  $\zeta$ - $Fe_2N$ -type phase  $\beta_r$ - $V_2C$  ( $\alpha$ - $V_2C$ ) is a low-temperature ordered phase of lower vanadium carbide. An increase in the temperature leads to the transformation of the latter phase into the high-temperature ordered  $\varepsilon$ - $Fe_2N$ -type hexagonal phase  $\beta'$ - $V_2C$  ( $\beta_h$ - $V_2C$ ). The authors of these studies hypothesised that samples of lower vanadium carbide, whose composition differs from stoichiometric  $V_2C$ , undergo a polymorphic transformation

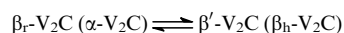


**Table 7.** Short-range order parameters ( $\alpha$ ), numbers of carbon atoms ( $n_C$ ) and vacancies ( $n_{\square}$ ) in the coordination spheres ( $hkl$ ) of carbide  $VC_{0.75}$ , the ideal ordered phase  $V_6C_5$  and disordered carbide  $VC_{0.75}$  (see Ref. 89).

| CS <sup>a</sup> | CN <sup>b</sup> | VC <sub>0.75</sub> |       |               | Ideal superstructure of V <sub>6</sub> C <sub>5</sub><br>(space group $C2/m$ , $C2$ , $P3_1$ ) |       |               | Disordered carbide |       |               |
|-----------------|-----------------|--------------------|-------|---------------|------------------------------------------------------------------------------------------------|-------|---------------|--------------------|-------|---------------|
|                 |                 | $\alpha$           | $n_C$ | $n_{\square}$ | $\alpha$                                                                                       | $n_C$ | $n_{\square}$ | $\alpha$           | $n_C$ | $n_{\square}$ |
| 110             | 12              | −0.178             | 10.6  | 1.4           | −0.2                                                                                           | 12    | 0             | 0                  | 9     | 3             |
| 200             | 6               | −0.260             | 5.7   | 0.3           | −0.2                                                                                           | 6     | 0             | 0                  | 4.5   | 1.5           |
| 211             | 24              | 0.176              | 14.8  | 9.2           | 0.2                                                                                            | 16    | 8             | 0                  | 18    | 6             |
| 220             | 12              | 0.008              | 8.9   | 3.1           | 0                                                                                              | 10    | 2             | 0                  | 9     | 3             |
| 310             | 24              | 0.041              | 17.3  | 6.7           | 0                                                                                              | 20    | 4             | 0                  | 18    | 6             |
| 222             | 8               | −0.171             | 7.0   | 1.0           | −0.2                                                                                           | 8     | 0             | 0                  | 6     | 2             |
| 321             | 48              | −0.070             | 38.5  | 9.5           | −0.1                                                                                           | 44    | 4             | 0                  | 36    | 12            |
| 400             | 6               | 0.143              | 3.8   | 2.2           | 0.2                                                                                            | 4     | 2             | 0                  | 4.5   | 1.5           |

<sup>a</sup> CS is the coordination sphere ( $hkl$ ) with the radius  $R_j = (a_{B1}/2)(h^2 + k^2 + l^2)^{1/2}$  ( $a_{B1}$  is the lattice parameter of disordered carbide  $VC_y$  with the  $B1$  structure; a vacancy is located in the centre of the coordination sphere). <sup>b</sup> CN is the coordination number of the sphere ( $hkl$ ).

**Table 8.** Ordered phases of strongly nonstoichiometric vanadium carbides.

| Ordered phase                                                     |                                                                                              |                                                   |              |                                                                                                   | Basic phase               |              | Note                                                                                                                                                                                    | Ref.                      |
|-------------------------------------------------------------------|----------------------------------------------------------------------------------------------|---------------------------------------------------|--------------|---------------------------------------------------------------------------------------------------|---------------------------|--------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| composition                                                       | non-metal content (at. %)                                                                    | symmetry                                          | space group  | unit cell parameters (lattice parameters in nm)                                                   | composition               | lattice type |                                                                                                                                                                                         |                           |
| $\beta_r\text{-V}_2\text{C}$<br>( $\alpha\text{-V}_2\text{C}$ )   | $\sim 33.0$ ( $\text{VC}_{0.5}$ )                                                            | orthorhombic,<br>$\zeta\text{-Fe}_2\text{N}$ type | $Pbcn$       | $a = 0.4567 = c_0$ ,<br>$b = 0.5744 = 2a_0$ ,<br>$c = 0.5026 \approx a_0\sqrt{3}$                 | $\text{V}_2\text{C}_{y'}$ | $L'3$        | $T_{tr} < 1100$ K                                                                                                                                                                       | 93, 94                    |
| $\beta'_r\text{-V}_2\text{C}$<br>( $\beta_h\text{-V}_2\text{C}$ ) | $\sim 33.0$ ( $\text{VC}_{0.5}$ )                                                            | hexagonal                                         | —            | $a = 0.4997 \approx a_0\sqrt{3}$ ,<br>$c = 0.4568 = c_0$                                          | $\text{V}_2\text{C}_{y'}$ | $L'3$        | prepared by quenching from 1800 K                                                                                                                                                       | 93, 94                    |
| $\text{V}_3\text{C}_2$                                            | $\text{VC}_{0.667} - \text{VC}_{0.710}$<br>( $\text{VC}_{0.67} - \text{VC}_{0.72}$ at 300 K) | —                                                 | —            | —                                                                                                 | $\text{VC}_y$             | $B1$         | calculation; $T_{tr} < 1155$ K; the homogeneity region corresponds to 800 K                                                                                                             | 27, 32                    |
| $\text{V}_6\text{C}_5$                                            | $\text{VC}_{0.745} - \text{VC}_{0.831}$                                                      | —                                                 | —            | —                                                                                                 | $\text{VC}_y$             | $B1$         | calculation; $T_{tr} < 1485$ K; the homogeneity region corresponds to 1100 K                                                                                                            | 27, 32                    |
| $\text{V}_6\text{C}_5$                                            | $\sim 45.5$ ( $\text{VC}_{0.83}$ )                                                           | trigonal                                          | $P3_1, P3_2$ | $a = 0.509, c = 1.44$                                                                             | $\text{VC}_y$             | $B1$         | according to the results of the studies, <sup>95–97</sup> the trigonal phase is intermediate between the disordered phase $\text{VC}_y$ and the monoclinic phase $\text{V}_6\text{C}_5$ | 13, 25, 26, 69, 95, 96    |
| $\text{V}_6\text{C}_5$                                            | $\sim 45.5$ ( $\text{VC}_{0.83}$ )                                                           | monoclinic                                        | $C2$         | $a = 0.509, b = 1.018, c = 0.882, \gamma = 109.8^\circ$                                           | $\text{VC}_y$             | $B1$         | $T_{tr} < 1420$ K                                                                                                                                                                       | 43, 45, 96, 97            |
| $\text{V}_6\text{C}_5$                                            | $\sim 45.5$ ( $\text{VC}_{0.83}$ )                                                           | monoclinic                                        | $C2/m$       | —                                                                                                 | $\text{VC}_y$             | $B1$         | $\text{Nb}_6\text{C}_5$ structure type (see Refs 99–102)                                                                                                                                | 98                        |
| $\delta'\text{-VC}_y$                                             | $\sim 45.5$ ( $\text{VC}_{0.83}$ )                                                           | trigonal                                          | —            | $a = 0.5885 \approx a_0\sqrt{2}$ ,<br>$c = 1.443 \approx 2a_0\sqrt{3}$                            | $\text{VC}_y$             | $B1$         | $T_{tr} < 1300$ K                                                                                                                                                                       | 93                        |
| $\delta''_M\text{-VC}_y$                                          | 45.0–47.0                                                                                    | monoclinic                                        | —            | $a = (a_0\sqrt{3})/2$ ,<br>$b = a_0\sqrt{6}$ ,<br>$c = 8a_0\sqrt{2}$ ,<br>$\gamma = 109.47^\circ$ | $\text{VC}_y$             | $B1$         | $T_{tr} < 1500$ K                                                                                                                                                                       | 93                        |
| $\text{V}_8\text{C}_7$                                            | $\sim 46.6$ ( $\text{VC}_{0.87}$ )                                                           | cubic                                             | $P4_332$     | $a = 0.8332 \approx 2a_0$                                                                         | $\text{VC}_y$             | $B1$         | first-order phase transition; $T_{tr} < 1500$ K                                                                                                                                         | 12, 43, 46–49, 69, 98–104 |

in a two-phase region ( $\beta_r\text{-V}_2\text{C} + \beta_h\text{-V}_2\text{C}$ ). For example, only orthorhombic ordered  $\zeta\text{-Fe}_2\text{N}$ -type phase was observed<sup>108</sup> in neutron diffraction patterns of lower carbide  $\text{VC}_{0.47}$  at temperatures up to 1373 K inclusive. At 1393 K, the neutron diffraction pattern has reflections of the orthorhombic and hexagonal ordered phases. At 1413 K, the diffraction pattern shows superstructure reflections corresponding only to the high-temperature ordered  $\varepsilon\text{-Fe}_2\text{N}$ -type phase.

As can be seen from Table 8,  $\text{M}_3\text{C}_2$ -,  $\text{M}_6\text{C}_5$ - and  $\text{M}_8\text{C}_7$ -type ordered phases can exist in nonstoichiometric cubic vanadium carbide. In carbide  $\text{VC}_y$ , the first of these phases has not been experimentally detected. However, the possibility of its existence is supported by thermodynamic calculations. The phase  $\text{V}_8\text{C}_7$  was experimentally found only in vanadium carbide and was not observed in carbides of other transition metals. The existence of this phase is associated with the specific position of the upper boundary of the homogeneity region of vanadium monocarbide for  $\text{VC}_{0.875}$ .

As for the symmetry of the ordered phases, the trigonal (space group  $P3_1$ )<sup>13, 25, 69</sup> and monoclinic (space group  $C2$ )<sup>43, 45</sup>  $\text{V}_6\text{C}_5$ -type ordered phases and the cubic (space group  $P4_332$ ) ordered phase  $\text{V}_8\text{C}_7$  were found in  $\text{VC}_y$ .<sup>12, 46–49, 69, 103, 104</sup> It should be noted that  $\text{V}_8\text{C}_7$  (see Ref. 12) is the first ordered phase experimentally found in nonstoichiometric carbides. Hardening of high-vanadium cast iron was demonstrated<sup>98</sup> to be accompanied

by the formation of the disperse ordered carbide phases  $\text{V}_6\text{C}_5$  and  $\text{V}_8\text{C}_7$ . The phase  $\text{V}_6\text{C}_5$  is monoclinic (space group  $C2/m$ ) and is structurally similar to monoclinic ordered niobium carbide  $\text{Nb}_6\text{C}_5$  (space group  $C2/m$ ).<sup>99–102</sup> In high-carbon cast iron, monoclinic carbide  $\text{V}_6\text{C}_5$  is located in the centre of eutectic grains, whereas the cubic (space group  $P4_332$ ) ordered phase  $\text{V}_8\text{C}_7$  can occur in the outer layer of the grains.<sup>98</sup> The formation of the ordered phase  $\text{V}_6\text{C}_5$  was observed in the study<sup>114</sup> of vanadium-containing steel annealed at 1000 K for 50–150 h by transmission electron microscopy and electron diffraction. Data on the symmetry of the  $\text{V}_6\text{C}_5$  phase found in this study are lacking. Calculations demonstrated that the ordered phase  $\text{V}_3\text{C}_2$  can exist,<sup>25–27, 32</sup> and this phase can have orthorhombic (space group  $Immm$  or  $C222_1$ ) or monoclinic symmetry (space group  $P2$ ).

Investigations of the trigonal ordered phase  $\text{V}_6\text{C}_5$  by electron diffraction and electron microscopy<sup>13, 115</sup> showed that this phase is stable at temperatures close to the transition temperature to the disordered state, because this phase is disordered as a result of its heating with electron beam.<sup>115</sup> The monoclinic ordered phase  $\text{V}_6\text{C}_5$  is, apparently, formed at temperatures lower than the temperature of formation of the trigonal phase  $\text{V}_6\text{C}_5$ .<sup>43</sup> Actually, neutron diffraction studies demonstrated<sup>95–97</sup> that the monoclinic phase is stable in the temperature range of 1050–1370 K, and the trigonal phase exists in the range of 1140–1520 K. According to the average experimental estimates, the lower



boundary of the homogeneity region of the ordered phase  $V_6C_5$  corresponds to carbide  $VC_{0.75-0.77}$ , and the upper boundary corresponds to carbide  $VC_{0.82-0.86}$ . An ambiguity of the boundaries, particularly, of the upper boundary, is associated with the difference in the conditions of annealing of carbide  $VC_y$  used in different experiments. Annealed samples of carbide  $VC_y$  with  $y \geq 0.83$  contained already two ordered phases, *viz.*,  $V_6C_5$  and  $V_8C_7$ . The single-phase region of existence of the cubic superstructure of  $V_8C_7$  is very narrow (no broader than from  $VC_{0.863}$  to  $VC_{0.875}$ , *i.e.*, to the upper boundary of the homogeneity region of disordered  $VC_y$ ). The precise determination of the chemical composition of vanadium carbide, as well as of other refractory carbides, is a rather complicated problem. However, taking into account the errors in the determination of the composition, it can be assumed that vanadium carbides containing only the ordered phase  $V_8C_7$  have the composition  $VC_{0.870 \pm 0.005}$ . This may be evidence that the ordered phase  $V_8C_7$  has no homogeneity region and is formed only upon annealing of carbide  $VC_{0.875}$ . If the carbon content of carbide is smaller, the phase  $V_8C_7$  is present along with the ordered phase  $V_6C_5$ .

Therefore, several ordered  $M_6C_5$ -type phases of different symmetry and the ordered cubic  $M_8C_7$ -type phase were found in nonstoichiometric carbide  $VC_y$ . Let us consider their structures in more detail using such concepts as the disorder–order transition channel and the distribution function  $n(\mathbf{r})$  of atoms between the sites  $\mathbf{r}$  in an ordered crystal lattice. The distribution function  $n(\mathbf{r})$  has the symmetry of the ordered crystal lattice and reflects the probability of finding an atom of this type in the site  $\mathbf{r}$ . In a disordered crystal, the probabilities  $n(\mathbf{r})$  are equal for all sites and coincide with the fraction of lattice sites occupied by atoms of this type. For example, the distribution function  $n(\mathbf{r})$  of the atoms X in the disordered nonstoichiometric compound  $MX_y \square_{1-y}$  is equal to the fraction of lattice sites occupied by these atoms, *i.e.*,  $n(\mathbf{r}) = y$ .

The space-periodic modulation of the atom distribution (the deviation of the probability  $n(\mathbf{r})$  from its value for the random distribution) resulting in the formation of an ordered phase can be represented as a superposition of several plane concentration waves.<sup>116</sup> The wave vectors of the latter are the superstructure vectors  $\mathbf{k}_s^{(j)}$  of the reciprocal lattice in the first Brillouin zone of the disordered lattice. In the static concentration wave method,<sup>116</sup> the distribution function of atoms of this type is described through a fraction of sites occupied by these atoms and the superposition of the static concentration waves

$$n(\mathbf{r}) = y + \sum_s \sum_{j \in s} \Delta(\mathbf{k}_s^{(j)}, \mathbf{r}), \quad (21)$$

where  $\Delta(\mathbf{k}_s^{(j)}, \mathbf{r})$  is the standing plane static concentration wave generated by the superstructure vector  $\mathbf{k}_s^{(j)}$  of the star  $\{\mathbf{k}_s\}$ .<sup>†</sup> The equation for this wave takes the form

$$\Delta(\mathbf{k}_s^{(j)}, \mathbf{r}) = \frac{1}{2} \left[ Q(\mathbf{k}_s^{(j)}) \exp(i\mathbf{k}_s^{(j)} \mathbf{r}) + Q^*(\mathbf{k}_s^{(j)}) \exp(-i\mathbf{k}_s^{(j)} \mathbf{r}) \right], \quad (22)$$

where  $Q(\mathbf{k}_s^{(j)})$  is the concentration wave amplitude

$$Q(\mathbf{k}_s^{(j)}) = \eta_s \gamma(\mathbf{k}_s^{(j)}), \quad (23)$$

$\eta_s$  is the long-range order parameter and  $\gamma(\mathbf{k}_s^{(j)}) = \gamma_s \exp(i\varphi_s^{(j)})$  is the coefficient taking into account the crystal symmetry. The coefficient  $\gamma(\mathbf{k}_s^{(j)})$  is chosen so that the long-range order parameters equal to unity correspond to a completely ordered crystal of stoichiometric composition. Taking into account Eqn (23), the expression (22) can be represented as follows

<sup>†</sup> The wave vector star is a set of all nonequivalent vectors generated from the vector  $\mathbf{k}$  by rotation elements of the point symmetry group of the crystal. The wave vector star is denoted by  $\{\mathbf{k}\}$ , and the individual vectors involved in this set are called the arms of the star. The detailed definition of the wave vector star was given in publications.<sup>3,4</sup>

$$\Delta(\mathbf{k}_s^{(j)}, \mathbf{r}) = \frac{1}{2} \eta_s \left[ \gamma(\mathbf{k}_s^{(j)}) \exp(i\mathbf{k}_s^{(j)} \mathbf{r}) + \gamma^*(\mathbf{k}_s^{(j)}) \exp(-i\mathbf{k}_s^{(j)} \mathbf{r}) \right]. \quad (24)$$

From Eqns (21) and (24) it follows that the long-range order parameter  $\eta_s$  corresponds to each star of the wave vector  $\{\mathbf{k}_s\}$ . In the sites  $\mathbf{r}$  located in the crystallographically equivalent positions, the distribution function takes the same value because it is invariant with respect to rotation and reflection involved in the point symmetry group of an ordered crystal. The number of values assumed by the distribution function at the sites of an ordered lattice is one unit larger than the number of long-range order parameters.

Summation in Eqn (21) is carried out over all non-equivalent superstructure vectors of the first Brillouin zone of the disordered lattice, *i.e.*, over all superstructure vectors involved in the disorder–order phase transition channel.<sup>3,4,117</sup>

Analysis of the symmetry of the  $M_6C_5$ -type ( $M_6C_5 \square$ -type) superstructures formed in nonstoichiometric transition metal carbides was carried out in the studies.<sup>117,118</sup>

The unit cell of the monoclinic (space group  $C2/m$ ) superstructure of  $M_6C_5$  is shown in Fig. 9. The translation vectors of this unit cell and the coordinates of atoms and vacancies are given in Table 9.

The translation of all superstructure sites of the reciprocal lattice of the monoclinic ordered phase  $M_6C_5$  shows that the first

**Table 9.** Monoclinic [space group  $C2/m$  ( $C_{2h}^3$ )] superstructure of  $M_6C_5$  ( $V_6C_5$ ).

| Atom      | Position and multiplicity | Atomic coordinates in ideal ordered structure <sup>a</sup> |         |         | Distribution function $n(x_1, y_1, z_1)$   |
|-----------|---------------------------|------------------------------------------------------------|---------|---------|--------------------------------------------|
|           |                           | $x/a_m$                                                    | $y/b_m$ | $z/c_m$ |                                            |
| C 1       | 2(a)                      | 0                                                          | 0       | 0       | $n_1 = y - \eta_9/6 - \eta_4/3 - \eta_3/3$ |
| (vacancy) |                           |                                                            |         |         |                                            |
| C 2       | 2(d)                      | 0                                                          | 1/2     | 1/2     | $n_2 = y + \eta_9/6 - \eta_4/3 + \eta_3/3$ |
| C 3       | 4(g)                      | 0                                                          | 1/3     | 0       | $n_3 = y - \eta_9/6 + \eta_4/6 + \eta_3/6$ |
| C 4       | 4(h)                      | 0                                                          | 1/6     | 1/2     | $n_4 = y + \eta_9/6 + \eta_4/6 - \eta_3/6$ |
| M 1       | 4(i)                      | 1/4                                                        | 0       | 3/4     |                                            |
| M 2       | 8(j)                      | 1/4                                                        | 2/3     | 3/4     |                                            |

<sup>a</sup> Parameters of the monoclinic unit cell:

$$\mathbf{a}_m = \frac{1}{2} \langle 1\bar{1}2 \rangle_{B1}, \mathbf{b}_m = \frac{3}{2} \langle 110 \rangle_{B1}, \mathbf{c}_m = \frac{1}{2} \langle 1\bar{1}2 \rangle_{B1}.$$

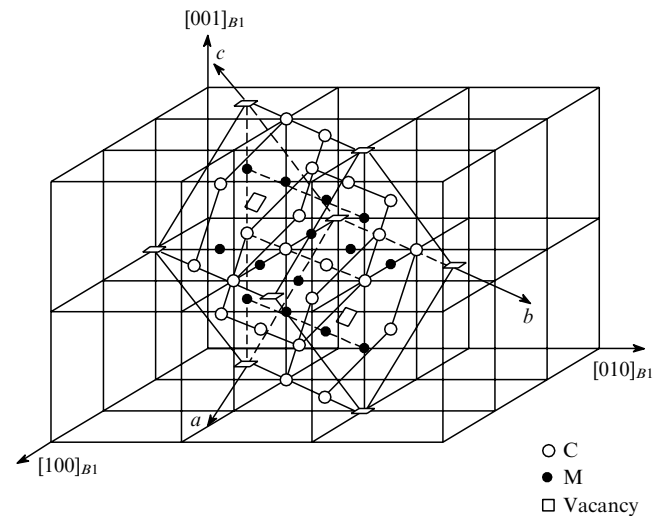


**Figure 9.** Position of the monoclinic (space group  $C2/m$ ) unit cell of the superstructure  $M_6C_5$  in the lattice with the  $B1$  structure.

Brillouin zone of the disordered face-centred cubic (FCC) lattice contains five non-equivalent superstructure vectors belonging to three stars  $\{\mathbf{k}_9\}$ ,  $\{\mathbf{k}_4\}$  and  $\{\mathbf{k}_3\}$ .<sup>‡</sup> These five vectors are involved in the phase transition channel associated with the formation of the ordered phase  $\text{M}_6\text{C}_5$  (space group  $C2/m$ ).

Calculations demonstrated<sup>3, 4, 53, 117</sup> that the distribution function describing the superstructure of  $\text{M}_6\text{C}_5$  takes the form

$$n(x_1, y_1, z_1) = y - \frac{\eta_9}{6} \cos[\pi(x_1 - y_1 + z_1)] - \frac{\eta_4}{3} \cos \frac{4\pi(x_1 + y_1)}{3} - \frac{\eta_3}{3} \cos \frac{\pi(x_1 - 5y_1 - 3z_1)}{3}, \quad (25)$$

where  $x_1, y_1, z_1$  are the coordinates of the nodes of the ordered non-metal FCC sublattice,  $\mathbf{r} \equiv x_1, y_1, z_1$ .

The distribution function (25) at all sites of the basic non-metal FCC sublattice takes four values (see Table 9). This indicates that, in the case of the above ordering, the non-metal sublattice of disordered nonstoichiometric carbide  $\text{MC}_y$  is divided into four non-equivalent sublattices. The probability of occupancy of the sites of the first sublattice by interstitial atoms is  $n_1$ , the probability of occupancy of the sites of the second sublattice is  $n_2$ , etc. The resulting distribution function is a superposition of three concentration waves related to three long-range order parameters,  $\eta_9, \eta_4$  and  $\eta_3$ , respectively.

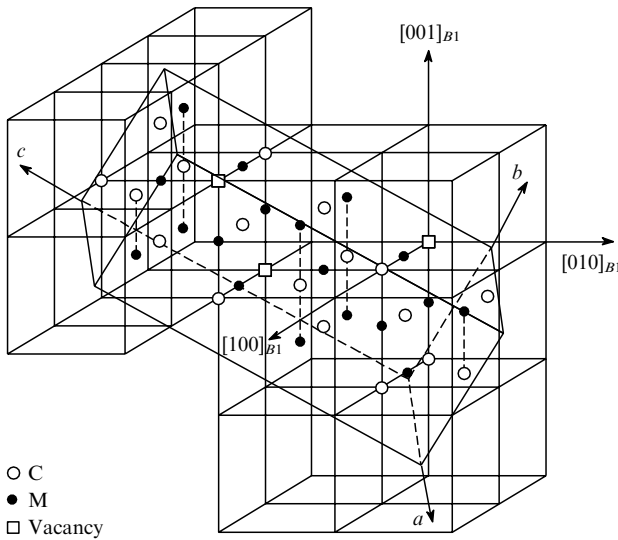


**Figure 10.** Position of the trigonal (space group  $P3_1$ ) unit cell of the superstructure  $\text{M}_6\text{C}_5$  in the lattice with the  $B1$  structure.

The trigonal (space group  $P3_1$ ) unit cell of the superstructure of  $\text{M}_6\text{C}_5$  is shown in Fig. 10. The translation vectors of this unit cell and the coordinates of atoms and vacancies in the ideal trigonal superstructure of  $\text{M}_6\text{C}_5$  are given in Table 10. The disorder – order phase transition channel giving rise to the trigonal superstructure of  $\text{M}_6\text{C}_5$  includes 13 arms belonging to three stars  $\{\mathbf{k}_9\}$ ,  $\{\mathbf{k}_4\}$  and  $\{\mathbf{k}_3\}$ . Hence, the distribution function, as in the above-considered case, depends on three long-range order parameters

<sup>‡</sup> Hereinafter, the numbering of the wave vector stars  $\{\mathbf{k}_s\}$  of the first Brillouin zone of the FCC crystal and the arms of the stars are given in accordance with the monographs<sup>3, 4</sup> where all  $\{\mathbf{k}_s\}$  stars were described in detail.

**Table 10.** Trigonal [space group  $P3_1 (C_3^2)$ ] superstructure of  $\text{M}_6\text{C}_5$  ( $\text{V}_6\text{C}_5$ ).

| Atom      | Position and multiplicity | Atomic coordinates in ideal ordered structure <sup>a</sup> |                   |                   | Distribution function $n(x_1, y_1, z_1)$   |
|-----------|---------------------------|------------------------------------------------------------|-------------------|-------------------|--------------------------------------------|
|           |                           | $x/a_{\text{tr}}$                                          | $y/b_{\text{tr}}$ | $z/c_{\text{tr}}$ |                                            |
| C 1       | 3(a)                      | 1/9                                                        | 8/9               | 1/6               | $n_1 = y - \eta_9/6 - \eta_4/3 - \eta_3/3$ |
| (vacancy) |                           |                                                            |                   |                   |                                            |
| C 2       | 3(a)                      | 4/9                                                        | 5/9               | 1/6               | $n_3 = y - \eta_9/6 + \eta_4/6 + \eta_3/6$ |
| C 3       | 3(a)                      | 7/9                                                        | 2/9               | 1/6               | $n_3 = y - \eta_9/6 + \eta_4/6 + \eta_3/6$ |
| C 4       | 3(a)                      | 1/9                                                        | 5/9               | 1/3               | $n_4 = y + \eta_9/6 + \eta_4/6 - \eta_3/6$ |
| C 5       | 3(a)                      | 4/9                                                        | 2/9               | 1/3               | $n_4 = y + \eta_9/6 + \eta_4/6 - \eta_3/6$ |
| C 6       | 3(a)                      | 7/9                                                        | 8/9               | 1/3               | $n_2 = y + \eta_9/6 - \eta_4/3 + \eta_3/3$ |
| M 1       | 3(a)                      | 1/9                                                        | 5/9               | 1/12              |                                            |
| M 2       | 3(a)                      | 4/9                                                        | 2/9               | 1/12              |                                            |
| M 3       | 3(a)                      | 7/9                                                        | 8/9               | 1/12              |                                            |
| M 4       | 3(a)                      | 1/9                                                        | 2/9               | 1/4               |                                            |
| M 5       | 3(a)                      | 4/9                                                        | 8/9               | 1/4               |                                            |
| M 6       | 3(a)                      | 7/9                                                        | 5/9               | 1/4               |                                            |

<sup>a</sup> Parameters of the trigonal unit cell:

$$\mathbf{a}_{\text{tr}} = \frac{1}{2} \langle 21\bar{1} \rangle_{B1}, \mathbf{b}_{\text{tr}} = \frac{1}{2} \langle \bar{1}12 \rangle_{B1}, \mathbf{c}_{\text{tr}} = 2 \langle 1\bar{1}1 \rangle_{B1}.$$

$$n(x_1, y_1, z_1) = y - \frac{\eta_9}{6} \cos[\pi(x_1 - y_1 + z_1)] - \frac{\eta_4}{6} \left[ \cos \frac{4\pi(x_1 + y_1)}{3} - \frac{\sqrt{3}}{3} \sin \frac{4\pi(x_1 + y_1)}{3} - \frac{2\sqrt{3}}{3} \sin \frac{4\pi(x_1 - z_1)}{3} + \cos \frac{4\pi(y_1 + z_1)}{3} + \frac{\sqrt{3}}{3} \sin \frac{4\pi(y_1 + z_1)}{3} \right] - \frac{\eta_3}{6} \left[ \cos \frac{\pi(x_1 - 5y_1 - 3z_1)}{3} - \frac{\sqrt{3}}{3} \sin \frac{\pi(x_1 - 5y_1 - 3z_1)}{3} + \frac{2\sqrt{3}}{3} \sin \frac{\pi(5x_1 + 5y_1 + z_1)}{3} + \cos \frac{\pi(3x_1 + y_1 - 5z_1)}{3} + \frac{\sqrt{3}}{3} \sin \frac{\pi(3x_1 + y_1 - 5z_1)}{3} \right]. \quad (26)$$

This distribution function describing the trigonal superstructure of  $\text{M}_6\text{C}_5$  takes the same four values,  $n_1, n_2, n_3$  and  $n_4$ , as the distribution function (25), which describes the monoclinic (space group  $C2/m$ ) superstructure of  $\text{M}_6\text{C}_5$ . However, the mutual arrangement of the sites of four sublattices in the trigonal ordered structure differs from that observed in the monoclinic superstructure. The values of the distribution function (26) are given in Table 10.

The unit cell of the monoclinic (space group  $C2$ ) superstructure of  $\text{M}_6\text{C}_5$  is shown in Fig. 11. The translation vectors of this unit cell and the coordinates of atoms and vacancies in the ideal monoclinic  $\text{M}_6\text{C}_5$ -type superstructure are given in Table 11. The monoclinic ordered phase of  $\text{M}_6\text{C}_5$  is formed through the transition channel involving nine superstructure vectors of the reciprocal lattice belonging to four stars  $\{\mathbf{k}_9\}$ ,  $\{\mathbf{k}_4\}$ ,  $\{\mathbf{k}_3\}$  and  $\{\mathbf{k}_0\}$ . Calculations demonstrated<sup>3, 4, 53, 117</sup> that this monoclinic superstructure of  $\text{M}_6\text{C}_5$  is described by the distribution function, which depends on four long-range order parameters

$$n(x_1, y_1, z_1) = y - \frac{\eta_9}{6} \cos[\pi(x_1 - y_1 + z_1)] - \frac{\eta_4}{12} \left[ \cos \frac{4\pi(x_1 + y_1)}{3} - \sqrt{3} \sin \frac{4\pi(x_1 + y_1)}{3} \right] - \frac{\eta_3}{12} \left[ \cos \frac{\pi(x_1 - 5y_1 - z_1)}{3} - \sqrt{3} \sin \frac{\pi(x_1 - 5y_1 - z_1)}{3} \right] - \quad (27)$$

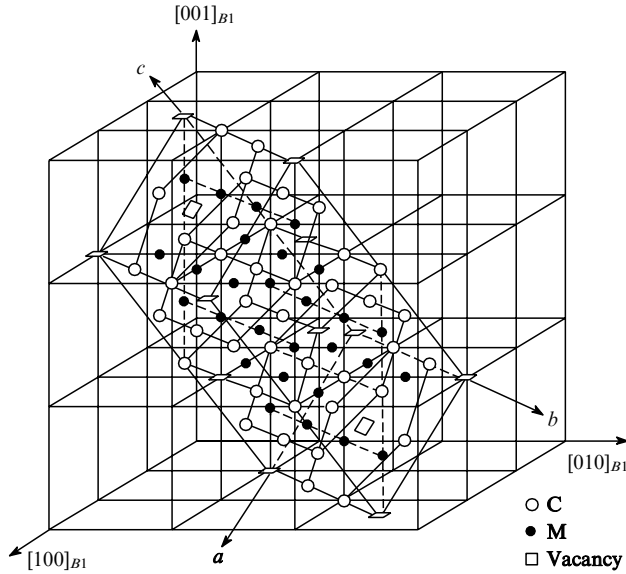


**Figure 11.** Position of the monoclinic (space group  $C2$ ) unit cell of the superstructure  $M_6C_5$  in the lattice with the  $B1$  structure.

$$-\frac{\eta_0}{12} \left[ 3 \cos \frac{\pi(x_1 + 7y_1 + 9z_1)}{6} - \sqrt{3} \sin \frac{\pi(x_1 + 7y_1 + 9z_1)}{6} + 3 \cos \frac{\pi(7x_1 + y_1 - 9z_1)}{6} - \sqrt{3} \sin \frac{\pi(7x_1 + y_1 - 9z_1)}{6} \right].$$

At all sites of the basic non-metal FCC sublattice, the distribution function (27) takes five values (see Table 11). Hence, as a result of the above-described ordering, the non-metal sublattice of disordered nonstoichiometric carbide is divided

**Table 11.** Monoclinic [space group  $C2$  ( $C_2^3$ )] superstructure of  $M_6C_5$  ( $V_6C_5$ ).

| Atom | Position and multiplicity | Atomic coordinates in ideal ordered structure <sup>a</sup> |         |         | Distribution function $n(x_1, y_1, z_1)$                |
|------|---------------------------|------------------------------------------------------------|---------|---------|---------------------------------------------------------|
|      |                           | $x/a_m$                                                    | $y/b_m$ | $z/c_m$ |                                                         |
| C 1  | 2(a) (vacancy)            | 0                                                          | 0       | 0       | $n_1 = y - \eta_9/6 - \eta_4/12 - \eta_3/12 - \eta_0/2$ |
| C 2  | 2(b) (vacancy)            | 0                                                          | 1/3     | 1/2     | $n_1 = y - \eta_9/6 - \eta_4/12 - \eta_3/12 - \eta_0/2$ |
| C 3  | 2(a)                      | 0                                                          | 1/3     | 0       | $n_5 = y - \eta_9/6 - \eta_4/12 - \eta_3/12 + \eta_0/2$ |
| C 4  | 2(a)                      | 0                                                          | 2/3     | 0       | $n_3 = y - \eta_9/6 + \eta_4/6 + \eta_3/6$              |
| C 5  | 2(b)                      | 0                                                          | 0       | 1/2     | $n_5 = y - \eta_9/6 - \eta_4/12 - \eta_3/12 + \eta_0/2$ |
| C 6  | 2(b)                      | 0                                                          | 2/3     | 1/2     | $n_3 = y - \eta_9/6 + \eta_4/6 + \eta_3/6$              |
| C 7  | 4(c)                      | 0                                                          | 1/6     | 1/4     | $n_4 = y + \eta_9/6 + \eta_4/6 - \eta_3/6$              |
| C 8  | 4(c)                      | 0                                                          | 1/2     | 1/4     | $n_2 = y + \eta_9/6 - \eta_4/12 + \eta_3/12$            |
| C 9  | 4(c)                      | 0                                                          | 5/6     | 1/4     | $n_4 = y + \eta_9/6 + \eta_4/6 - \eta_3/6$              |
| M 1  | 4(c)                      | 1/4                                                        | 1/6     | 1/8     |                                                         |
| M 2  | 4(c)                      | 1/4                                                        | 1/2     | 1/8     |                                                         |
| M 3  | 4(c)                      | 1/4                                                        | 5/6     | 1/8     |                                                         |
| M 4  | 4(c)                      | 1/4                                                        | 0       | 3/8     |                                                         |
| M 5  | 4(c)                      | 1/4                                                        | 1/3     | 3/8     |                                                         |
| M 6  | 4(c)                      | 1/4                                                        | 2/3     | 3/8     |                                                         |

<sup>a</sup> Parameters of the monoclinic unit cell:

$$a_m = \frac{1}{2} \langle 1\bar{1}2 \rangle_{B1}, b_m = \frac{3}{2} \langle 110 \rangle_{B1}, c_m = \langle 1\bar{1}2 \rangle_{B1}.$$

into five non-equivalent sublattices, which differ in the probabilities of occupancy of their sites by interstitial atoms.

For all the completely ordered  $M_6C_5$ -type phases under consideration, the relative stoichiometric concentration of carbon atoms is  $y_{st} = 5/6$ . If only non-metal sublattices of these superstructures are considered, the complete atomic planes  $(1\bar{1}1)_{B1}$ , in which all sites are occupied by carbon atoms, alternate with the imperfect  $(1\bar{1}1)_{B1}$  planes, in which one-third of sites are vacant, along the  $[1\bar{1}1]_{B1}$  direction (see Figs 9–11). In the imperfect planes, one-third of all sites are vacant, and each vacancy is surrounded by interstitial atoms, which form a regular hexagon.

In the completely ordered monoclinic (space group  $C2/m$  and  $C2$ ) and trigonal (space group  $P3_1$ )  $M_6C_5$ -type carbide structures, the metal atoms are in the same environment formed by non-metal sublattice sites (see Table 6, which gives the short-range order parameters and the distributions of carbon atoms and vacancies from the first to the eighth coordination spheres in the non-metal sublattice for the ideal superstructures of  $V_6C_5$  crystallising in these space groups). If consideration is restricted to the first and second coordination spheres, these completely ordered structures have only two types of metal atom positions (Fig. 12),  $M_1^1$  or  $V_1^1$  (a metal atom with one vacancy in the first coordination sphere and one vacancy in the second coordination sphere) and  $M_1^2$  ( $V_1^2$ ) (a metal atom with one vacancy in the first coordination sphere and two vacancies in the second coordination sphere). In the ideal completely ordered structures of  $V_6C_5$  (space group  $C2/m$ ,  $P3_1$  and  $C2$ ), two-thirds of all vanadium atoms occupy the  $V_1^1$  positions and one-third of vanadium atoms occupy the  $V_1^2$  positions. Actually, the  $^{51}\text{V}$  NMR spectra of annealed single crystals of vanadium carbide  $\text{VC}_{0.84}$  show lines corresponding to the  $V_1^0$ ,  $V_1^1$  and  $V_1^2$  positions with the intensity ratio of the  $V_1^1$  and  $V_1^2$  lines equal to 2 : 1.<sup>13,84</sup> Taking into account high intensities of these lines,  $V_1^1$  and  $V_1^2$  were considered<sup>13,84</sup> as positions of an ordered structure of  $V_6C_5$  (see Section III.1).

The identity of the short-range order in three superstructures of  $V_6C_5$  does not allow one to distinguish them based on the NMR spectroscopic data. It is also difficult to distinguish these superstructures with the use of diffraction data. That is why the results obtained in different studies of the structures of ordered phases  $V_6C_5$  are so contradictory. In the study,<sup>117</sup> a procedure was developed for calculations of diffraction spectra of superstructures using the data on the disorder–order phase transition channel, and the diffraction spectra of all  $M_{2t}X_{2t-1}$ -type superstructures ( $X = \text{C, N, O}$ ;  $t = 1, 1.5, 2, 3, 4$ ), which can exist in strongly nonstoichiometric compounds, were calculated.

The calculated neutron diffraction spectra of the superstructures of  $V_6C_5$  are presented in Fig. 13. It can be seen that the theoretical diffraction patterns of the ideal monoclinic (space

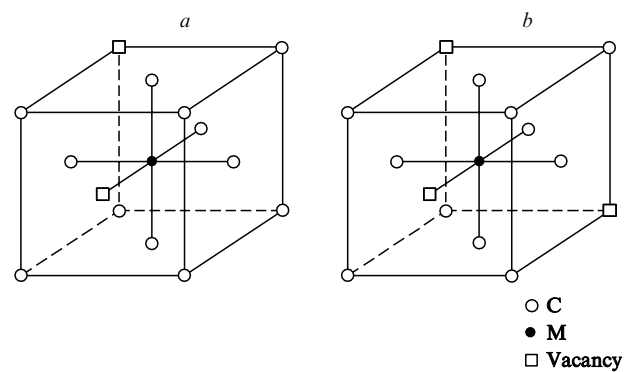


**Figure 12.** The  $M_1^1$  (a) and  $M_1^2$  (b) sites occupied by metal atoms in ideal completely ordered  $M_6C_5$ -type structures (space group  $C2/m$ ,  $P3_1$  and  $C2$ ).

Two-thirds of all metal atoms occupy the  $M_1^1$  sites and one-third of metal atoms occupy the  $M_1^2$  sites.

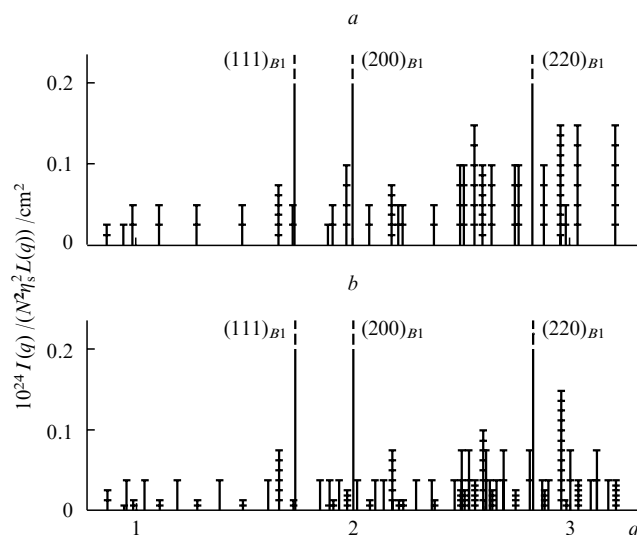


**Figure 13.** Theoretical neutron diffraction spectra of the ideal superstructures  $V_6C_5$  (space group  $C2/m$  and  $P3_1$ ) (a) and  $V_6C_5$  (space group  $C2/m$ ) (b) constructed depending on the magnitude of the diffraction vector  $q = (2a_{B1}\sin\theta)/\lambda$ .

The intensities of reflections were calculated for the neutron scattering factors of vanadium and carbon atoms,  $f_V = -0.038 \times 10^{-12}$  and  $f_C = 0.665 \times 10^{-12}$  cm. The number of unit segments along the vertical lines representing the intensities of superstructure reflections is equal to the repetition factor of the corresponding reflection. For comparison, the intensities of the  $(111)_{B1}$  and  $(200)_{B1}$  structure reflections are 2.806 and 1.598 in units of the y axis, i.e., these intensities are 10–20 times higher than the intensities of the strongest superstructure reflections.

group  $C2/m$ ) superstructure of  $V_6C_5$  is identical to the trigonal (space group  $P3_1$ ) superstructure, which is reasonable taking into account that the disorder–order phase transition channel corresponding to each superstructure includes the arms of the same stars  $\{k_9\}$ ,  $\{k_4\}$  and  $\{k_3\}$ , and the parameters determining the length of the arms  $k_4^{(j)}$  and  $k_3^{(l)}$  are equal for both superstructures. If these superstructures are characterised by the equal long-range order parameters  $\eta_s$ , there are no differences in the intensity of the superstructure reflections determined by the same star  $\{k_s\}$ .<sup>4, 117</sup> Therefore, if the corresponding long-range order parameters are equal, the diffraction spectra of these ideal superstructures of  $V_6C_5$  (space group  $C2/m$  and  $P3_1$ ) have superstructure reflections identical in both position and intensity.

However, the intensities of superstructure diffraction reflections in the spectra of real ordered phases of  $V_6C_5$  (space group  $C2/m$  and  $P3_1$ ) will be different because the static atomic displacements differ in direction and magnitude. Analysis of diffraction spectra taking into account possible static atomic displacements allows one to determine whether ordered  $V_6C_5$ -type phases have monoclinic or trigonal symmetry.

The diffraction pattern of the monoclinic (space group  $C2$ ) superstructure of  $V_6C_5$  is more complex than those of the above two superstructures of  $V_6C_5$  (space group  $C2/m$  and  $P3_1$ ) (see Fig. 13), because the diffraction spectrum of this ordered phase has superstructure reflections associated with four stars  $\{k_9\}$ ,  $\{k_4\}$ ,  $\{k_3\}$  and  $\{k_0\}$ . Therefore, it is easier to distinguish the monoclinic (space group  $C2$ ) phase of  $V_6C_5$  in studies of ordered  $V_6C_5$  phases by diffraction methods.

The relation between three superstructures of  $V_6C_5$  is illustrated by Fig. 14.<sup>1, 4, 118</sup> If only the non-metal sublattice is considered, complete planes containing only carbon atoms alternate with partially imperfect planes containing carbon atoms and vacancies along the  $[1\bar{1}1]_{B1}$  direction in these superstructures. In the imperfect planes, vacancies occupy one-third of carbon sites. In the plane, the vacancies form regular hexagons. The mutual arrangement of the imperfect planes giving rise to three different

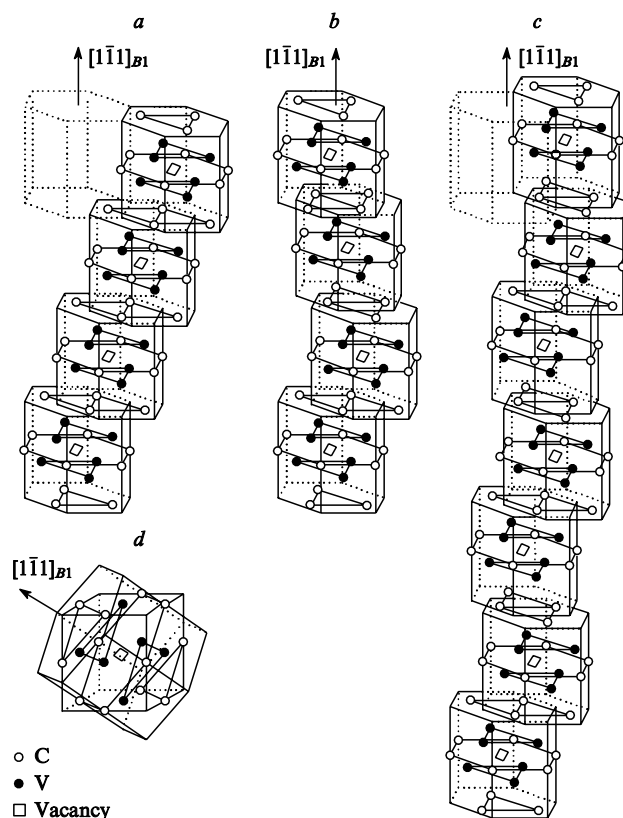


**Figure 14.** Models of related structures of the ordered carbide phases  $V_6C_5$  ( $M_6C_5$ ).<sup>1, 117</sup>

(a) the monoclinic (space group  $C2/m$ ) structure of  $V_6C_5$ , (b) the trigonal (space group  $P3_1$ ) structure of  $V_6C_5$ , (c) the monoclinic (space group  $C2$ ) structure of  $V_6C_5$ , (d) the position of the  $V_6C_5\square$  quasimolecule in  $B1$ -type lattice.

$M_6C_5$ -type structures is presented in Fig. 14. The successive threefold shift of the atoms with respect to the vacancies located in the equidistant imperfect planes along the  $\{1/2 - 1/2 1\}_{B1}$  direction gives rise to the monoclinic (space group  $C2/m$ ) structure of  $V_6C_5$  (see Fig. 14a). The successive helical shift along the  $\{1/2 - 1/2 1\}_{B1}$ ,  $\{1/2 - 1/2 1/2\}_{B1}$  and  $\{1 - 1/2 1/2\}_{B1}$  vectors gives rise to the trigonal (space group  $P3_1$ ) structure of  $V_6C_5$  (see Fig. 14b). Alternate shifts of the atoms and vacancies located in the imperfect planes along the  $\{1/2 - 1/2 1\}_{B1}$  and  $\{1/2 - 1/2 1/2\}_{B1}$  vectors (see Fig. 14c) give rise to the monoclinic (space group  $C2$ ) superstructure.

All superstructures of  $V_6C_5$  can be represented as a set of  $V_6C_5\square$  quasimolecules (see Fig. 14d) arranged in a certain order. These superstructures differ only in the mutual arrangement of partially imperfect planes. Since such superstructures are identical in character of the short-range order, they have similar energies of formation. This is responsible for mixing of the sequences of the mutual arrangement of partially imperfect planes typical of each structure. As a result, the regular alternation of the planes along the  $c$  axis can be distorted, resulting in weakening of particular superstructure reflections.

The cubic ordered phase  $V_8C_7$  with the space group  $P4_332$  is observed only in the vicinity of the upper boundary of the homogeneity region of carbide  $VC_y$  corresponding to  $VC_{0.875}$ . The translation vectors of the unit cell of this ordered phase (Fig. 15) are twice as large as those of the basic structure  $B1$ ,  $a_1 = \{2 0 0\}_{B1}$ ,  $a_2 = \{0 2 0\}_{B1}$  and  $a_3 = \{0 0 2\}_{B1}$ .

The cubic (space group  $P4_332$ ) superstructure of  $V_8C_7$  is formed through the transition channel including all arms belonging to three stars  $\{k_9\}$ ,  $\{k_8\}$  and  $\{k_4\}$ .<sup>117</sup> The corresponding

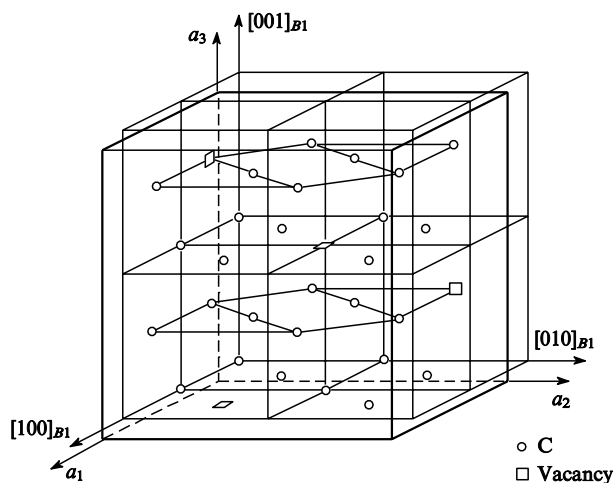


Figure 15. Position of the cubic (space group  $P4_332$ ) unit cell of the superstructure  $V_8C_7$  in the lattice with the  $B1$  structure.

distribution function depends on three long-range order parameters

$$n(x_1, y_1, z_1) = y - \frac{\eta_9}{16} [\cos \pi(x_1 + y_1 + z_1) - \cos \pi(x_1 - y_1 + z_1) - \cos \pi(x_1 + y_1 - z_1) - \cos \pi(-x_1 + y_1 + z_1)] - \frac{\eta_8}{8} [-\cos \pi(2x_1 + z_1) + \sin \pi(2x_1 + z_1) - \cos \pi(y_1 + 2z_1) + \sin \pi(y_1 + 2z_1) - \cos \pi(x_1 + 2y_1) + \sin \pi(x_1 + 2y_1)] - \frac{\eta_4}{8} [\cos \pi(x_1 + y_1) + \cos \pi(x_1 + z_1) + \cos \pi(y_1 + z_1) + \sin \pi(x_1 - y_1) - \sin \pi(x_1 - z_1) + \sin \pi(y_1 - z_1)]. \quad (28)$$

For this function,  $y_{st} = 7/8$ . In the case of the above-considered ordering, the non-metal sublattice of disordered nonstoichiometric carbide  $VC_y$  is divided into four non-equivalent sublattices. The probability of occupancy of the sites in these sublattices by carbon atoms [values of the distribution function (28)] are given in Table 12. In the ideal ordered cubic (space group  $P4_332$ ) phase  $V_8C_7$ , three-fourths of all metal atoms occupy the  $V_1^0$  positions, and the other atoms occupy the  $V_1^1$  positions.

The structures of ordered phases of carbide  $VC_y$  determined by X-ray diffraction<sup>49, 69</sup> were refined<sup>25, 26</sup> taking into account the

Table 12. Characteristics of the cubic [space group  $P4_332$  ( $O^6$ )] superstructure of  $M_8C_7$  ( $V_8C_7$ ).

| Atom                  | Position | Atomic coordinates and mul- in ideal ordered tiplicity structure <sup>a</sup> |         |         | Distribution function $n(x_1, y_1, z_1)$     |
|-----------------------|----------|-------------------------------------------------------------------------------|---------|---------|----------------------------------------------|
|                       |          | $x/a_1$                                                                       | $y/a_2$ | $z/a_3$ |                                              |
| C 1<br>(vac-<br>ancy) | 4(b)     | 5/8                                                                           | 5/8     | 5/8     | $n_1 = y - \eta_9/8 - 3\eta_8/8 - 3\eta_4/8$ |
| C 2                   | 4(a)     | 1/8                                                                           | 1/8     | 1/8     | $n_2 = y + \eta_9/8 + 3\eta_8/8 - 3\eta_4/8$ |
| C 3                   | 12(d)    | 1/8                                                                           | 5/8     | 5/8     | $n_3 = y + \eta_9/8 - \eta_8/8 + \eta_4/8$   |
| C 4                   | 12(d)    | 1/8                                                                           | 3/8     | 7/8     | $n_4 = y - \eta_9/8 + \eta_8/8 + \eta_4/8$   |
| M 1                   | 8(c)     | 3/8                                                                           | 3/8     | 3/8     |                                              |
| M 2                   | 24(e)    | 1/8                                                                           | 3/8     | 1/8     |                                              |

<sup>a</sup> Parameters of the cubic unit cell:  $a_1 = \langle 200 \rangle_{B1}$ ,  $a_2 = \langle 020 \rangle_{B1}$ ,  $a_3 = \langle 002 \rangle_{B1}$ .

data on disorder–order transition channels. In the latter studies, samples of nonstoichiometric carbide  $VC_y$  containing different amounts of carbon ( $y = 0.66, 0.79, 0.83$  and  $0.87$ ) were prepared by hot pressing of a mixture of powders of vanadium metal and carbide  $VC_{0.875}$  at  $\sim 2200$  K and a pressure of 35 MPa under an atmosphere of argon of special purity. Graphite foil was placed between the powder mixture and a graphite press-mould to avoid cracking. The hot-pressing time was 30 min. All samples had a porosity of  $< 3\%$ , were homogeneous and contained only one  $VC_y$  phase with the  $B1$  structure.

To prepare ordered carbides  $VC_y$ , compact samples synthesised as described above were annealed in evacuated sealed quartz tubes. Disordered carbide  $VC_{0.875}$  was prepared by water quenching of a sample, which was pre-annealed at 1450 K and sealed in a quartz tube. Free carbon in the  $VC_y$  samples was absent. The nitrogen content was no higher than 0.09 mass %, and the oxygen content was 0.1 mass %–0.3 mass %.

X-Ray diffraction studies ( $CuK\alpha_{1,2}$  radiation) were carried out in the angle range  $2\theta = 14–120^\circ$  in a step-scan mode with a step of  $0.02^\circ$ . The exposure time per step was 10 s. Metallographic studies were performed in reflected light using polished samples of sintered and annealed carbides. Before study, the surface of metallographic sections was subjected to etching.

X-Ray diffraction patterns of  $VC_{0.79}$ ,  $VC_{0.83}$  and  $VC_{0.87}$  samples prepared by annealing nonstoichiometric vanadium carbide had not only intense reflections but also additional peaks, whose intensities were no higher than 5% of the intensities of structure lines. The appearance of low-intensity additional reflections is indicative of the formation of ordered phases in thermally treated samples. In the X-ray pattern of carbide  $VC_{0.66}$  subjected to thermal treatment, no additional reflections were observed.

Figure 16 shows fragments of X-ray diffraction patterns of annealed samples of carbides  $VC_{0.79}$ ,  $VC_{0.83}$  and  $VC_{0.87}$ .<sup>25, 26</sup> The intense lines observed in all X-ray diffraction patterns in the angle ranges  $2\theta = 37.4^\circ$  and  $43.4^\circ$  are the  $(111)_{B1}$  and  $(200)_{B1}$  structure reflections. The X-ray diffraction patterns of all annealed carbides have diffuse peaks in the  $2\theta$  angle ranges of  $21.2–22.0^\circ$  and  $\sim 30.0–31.0^\circ$ . These peaks are absent in the X-ray diffraction

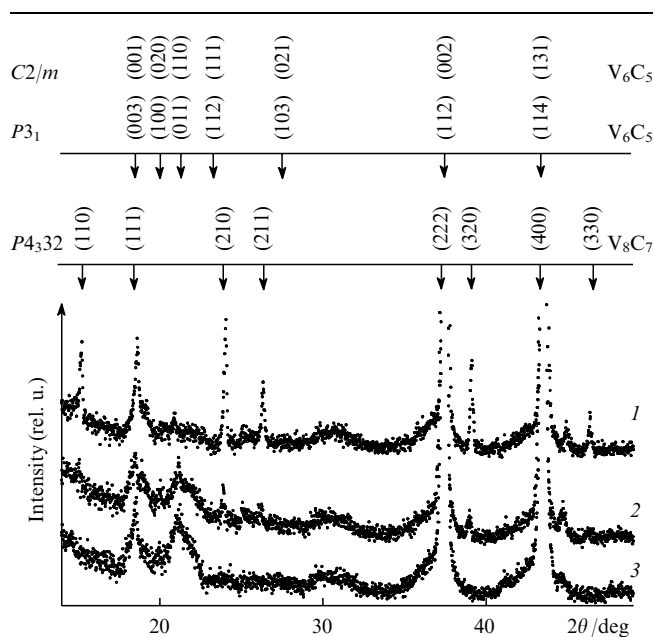


Figure 16. Fragments of X-ray diffraction patterns of annealed nonstoichiometric vanadium carbides  $VC_{0.87}$  (1),  $VC_{0.83}$  (2) and  $VC_{0.79}$  (3).<sup>25, 26</sup> The positions of superstructure reflections for the ordered  $V_6C_5$  and  $V_8C_7$  phases are indicated by arrows; for all reflections, the Miller indices corresponding to the space group of the ordered phase are given.

patterns of disordered carbides. They are parasitic reflections from radiation with the wavelength  $\lambda/2$  and correspond to the  $(200)_{B1}$  and  $(220)_{B1}$  structure reflections. The appearance of these peaks is associated with large accumulation of the signal during measurements of X-ray diffraction patterns of annealed carbides.

In the X-ray diffraction pattern of annealed carbide  $VC_{0.87}$ , the first superstructure reflection with the following diffraction vector

$$|q| = 2a_{B1} \frac{\sin \theta}{\lambda} \approx 0.710$$

is observed for the angle  $2\theta = 15.14^\circ$  (see Fig. 16). This reflection corresponds to the  $\{1/2 \ 1/2 \ 0\}$  superstructure vector with a length  $|q| \approx 0.707$  belonging to the star  $\{k_4\}$  with the running index  $\mu_4 = 1/4$ . The next reflection with  $|q| \approx 0.871$  is observed at  $2\theta = 18.55^\circ$  and corresponds to the  $\{1/2 \ 1/2 \ 1/2\}$  vector of the star  $\{k_9\}$ . The intensity of the third reflection ( $2\theta = 24.04^\circ$ ) corresponding to the  $\{1 \ 1/2 \ 0\}$  vector of the star  $\{k_8\}$  is the highest of all superstructure peaks. The next three superstructure reflections in the X-ray diffraction pattern of an annealed  $VC_{0.87}$  sample (see Fig. 16) are observed at the angles  $2\theta = 26.34, 39.14$  and  $46.34^\circ$  and correspond to the  $\{1 \ 1/2 \ 1/2\}$  vector of the star  $\{k_4\}$ , the  $\{3/2 \ 1 \ 0\}$  vector of the star  $\{k_8\}$  and the  $\{3/2 \ 3/2 \ 0\}$  vector of the star  $\{k_4\}$ . The X-ray diffraction spectrum of annealed carbide  $VC_{0.87}$  has 19 superstructure reflections corresponding to three stars  $\{k_9\}$ ,  $\{k_8\}$  and  $\{k_4\}$  in the  $2\theta$  angle range from  $14^\circ$  to  $110^\circ$ .

Analysis of the positions and intensities of the observed superstructure reflections demonstrated that thermal treatment of carbide  $VC_{0.87}$  afforded the cubic ordered phase  $V_8C_7$  (space group  $P4_332$ ). The disorder–order phase transition channel  $VC_{0.87} \rightarrow V_8C_7$  includes all arms of the Lifshitz stars  $\{k_9\}$  and  $\{k_8\}$  and the non-Lifshitz star  $\{k_4\}$  (at  $\mu_4 = 1/4$ ). The Landau group-theoretical criterion for the occurrence of the second-order phase transition is not fulfilled, because the transition channel involves arms of the non-Lifshitz star  $\{k_4\}$ , the sum  $(k_4^{(1)} + k_4^{(5)} + k_4^{(9)})$  being equal to the  $(111)$  structure vector of the reciprocal lattice. Even from symmetry considerations, it is evident that the formation of the ordered  $V_8C_7$  phase can occur only as the first-order phase transition. This is consistent with the conclusions drawn in the studies.<sup>4,117</sup>

Metallographic analysis of annealed carbide  $VC_{0.87}$  confirmed the presence of an ordered phase belonging to the cubic system. As a result of ordering, each grain of the basic disordered phase is divided into domains of an ordered phase of isometric shape (Fig. 17). In reflected polarised white light, the ordered domains give no interference, which indicates that the ordered  $V_8C_7$  phase is isotropic. Microstructural studies demonstrated also that the disorder–order phase transition in carbide  $VC_{0.87}$  starts at the grain boundaries of the disordered phase. In disordered carbide, grains of the basic phase have distinct straight boundaries (see Fig. 17a). After annealing, these boundaries become broken due to ordering (see Fig. 17b). The domains intergrow with grains of the basic phase from the boundaries to the centres of the grains and penetrate into crystallites with time. Due to small domain sizes and the same cubic symmetry of the disordered and ordered phases, the domain boundaries cannot be observed by optical microscopy.

Analysis of the X-ray diffraction pattern of annealed carbide  $VC_{0.83}$  (see Fig. 16) demonstrated that the sample contained two ordered phases. The X-ray pattern has superstructure reflections of the ordered phase  $V_8C_7$  along with lines of the phase  $V_6C_5$  with trigonal (space group  $P3_1$ ) or monoclinic (space group  $C2/m$ ) symmetry. In the X-ray pattern of annealed carbide  $VC_{0.83}$ , the ordered  $V_6C_5$  phase is characterised by the  $\{1/2 \ 1/2 \ 1/2\}$  superstructure reflection ( $2\theta = 18.54^\circ$ ), which belongs to the star  $\{k_9\}$  and whose position is identical to that of the analogous reflection for the cubic ordered phase  $V_8C_7$ , and the  $\{2/3 \ 2/3 \ 0\}$  ( $2\theta = 20.11^\circ$ ),  $\{1/6 \ -5/6 \ -1/2\}$  ( $2\theta = 21.14^\circ$ ),  $\{-1/3 \ -1/3 \ 1\}$  ( $2\theta = 23.74^\circ$ ) and  $\{7/6 \ 1/6 \ 1/2\}$  ( $2\theta = 27.34^\circ$ ) reflections belonging to the stars  $\{k_4\}$  (with  $\mu_4 = 1/3$ ) and  $\{k_3\}$  (with  $\mu_3 = 1/6$ ).

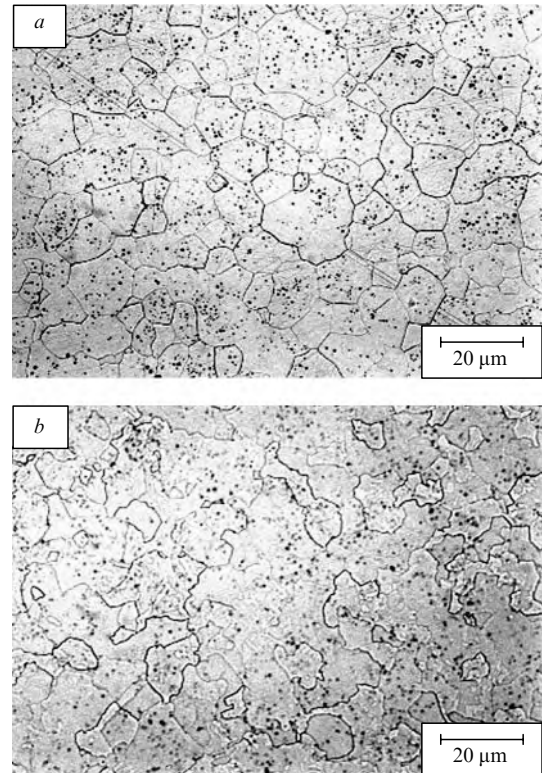


**Figure 17.** Changes in the microstructure of compact nonstoichiometric vanadium carbide  $VC_{0.87}$  upon ordering;

(a) in disordered carbide  $VC_{0.87}$ , grains have distinct linear boundaries, (b) in ordered carbide  $V_8C_7$  ( $VC_{0.87}$ ), the grain boundaries of the basic phase are corroded due to formation of domains of the ordered phase  $V_8C_7$ .

Therefore, the disorder–order phase transition channel associated with the formation of the superstructure of  $V_6C_5$  involves the arms of the Lifshitz star  $\{k_9\}$  and the non-Lifshitz stars  $\{k_4\}$  and  $\{k_3\}$ . From symmetry considerations, the formation of the ordered phase  $V_6C_5$  should occur as the first-order phase transition.

A set of the observed superstructure wave vectors giving rise to the transition channel  $VC_{0.83} \rightarrow V_6C_5$  can correspond to either trigonal (space group  $P3_1$ ) or monoclinic (space group  $C2/m$ ) superstructures of the  $V_6C_5$  type.

Investigation of the microstructure of annealed carbide  $VC_{0.83}$  in reflected polarised white light demonstrated that the sample contained domains of two ordered phases. One phase is composed predominantly of isometric grains and gives no interference, i.e., it is isotropic. Hence, this phase is apparently the cubic ordered phase  $V_8C_7$  and comprises 15%–20% of the sample. The second phase comprises 80%–85% of the sample. Domains of the second phase are of platelet-like and prismatic shape characteristic of crystals belonging to the monoclinic and trigonal systems and show an interference colour, i.e., they are anisotropic. In reflected polarised white light, the domains of the second phase are blue and yellow in colour. These facts suggest that the second phase is carbide  $V_6C_5$ . Therefore, the results of microstructural studies are consistent with the conclusions drawn from X-ray diffraction data.

The X-ray diffraction pattern of annealed carbide  $VC_{0.79}$  has superstructure reflections of only the ordered  $V_6C_5$ -type structure (see Fig. 16). Its microstructure contains domains of only an anisotropic ordered phase. Consequently, prolonged annealing of vanadium carbide  $VC_{0.79}$  afforded the only ordered  $V_6C_5$  phase.

The X-ray diffraction pattern of annealed carbide  $VC_{0.66}$  have reflections of only the basic cubic phase with the  $B1$  structure and

shows no additional reflections, although reflections of the rhombohedral (trigonal) phase  $\zeta\text{-V}_4\text{C}_{3-x}$  would be expected to appear. Carbides  $\zeta\text{-M}_4\text{C}_{3-x}$  ( $x \leq 0.33$ ) have an imperfect carbon sublattice and are formally (without consideration for the crystal structure) identical in composition to  $\text{M}_3\text{C}_2$  ( $\text{MC}_{0.67}$ ). Carbide  $\zeta\text{-V}_4\text{C}_{3-x}$  is not an ordered phase of cubic carbide  $\text{VC}_y$ , because it has the trigonal rather than the FCC metal sublattice.<sup>119</sup> According to the results of the study,<sup>52</sup> the rhombohedral phase  $\zeta\text{-V}_4\text{C}_{3-x}$  contains 37.9 at. % carbon, has a very narrow homogeneity region ( $\text{VC}_{0.605}\text{--VC}_{0.615}$ ), is generated by a peritectoid reaction at 2150 K and is observed up to 1540 K. The absence of the  $\zeta\text{-V}_4\text{C}_{3-x}$  phase in annealed carbide  $\text{VC}_{0.66}$  (see Refs 25 and 69) is, apparently, associated with the fact that annealing was carried out starting from a lower temperature (1200 K). It should be noted that the composition of carbide  $\text{VC}_{0.66}$  corresponds to the lower boundary of the homogeneity region of the  $\zeta\text{-V}_4\text{C}_{3-x}$  phase.

Additional analysis of the X-ray diffraction spectral patterns of ordered carbide  $\text{V}_8\text{C}_7$  (Fig. 18) led authors of the publication<sup>49</sup> to the conclusion that this superstructure is characterised by large static atomic displacements. The vanadium atoms, which form an octahedral environment of the structural non-metal vacancy, are shifted toward the vacancy by 0.003–0.006 nm. The carbon atoms are also shifted toward the vacancies, but these shifts are substantially larger (as large as 0.05 nm). In disordered carbide  $\text{VC}_{0.87}$  with the period  $a_{B1} = 0.4172$  nm, the V–V and V–C interatomic distances are 0.295 and 0.209 nm, respectively, whereas these distances in the vacant  $\square\text{V}_6$  octahedron in ordered carbide  $\text{V}_8\text{C}_7$  are smaller (0.282–0.293 and 0.180–0.209 nm), which is indicative of contraction of the octahedron. In the filled  $\text{CV}_6$  octahedron of ordered carbide  $\text{V}_8\text{C}_7$ , the V–V and V–C distances are 0.295–0.311 and 0.209–0.258 nm, respectively. Such large shifts of the metal atoms can give rise to additional reflections, which are absent in the X-ray diffraction pattern of the ideal (without consideration for atomic displacements) ordered  $\text{V}_8\text{C}_7$ -type cubic (space group  $P4_332$ ) phase.

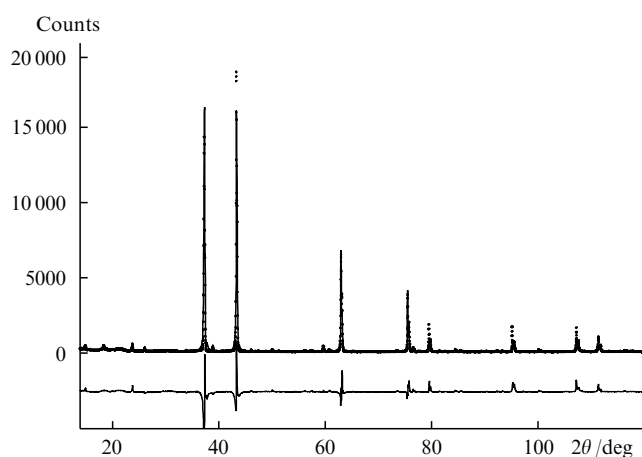


**Figure 18.** Experimental (dotted line) and calculated (solid line) X-ray diffraction patterns ( $\text{Cu K}\alpha_{1,2}$  radiation) of the ordered phase  $\text{V}_8\text{C}_7$ .<sup>49</sup> The intensity differences between the experimental and calculated X-ray diffraction patterns are shown at the bottom of the figure.

#### IV. Nanocrystalline carbide $\text{V}_8\text{C}_7$ and molecular clusters $\text{V}_m\text{C}_n$

In the last 15–20 years, methods for the preparation of nanostructured substances and materials were extensively developed, and the influence of the particle (grain) size on the properties of nanocrystalline compounds was actively studied.<sup>120–126</sup> For example, vanadium carbide  $\text{VC}_{0.875}$  was prepared in the nano-

crystalline state by atom-vacancy ordering as a result of the disorder–order transformation  $\text{VC}_{0.875} \rightarrow \text{V}_8\text{C}_7$ .<sup>127–131</sup>

##### 1. Nanocrystalline vanadium carbide

A coarse-grained powder (with a particle size of 1–2  $\mu\text{m}$ ) of vanadium carbide  $\text{VC}_{0.875}$  was subjected to long-term ageing at an environmental temperature in a closed vessel (to avoid penetration of water vapour from air). An aged vanadium carbide powder appeared to be very hygroscopic. Immediately after withdrawal from the vessel, the powder contained no more than 0.2 mass % of physically adsorbed water. After storage under environmental conditions for several months, the water content reached 2.0 mass % and then remained unchanged. Generally, coarse-grained vanadium carbide powders do not possess such a high hygroscopicity.

Chemical analysis of an aged vanadium carbide powder demonstrated that it has the composition  $\text{VC}_{0.875}$  corresponding to the upper boundary of the homogeneity region of the cubic phase with the  $B1$  structure.

A vanadium carbide powder was studied by the microscopic method. Discrete irregularly shaped agglomerates with sizes of 5–50  $\mu\text{m}$  are observable under  $\sim 100$  magnification. These agglomerates consist of particles with sizes of  $\sim 1$   $\mu\text{m}$ . Under higher magnification, it is seen that these particles have a complex structure and are composed of a large number of very small, nanometre-size, particles (hereinafter, these particles will be referred to as nanoparticles or nanocrystallites). Figure 19 shows a photomicrograph taken with a high-resolution DSM 982 Gemini scanning electron microscope. Each particle with a size of  $\sim 1$   $\mu\text{m}$  looks like an opened rosebud or a loose head of cabbage and consists of nanocrystallites. Under 50 000 magnification it can be seen that the observed nanocrystallites appear as curved leaves, which, as a first approximation, can be modelled by disks with a diameter of  $\sim 400\text{--}600$  nm and a thickness of  $\sim 15\text{--}20$  nm. The volume of these disks corresponds to that of a rather large spherical particle with a diameter of 150–220 nm. However, due to the small thickness of the disk, the ratio of its surface area to the volume is  $0.107\text{--}0.143\text{ nm}^{-1}$ , which corresponds to the specific surface area of the powder of  $19\text{--}26\text{ m}^2\text{ g}^{-1}$ .

The crystal structure of vanadium carbide was studied by X-ray diffraction using  $\text{Cu K}\alpha_{1,2}$  radiation. The X-ray diffraction patterns of disordered carbide  $\text{VC}_{0.875}$ , annealed coarse-grained ordered carbide  $\text{VC}_{0.875}$  ( $\text{V}_8\text{C}_7$ ) and nanostructured carbide  $\text{VC}_{0.875}$  are shown in Fig. 20. The X-ray pattern of the  $\text{VC}_{0.875}$  nanopowder (see Fig. 20c) has structure reflections of the basic  $B1$  phase along with superstructure reflections corresponding to the cubic ordered phase  $\text{V}_8\text{C}_7$  with the space group  $P4_332$ . The

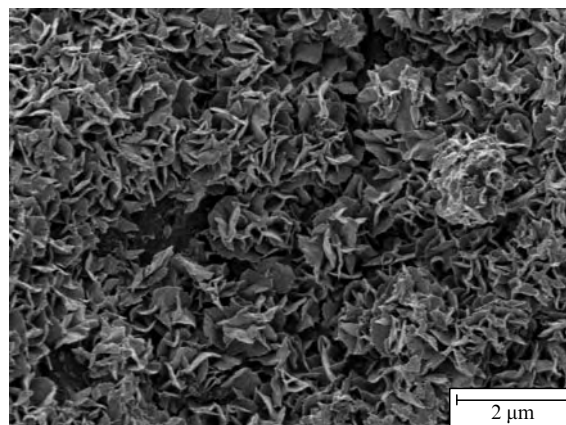


**Figure 19.** Microstructure of a powder of vanadium carbide  $\text{VC}_{0.875}$  subjected to long-term ageing at environmental temperature and under an environmental atmosphere (10 000 magnification).<sup>127, 131</sup>

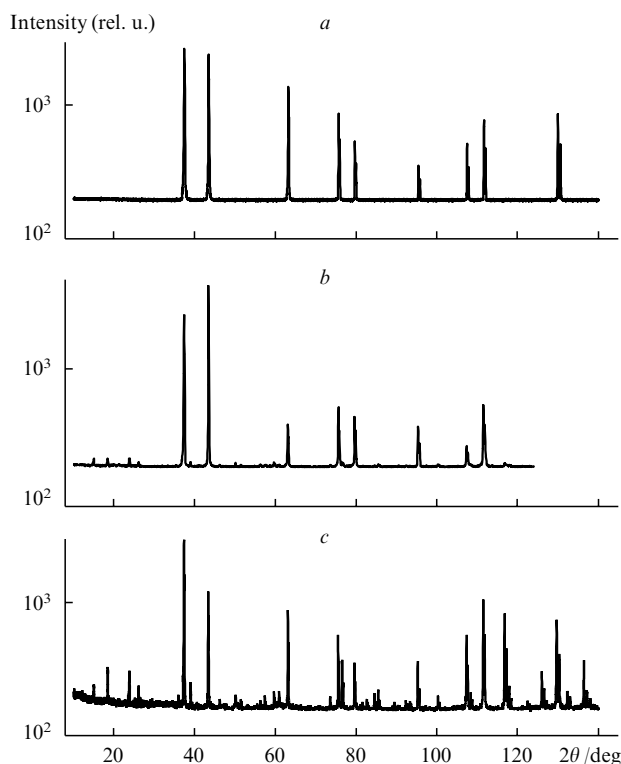


**Figure 20.** Powder X-ray diffraction patterns of disordered carbide  $\text{VC}_{0.875}$  ( $a_{B1} = 0.41638$  nm) (a), ordered coarse-grained carbide  $\text{VC}_{0.875}$  ( $\text{V}_8\text{C}_7$ ) ( $a_{B1} = 0.41682$  nm) (b) and nanostructured carbide  $\text{VC}_{0.875}$  ( $a_{B1} = 0.41685$  nm) (c) (Cu  $K\alpha_{1,2}$  radiation).<sup>127, 130, 131</sup> Superstructure reflections observed in the X-ray diffraction patterns of b and c correspond to the cubic (space group  $P4_332$ ) ordered phase  $\text{V}_8\text{C}_7$ . High intensities of superstructure reflections for a  $\text{VC}_{0.875}$  nanopowder and an anomalous increase in their intensity in the region  $2\theta > 100^\circ$  can be a consequence of large static displacements of vanadium atoms.

lattice parameter of the ordered phase is  $0.8337 \pm 0.0001$  nm. The ideal cubic  $\text{M}_8\text{C}_7$ -type superstructure with the space group  $P4_332$  (see Fig. 15) has the doubled (compared to the disordered basic B1 phase) lattice parameter.<sup>17, 117</sup> Hence, the lattice parameter of the basic phase of the vanadium carbide under consideration is  $a_{B1} = 0.41685$  nm. This parameter is substantially (by  $0.00047$  nm) larger than the lattice parameter of disordered carbide  $\text{VC}_{0.875}$ . The authors speculated<sup>17, 25, 26, 55</sup> that this large difference in the lattice parameter of ordered and disordered carbides  $\text{VC}_{0.875}$  can be observed only in the case of the highest or near-highest degree of ordering.

The intensity ratio of the structure and superstructure reflections supports the conclusion that the degree of long-range order in vanadium carbide is close to the maximum value. Besides, this ratio indicates that the ordered phase occupies the whole volume of the substance, i.e., the latter is a single-phase powder.

The intensities of superstructure reflections of coarse-grained ordered carbide  $\text{VC}_{0.875}$  ( $I_{\text{super}}$ ) decrease with increasing diffraction angle  $2\theta$  (see Fig. 20b), whereas the intensities of superstructure reflections of a vanadium carbide nanopowder at  $2\theta > 100^\circ$  even increase (see Fig. 20c). This is probably attributable to large relaxation static displacements of vanadium atoms in the vicinity of carbon vacancies. These displacements were actually observed in ordered carbide  $\text{V}_8\text{C}_7$ .<sup>49</sup>

Defects in a nanostructured vanadium carbide powder were studied<sup>127, 130</sup> by positron lifetime measurements using a powder of carbide  $\text{VC}_{0.875}$ , which was precalcinated at  $400$  K to remove adsorbed water. For comparison, the positron lifetime in coarse-grained sintered vanadium carbide with the same composition

$\text{VC}_{0.875}$  was measured. The spectrum of coarse-grained vanadium carbide has only a short-lifetime component at  $157 \pm 2$  ps, which corresponds to positron annihilation at a structural vacancy of the carbon sublattice.<sup>132–134</sup> Quantitative analysis of the spectrum of the nanostructured powder demonstrated that this spectrum has a short-lifetime component along with a long-lifetime component at  $500$  ps with a relative intensity of  $7\%$  associated with positron annihilation at defects on the particle surface. The thickness of the surface layer in a vanadium carbide nanopowder was estimated<sup>127–131</sup> at  $0.5–0.7$  nm by comparing the relative intensities of the short- and long-lifetime components. Therefore, the results of positron lifetime measurements demonstrated that only non-metal structural vacancies are present in the interior of vanadium carbide nanocrystallites, whereas their surface layer contains vacancy agglomerates as defects.

The microhardness of a nanostructured powder of  $\text{VC}_{0.875}$ , which was cold pressed at  $10$  MPa and then sintered under vacuum ( $1 \times 10^{-3}$  Pa) with a rise in temperature from  $400$  to  $2000$  K, was measured under a load of  $200$  and  $500$  g. The microhardness was  $H_V = 60–80$  GPa, which is  $\sim 3$  times larger than that of macrocrystalline vanadium carbide ( $29$  GPa under a load of  $0.1$  and  $0.2$  kg) and approaches to the microhardness of diamond. The substantially higher microhardness of carbide  $\text{VC}_{0.875}$ , which was prepared by sintering a nanopowder, can be explained taking into account the Hall–Petch law, according to which  $H_V$  is proportional to  $d^{-1/2}$  ( $d$  is the grain size).

Based on the results of investigations of the structure and properties of vanadium carbide powders, the following model of the nanocrystallite structure was proposed.<sup>127, 129–131</sup> Nanocrystallites have a shape of strongly curved disks with a diameter of  $400–600$  nm and a thickness of  $15–20$  nm. Their interior consists of ordered carbide  $\text{V}_8\text{C}_7$  with a high degree of long-range order and contains a negligible amount of dissolved oxygen. The surface layer of nanocrystallites contains chemisorbed oxygen in an amount of  $3.1$  mass % and a substantial amount of vacancy agglomerates, which is indicative of its loose structure. The thickness of the surface phase is no larger than  $0.7$  nm or four atomic monolayers.

The observed morphology of the nanocrystalline vanadium carbide powder may be a consequence of grain cracking at the interface between disordered and ordered phases. Actually, a jump increase in the FCC-sublattice parameter by  $0.0004$  nm (as a result of the disorder–order phase transition  $\text{VC}_{0.875} \rightarrow \text{V}_8\text{C}_7$ ; the domain size of the ordered phase is  $\sim 20$  nm) was observed at  $1413 \pm 20$  K by high-temperature X-ray diffraction.<sup>48</sup> At  $300$  K, the parameter  $a_{B1}$  of the basic crystal lattice of quenched disordered carbide  $\text{VC}_{0.875}$  differs from that of ordered carbide with the same carbon content, but this difference (published data) is  $0.0002$  nm. The difference in the volumes of the disordered and ordered phases is responsible for strains followed by cracking.

Strains can occur also due to the mismatch between the atomic structures of antiphase domains in ordered vanadium carbide. In any case, the formation of a nanostructure of a powder of nonstoichiometric vanadium carbide  $\text{VC}_{0.875}$  is caused by the disorder–order phase transition  $\text{VC}_{0.875} \rightarrow \text{V}_8\text{C}_7$ .

## 2. Metallocarbohedrene $\text{V}_8\text{C}_{12}$

In 1992, the  $\text{V}_8\text{C}_{12}$  molecular cluster was detected in the V–C system by mass-spectrometric study of the products of the plasma-chemical gas-phase synthesis from hydrocarbons and vanadium vapour, which was prepared by laser heating of the metal. This cluster along with  $\text{Ti}_8\text{C}_{12}$  and analogous compounds belong to metallocarbohedrenes (metallocarbons, metcars)  $\text{M}_8\text{C}_{12}$ .<sup>35, 36</sup> In the synthesis, helium was used as an inert gas.

The molecular cluster of stoichiometric composition  $\text{V}_8\text{C}_{12}$  presumably has a pentagondodecahedral shape (Fig. 21a). In the ideal molecule, all atoms are located on the sphere, and its surface is formed by linking the adjacent atoms and consists of  $12$  regular pentagons. In this molecule, all vanadium and carbon atoms have



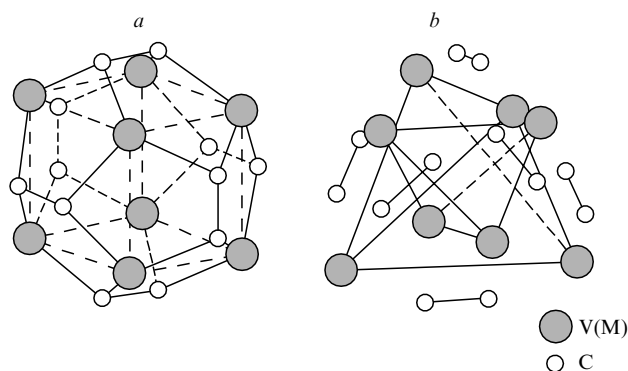


**Figure 21.** Dodecahedral structure of the molecular cluster  $V_8C_{12}$  ( $M_8C_{12}$ ) with symmetry  $T_h$  (a) and  $T_d$  (b).

identical (as in fullerene  $C_{60}$ ) coordination (the coordination number is three), occupy identical positions and are distributed between the vertices of the dodecahedron so that the vanadium atoms are bound only to the carbon atoms and six  $C_2$  fragments alternate with eight vanadium atoms. The dodecahedral structure of  $V_8C_{12}$  can be represented as a cube formed by vanadium atoms, the  $C_2$  fragment being bound to each face of the cube. The point symmetry group  $T_h$  of this ideal structure includes 24 symmetry elements (rotations and reflections).

The electronic structure of  $V_8C_{12}$  with symmetry  $T_h$  was calculated<sup>135</sup> with the use of the following bond lengths:

| Bond      | C–C   | V–C   | V–V   |
|-----------|-------|-------|-------|
| Length/nm | 0.144 | 0.189 | 0.285 |

The electronic energy spectrum of  $V_8C_{12}$  was demonstrated to be similar to the spectrum of  $Ti_8C_{12}$ , but it is slightly shifted to negative energies due to a larger electronegativity of vanadium compared to titanium. The populations of the atomic orbitals corresponding to M–C interactions involving vanadium are  $\sim 9\%$  lower than those involving titanium because the atomic orbitals of vanadium are more localised. The  $V_8C_{12}$  molecular cluster is chemically less stable than  $Ti_8C_{12}$ .

In another structure of the  $V_8C_{12}$  cluster with the point symmetry group  $T_d$  (see Fig. 21 b), the vanadium atoms occupy two types of positions, and the sites belonging to positions of each type form a tetrahedron. The smaller tetrahedron is rotated with respect to the larger tetrahedron by  $90^\circ$ . The vanadium atoms differ in the arrangement relative to the  $C_2$  dimers. Six  $C_2$  fragments are parallel to the edges of the larger tetrahedron formed by the V(1) atoms and perpendicular to the edge of the smaller tetrahedron formed by the V(2) atoms. The V(1) atoms are bound to three nearest carbon atoms, and the V(2) atoms are bound to six carbon atoms.

The question as to which of these two structures (with symmetry  $T_h$  or  $T_d$ ) actually exists remains open, because molecular crystals of metallocarbons are unavailable.

Initially, the plasma-chemical gas-phase synthesis of titanium, zirconium, hafnium and vanadium molecular clusters have afforded predominantly the  $M_8C_{12}$  and  $M_mC_n$  cluster particles with a ratio of C : M  $\approx 1.5$ – $2.0$ .<sup>35, 36, 136</sup> Nanoparticles of carbides TiC, ZrC, HfC and VC with a metal FCC sublattice were absent. At the same time, only monocarbide nanoparticles can be prepared by the conventional plasma-chemical synthesis (without laser heating of the plasma). More recently, particles with cubic ( $M_{14}C_{13}$ ) and dodecahedral ( $M_8C_{12}$ ) structures were simultaneously prepared by the plasma-chemical gas-phase synthesis in the V–C and Ti–C systems.<sup>137</sup> The synthesis with the use of low-power laser heating afforded a larger amount of ‘cubic’  $M_{14}C_{13}$  nanoparticles compared to  $M_8C_{12}$ . An increase in the power of laser radiation and an increase in the hydrocarbon concentration lead to the predominant formation of dodecahedral particles with

the metal-to-carbon ratio varying from 1 : 1.5 to 1 : 2, which was demonstrated in the study of the Nb–C and Zr–C systems.<sup>138, 139</sup> Therefore, a decrease in the carbon concentration in the plasma due to a decrease in the hydrocarbon concentration or a decrease in the power of laser radiation results in a relative carbon deficiency and the predominant formation of monocarbide nanoparticles, whereas an increase in the carbon concentration in the plasma makes it possible to synthesise the  $M_mC_n$  clusters varying from  $M_8C_{12}$  to  $M_{11}C_{21}$  and  $M_{13}C_{22}$ .<sup>138, 139</sup>

Such facts, as the synthesis of the  $V_8C_{12}$  molecular cluster in the V–C system and the formation of cubic  $V_{14}C_{13}$  nanoparticles in the plasma,<sup>137</sup> provide indirect evidence that it is possible to synthesise stoichiometric monocarbide  $VC_{1.0}$  with the B1 structure.

## V. Phase diagram for the V–C system with consideration for ordering of $VC_y$

Ordering of nonstoichiometric cubic vanadium carbide  $VC_y$  has been studied for many years. However, until recently, a reliable phase diagram of the V–C system, which takes into account the formation of ordered phases, has been lacking in the literature. The first attempt to construct a fragment of the phase diagram, where the ordered phases  $V_6C_5$  and  $V_8C_7$  co-exist, has been made in the publication.<sup>43</sup> Later on, an attempt was made<sup>48</sup> to take into account phase equilibria in  $VC_y$  in the narrow composition range  $0.84 \leq y \leq 0.93$  at  $1273 < T < 1473$  K. The main problem associated with the construction of the phase diagram of the V–C system is that  $VC_{0.875}$  rather than the  $MC_{1.0}$  compound of stoichiometric composition serves as the upper boundary of the homogeneity region of disordered cubic vanadium carbide  $VC_y$ , as opposed to other transition metal carbides. The unusual position of the upper boundary of the homogeneity region of carbide  $VC_y$  is responsible for the edge effect, which is manifested in the formation of the ordered phase  $V_8C_7$ , which is absent in other carbides.

As mentioned above, disordered vanadium carbide  $VC_y$  ( $VC_y \square_{1-y}$ ) has a rather extended homogeneity region, within which the carbon atoms and structural vacancies form a substitutional solution in the non-metal sublattice. Depending on the composition and the conditions of the synthesis and thermal treatment, carbide  $VC_y$  can exist in the disordered or ordered state. The disordered state is in thermodynamic equilibrium at temperatures higher than 1300–1400 K, whereas the ordered state is in thermodynamic equilibrium at  $T < 1300$  K. However, due to low diffusion mobility of atoms, the disordered state of nonstoichiometric vanadium carbide is easily retained upon quenching from  $T > 1400$  K to lower temperatures ( $\sim 300$  K) and exists as a metastable state at  $T < 1000$  K.

In the studies,<sup>27, 32</sup> the phase equilibria in the ordering region of nonstoichiometric cubic carbide  $VC_y$  were calculated by the order parameter functional method.<sup>1–4, 16, 53, 140–142</sup>

In the first version of calculations, it was assumed that the ordered phase  $V_8C_7$  has no homogeneity region. Actually, single-phase samples with the cubic superstructure  $V_8C_7$  are formed only in the case of carbide  $VC_{0.87-0.875}$ , whereas at lower carbon concentrations ( $0.83 < y < 0.87$ ), the phase  $V_6C_5$ , which has an extended homogeneity region,<sup>2</sup> is always present in samples containing the ordered phase  $V_8C_7$ .<sup>5, 47, 68, 69, 143</sup> In the studies,<sup>62, 144, 145</sup> the temperature of the  $V_8C_7 \rightleftharpoons VC_y$  transition was demonstrated to be virtually independent (within experimental error) of the composition of carbide  $VC_y$  (Fig. 22). To take into account the specific features of the ordered phase  $V_8C_7$  ( $VC_{0.875}$ ), where no homogeneity region was observed, its free energy was represented as follows

$$F_{V_8C_7(VC_{0.875})}(T) = F(T) - TS_c + \frac{\Delta H_{tr}}{T_{tr}}(T - T_{tr}), \quad (29)$$

where

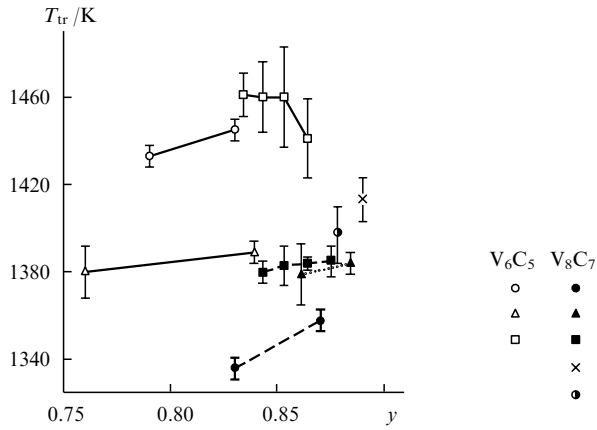


**Figure 22.** Dependence of the temperature of the phase transitions  $V_6C_5 \rightleftharpoons VC_y$  (empty balls) and  $V_8C_7 \rightleftharpoons VC_y$  (solid balls) on the composition of vanadium carbide  $VC_y$ ; (1–5) the results of the studies,<sup>25, 62, 48, 144, 145</sup> respectively.

$$F(T) = F_0(T) + x F_1(T) + x^2 F_2(T)$$

at  $x = 0.875$  [ $F_0(T)$ ,  $F_1(T)$  and  $F_2(T)$  are the parameters of the free energy of disordered carbide  $VC_y$ , see Eqn (8)];  $S_c = 3.132 \cdot 10^{-3} \text{ kJ mol}^{-1} \text{ K}^{-1}$  is the configurational entropy of carbide  $VC_{0.875}$ ;  $\Delta H_{tr} = 3 \text{ kJ mol}^{-1}$  and  $T_{tr} = 1380 \text{ K}$  are the heat and temperature of the  $V_8C_7 \rightarrow VC_{0.875}$  transition estimated from experimental data.<sup>25, 62, 69, 143</sup>

The phase boundary between the homogeneity region of disordered carbide  $VC_y$  and the two-phase region ( $VC_y + V_8C_7$ ) was determined using<sup>27</sup> the equation

$$F_{V_8C_7}(VC_{0.875})(T) = F(y, 0, T) - (y - y_b) \frac{\partial F(y, 0, T)}{\partial y}, \quad (30)$$

where

$$F(y, 0, T) - (y - y_b) \frac{\partial F(y, 0, T)}{\partial y} = F_0(T) + y_b F_1(T) + y(2y_b - y)F_2(T) + kT \left[ \ln(1 - y) + y_b \ln \frac{y}{1 - y} \right], \quad (31)$$

$y_b = 0.875$ .

The position of the phase boundary between the homogeneity region of the ordered phase  $V_{2t}C_{2t-1}$  ( $V_6C_5$ ) and the two-phase region ( $V_{2t}C_{2t-1} + V_8C_7$ ) was specified analogously

$$F_{V_8C_7}(VC_{0.875})(T) = F(y, \eta, T) - (y - y_b) \frac{\partial F(y, \eta, T)}{\partial y}, \quad (32)$$

where

$$F(y, \eta, T) - (y - y_b) \frac{\partial F(y, \eta, T)}{\partial y} = F_0(T) + y_b F_1(T) + y(2y_b - y)F_2(T) + \frac{a^{(s)}}{4t^2} \eta_{eq}^2 F_2(T) + \frac{kT}{2t} \left\{ \ln \left[ n_1^{y_b} (1 - n_1)^{(1-y_b)} \right] + (2t - 1) \ln \left[ n_2^{y_b} (1 - n_2)^{(1-y_b)} \right] \right\}. \quad (33)$$

The parameters  $n_1$ ,  $n_2$ ,  $\eta_{eq}$ ,  $t$  and  $a^{(s)}$  (see below) refer to the phase  $V_{2t}C_{2t-1}$  ( $V_6C_5$ ).

In calculations of the phase equilibria involving lower disordered hexagonal carbide  $\beta\text{-}V_2C$  ( $V_2C_y$ ), its homogeneity region was not taken into account, and the composition of the lower carbide was interpreted as  $V_2C$  ( $VC_{0.50}$ ). Calculations were carried out according to the equation

$$0.5 F_{V_2C}(T) = F_0(T) + 0.5 F_1(T) + y(1 - y)F_2(T) + \quad (34)$$

$$+ \frac{a^{(s)}}{4t^2} \eta_{eq}^2 F_2(T) + \frac{kT}{4t} \left\{ \ln \left[ n_1(1 - n_1) \right] + (2t - 1) \ln \left[ n_2(1 - n_2) \right] \right\}_{\eta = \eta_{eq}},$$

where  $F_{V_2C}(T)$  is the free energy of lower hexagonal vanadium carbide  $\beta\text{-}V_2C$  described by Eqn (9).

Equations (33) and (34) include the parameters  $n_1$ ,  $n_2$ ,  $\eta_{eq}$ ,  $t$  and  $a^{(s)}$ . The numerical coefficients  $t$  and  $a^{(s)}$ , which characterise the possible  $M_{2t}C_{2t-1}$ -type superstructures of cubic carbides  $MC_y$ , are given in Table 13. The parameters  $n_1$  and  $n_2$  are the probabilities of finding a carbon atom in a site of the vacancy and carbon sublattices of the ordered phase  $M_{2t}C_{2t-1}$  (see Refs 3 and 4):

$$n_1 = y - \frac{\eta(2t - 1)}{2t}, \quad (35)$$

$$n_2 = y \frac{\eta}{2t}.$$

**Table 13.** Structural characteristics of possible ordered phases  $M_{2t}C_{2t-1}$  of strongly nonstoichiometric compounds  $MC_y$  with the B1 basic structure (NaCl).<sup>3, 4</sup>

| Type of the ordered phase | Space group      | $t$ | $a^{(s)}$    | $2a^{(s)}/(2t - 1)$ |
|---------------------------|------------------|-----|--------------|---------------------|
| $M_2C$                    | $R3m, Fd3m$      | 1   | 0.2          | 0.4                 |
| $M_2C$                    | $I4_1/amd$       | 1   | 0.2          | 0.4                 |
| $M_2C$                    | $P4/mmm$         | 1   | 0.067 (1/15) | 0.133 (2/15)        |
| $M_3C_2$                  | $Immm, P2$       | 1.5 | 0.4          | 0.4                 |
| $M_3C_2$                  | $C222_1$         | 1.5 | 0.4          | 0.4                 |
| $M_3C_2$                  | $P3m1$           | 1.5 | -0.2         | -0.2                |
| $M_4C_3$                  | $Pm3m$           | 2   | 0.2          | 0.133 (2/15)        |
| $M_4C_3$                  | $I4/mmm$         | 2   | 0.467 (7/15) | 0.311 (14/45)       |
| $M_6C_5$                  | $C2/m, P3_1, C2$ | 3   | 1.0          | 0.4                 |
| $M_8C_7$                  | $Fm3m, P4_332$   | 4   | 1.0          | 0.286 (2/7)         |

The equilibrium long-range order parameter  $\eta_{eq}$  in the ordered phase  $M_{2t}C_{2t-1}$  at the temperature  $T$  satisfies the equation<sup>3, 4</sup>

$$\frac{1}{\eta_{eq}} \ln \left[ \frac{n_2(1 - n_1)}{n_1(1 - n_2)} \right]_{\eta = \eta_{eq}} = \frac{2a^{(s)}}{2t - 1} \frac{F_2(T)}{kT}. \quad (36)$$

The phase diagram of the V–C system published in the papers<sup>27, 32</sup> is shown in Fig. 23. Calculations demonstrated<sup>27</sup> that ordering of nonstoichiometric cubic carbide  $VC_y$  in different temperature and concentration ranges can give rise to three ordered phases, viz.,  $V_3C_2$ ,  $V_6C_5$  and  $V_8C_7$ .

The phase  $V_6C_5$  is the main ordered vanadium carbide phase. This phase appears at a temperature lower than 1485 K, and its homogeneity region extends from  $VC_{0.745}$  to  $VC_{0.831}$  at 1100 K. This phase can also be observed in two-phase regions, i.e., it exists almost throughout the homogeneity region of carbide  $VC_y$  (see Fig. 23). The ordered phase  $V_8C_7$  is formed at a lower temperature (1380 K). At 1330 K, it can be observed along with  $V_6C_5$  in the two-phase region extended from  $VC_{0.83}$  to  $VC_{0.875}$ , which is consistent with experimental data.<sup>47, 144, 146</sup> The  $V_6C_5 + V_8C_7$  two-phase region, where the ordered phase  $V_8C_7$  exists, becomes narrower with decreasing temperature. The ordered phases  $V_6C_5$  and  $V_8C_7$  form an eutectic with  $T_e = 1331 \text{ K}$  and  $y_e = 0.852$ . These parameters are close to the estimate obtained in the study:<sup>48</sup>  $T_e \approx 1300 \text{ K}$  and  $y_e \approx 0.852$ . The calculations also demonstrated that the ordered phase  $V_3C_2$ , which has a narrow homogeneity region (from  $VC_{0.667}$  to  $VC_{0.710}$  at 800 K), can be generated in

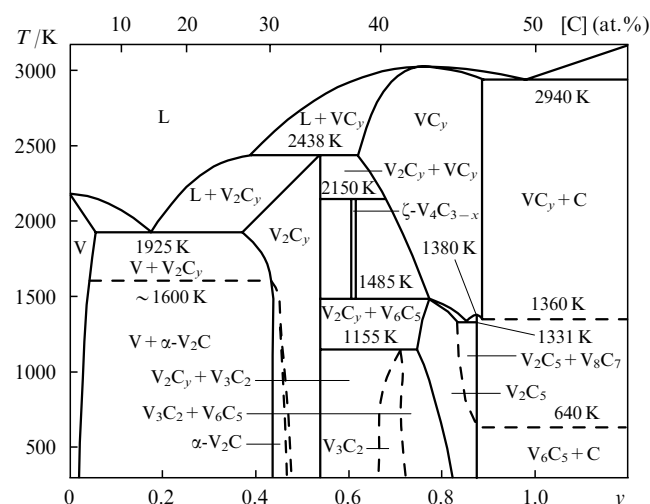
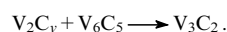


**Figure 23.** Phase diagram of the V–C equilibrium system, which was constructed taking into account the atomic ordering of nonstoichiometric cubic vanadium carbide  $VC_y$ .<sup>27, 32</sup>

The phase boundaries outside the ordering region are those published in the studies;<sup>41, 147</sup> the position of the phase  $\zeta$ - $V_4C_{3-x}$  is given according to the publication;<sup>52</sup>  $V_8C_7$ ,  $V_6C_5$  and  $V_3C_2$  are the ordered phases of cubic carbide  $VC_y$ ,  $\alpha$ - $V_2C$  is the ordered phase of lower hexagonal carbide  $V_2C_y$  ( $\beta$ - $V_2C$ ).

vanadium carbide at 1155 K (lower temperatures) under equilibrium conditions according to the peritectoid reaction

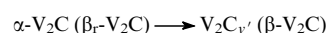


This phase has not been experimentally observed. According to the results of calculations,<sup>27</sup> the region of existence of the ordered phase  $V_3C_2$  is close to the concentration range, in which the rhombohedral (trigonal) phase  $\zeta$ - $V_4C_{3-x}$  is actually observed, but its existence was not taken into account in calculations of ordering of carbide  $VC_y$ , because the thermodynamic characteristics of this

phase are unknown. If the free energy of the  $\zeta$ -phase at  $T < 1150$  K is lower than that of the ordered phase  $V_3C_2$ , the phase  $V_3C_2$  cannot exist. Taking into consideration this fact, the region of existence of the ordered phase  $V_3C_2$  is shown hypothetically.

The position of the phase  $\zeta$ - $V_4C_{3-x}$  is given based on the results of the study.<sup>52</sup> The lowest temperature, at which it was detected after long-term annealing, is 1540 K. This temperature is close to the calculated maximum temperature of the disorder–order  $VC_y$ – $V_6C_5$  transition (1485 K) and is taken as the lower temperature boundary of existence of the phase  $\zeta$ - $V_4C_{3-x}$ .

In the homogeneity region of lower carbide  $V_2C_y$  ( $\beta$ - $V_2C$ ), the ordered orthorhombic phase  $\alpha$ - $V_2C$  ( $\beta$ - $V_2C$ ) is formed.<sup>108–113</sup> The precise temperature of ordering is unknown. According to the results of the studies,<sup>41, 147</sup> this temperature is lower than 1870 K. Magnetic susceptibility measurements of ordered carbide  $\alpha$ - $V_2C$  ( $\beta$ - $V_2C$ ) in the temperature range of 300–1300 K did not reveal the structural phase transition



up to 1300 K.<sup>148</sup> Taking into account this fact and the results of the investigation,<sup>147</sup> the temperature of the order–disorder phase transition in the phase diagram of the V–C system was assumed to be equal to  $\sim 1600$  K (see Fig. 23). The new  $V_8C_{12}$  compound, which was discovered in 1992,<sup>35</sup> was omitted in the phase diagram of the V–C system published in the papers,<sup>27, 32</sup> because it is outside the range of the compositions under consideration.

All disorder–order transitions in vanadium carbide  $VC_y$  belong to first-order phase transitions (see Fig. 23). The same conclusion was drawn in the publications,<sup>25, 69</sup> where the changes in the heat capacities of carbides  $VC_{0.79}$ ,  $VC_{0.83}$  and  $VC_{0.87}$  upon heating and cooling were considered.

The calculated<sup>27</sup> values of  $T_{tr}$ ,  $\Delta S_{tr}$  and  $\Delta H_{tr}$  for phase transitions associated with ordering of nonstoichiometric carbide  $VC_y$  are listed in Table 14, which gives also experimental  $T_{tr}$  and  $\Delta H_{tr}$  for comparison.<sup>25, 69</sup> For carbide  $VC_{0.79}$ , the calculated temperature  $T_{tr}$  and heat  $\Delta H_{tr}$  of the  $V_6C_5 \rightarrow VC_{0.79}$  transition are 1450 K and 2.84 kJ mol<sup>−1</sup>, respectively; the experimental  $\Delta H_{tr}$  value is somewhat lower, because a small amount of the

**Table 14.** Temperatures ( $T_{tr}$ /K), entropies ( $\Delta S_{tr}$ /J mol<sup>−1</sup> K<sup>−1</sup>) and heats ( $\Delta H_{tr}$ /kJ mol<sup>−1</sup>) of order–order and order–disorder phase transitions in nonstoichiometric vanadium carbide  $VC_y$ .

| y     | $V_3C_2$ – $V_6C_5$<br>(calculation <sup>25, 27</sup> ) |                 |                 | $V_6C_5$ – $VC_y$             |                              |                                                  |                              | $V_8C_7$ – $VC_y$             |                              |                                                  |                              |
|-------|---------------------------------------------------------|-----------------|-----------------|-------------------------------|------------------------------|--------------------------------------------------|------------------------------|-------------------------------|------------------------------|--------------------------------------------------|------------------------------|
|       |                                                         |                 |                 | $T_{tr}$                      |                              | $\Delta S_{tr}$ (calculation <sup>25, 27</sup> ) |                              | $T_{tr}$                      |                              | $\Delta S_{tr}$ (calculation <sup>25, 27</sup> ) |                              |
|       | $T_{tr}$                                                | $\Delta S_{tr}$ | $\Delta H_{tr}$ | calculation <sup>25, 27</sup> | experiment <sup>25, 69</sup> | calculation <sup>25, 27</sup>                    | experiment <sup>25, 69</sup> | calculation <sup>25, 27</sup> | experiment <sup>25, 69</sup> | calculation <sup>25, 27</sup>                    | experiment <sup>25, 69</sup> |
| 0.73  | 1138                                                    | 1.38            | 1.57            | —                             | —                            | —                                                | —                            | —                             | —                            | —                                                | —                            |
| 0.74  | 993                                                     | 1.17            | 1.16            | —                             | —                            | —                                                | —                            | —                             | —                            | —                                                | —                            |
| 0.75  | 728                                                     | 0.82            | 0.60            | —                             | —                            | —                                                | —                            | —                             | —                            | —                                                | —                            |
| 0.76  | —                                                       | —               | —               | —                             | —                            | —                                                | —                            | —                             | —                            | —                                                | —                            |
| 0.77  | —                                                       | —               | —               | 1481                          | —                            | 1.75                                             | 2.59                         | —                             | —                            | —                                                | —                            |
| 0.78  | —                                                       | —               | —               | 1466                          | —                            | 1.85                                             | 2.72                         | —                             | —                            | —                                                | —                            |
| 0.79  | —                                                       | —               | —               | 1450                          | 1430 ± 5                     | 1.96                                             | 2.84                         | 2.16 ± 0.1                    | —                            | —                                                | —                            |
| 0.80  | —                                                       | —               | —               | 1433                          | —                            | 2.05                                             | 2.94                         | —                             | —                            | —                                                | —                            |
| 0.81  | —                                                       | —               | —               | 1413                          | —                            | 2.13                                             | 3.01                         | —                             | —                            | —                                                | —                            |
| 0.82  | —                                                       | —               | —               | 1391                          | —                            | 2.19                                             | 3.04                         | —                             | —                            | —                                                | —                            |
| 0.83  | —                                                       | —               | —               | 1366                          | 1442 ± 5                     | 2.21                                             | 3.02                         | 1.26 ± 0.1 <sup>a</sup>       | 1334 ± 5                     | —                                                | 0.70 ± 0.1 <sup>a</sup>      |
| 0.84  | —                                                       | —               | —               | 1338                          | —                            | 2.20                                             | 2.95                         | —                             | —                            | —                                                | —                            |
| 0.85  | —                                                       | —               | —               | 1307                          | —                            | 2.15                                             | 2.81                         | —                             | —                            | —                                                | —                            |
| 0.86  | —                                                       | —               | —               | 1272                          | —                            | 2.06                                             | 2.62                         | —                             | —                            | —                                                | —                            |
| 0.87  | —                                                       | —               | —               | —                             | —                            | —                                                | —                            | —                             | 1355 ± 5                     | —                                                | 2.30 ± 0.1                   |
| 0.875 | —                                                       | —               | —               | —                             | —                            | —                                                | —                            | 1380                          | —                            | 2.17                                             | 3.00                         |

<sup>a</sup> In the study,<sup>69</sup> the total thermal effect  $\Delta H_{tr} = 2.11$  kJ mol<sup>−1</sup>, which includes the thermal effects of two transformations,  $VC_{0.83} \rightarrow V_6C_5$  ( $\Delta H_{tr} \approx 1.37$  kJ mol<sup>−1</sup>) and  $VC_{0.83} \rightarrow V_8C_7$  ( $\Delta H_{tr} \approx 0.75$  kJ mol<sup>−1</sup>), is given for the transformation occurring in carbide  $VC_{0.83}$  on cooling.

phase  $\zeta$ - $V_4C_{3-x}$  is present (which was demonstrated by calorimetric measurements<sup>69</sup>) in carbide  $VC_{0.79}$ .

Additional model calculations were carried out<sup>27</sup> to refine the phase diagram of the V–C system in the event that the phase  $V_8C_7$  has a small homogeneity region. In these calculations, the free energy of the ordered phase  $V_8C_7$  is represented as follows:

$$F_{V_8C_7(VC_{0.875})}(T) = F(T) - TS_c + \frac{\Delta H_{tr}(y)}{T_{tr}(y)} [T - T_{tr}^{\max}(a + by + cy^2)], \quad (37)$$

where  $F(T)$  and  $S_c$  are the same parameters as those in Eqn (29);

$$\frac{\Delta H_{tr}(y)}{T_{tr}(y)} \equiv \Delta S_{tr} = 2.174 \text{ J mol}^{-1} \text{ K}^{-1};$$

$T_{tr}^{\max} = 1380 \text{ K}$  is the maximum temperature of the  $V_8C_7 \rightarrow VC_y$  transition corresponding to  $VC_{0.875}$ ;  $a = 40.7455$ ,  $b = -93.367$  and  $c = 54.793$ .

If the phase  $V_8C_7$  has a homogeneity region, the boundaries of the  $VC_y + V_8C_7$  two-phase region were calculated according to the following equations:<sup>27</sup>

$$\begin{aligned} y_1^2 F_2(T) - kT \ln(1 - y_1) &= \\ &= y_2^2 F_2(T) - kT \ln(1 - y_2) - \Delta S_{tr} [T - (a - cy_2^2) T_{tr}^{\max}], \\ y_1(2 - y_1) F_2(T) + kT \ln y_1 &= \\ &= y_2(2 - y_2) F_2(T) + kT \ln y_2 + \\ &+ \Delta S_{tr} [T - (a + b + 2cy_2 - cy_2^2) T_{tr}^{\max}]. \end{aligned} \quad (38)$$

In the event that the phase  $V_8C_7$  has a homogeneity region, the phase boundaries of the  $V_6C_5 + V_8C_7$  two-phase region were determined analogously

$$\begin{aligned} y_1^2 F_2(T) - \frac{a^{(s)}}{4t^2} \eta_{eq}^2 F_2(T) - \\ - \frac{kT}{2t} [\ln(1 - n_1^{(d)}) + (2t - 1) \ln(1 - n_2^{(d)})]_{\eta=\eta_{eq}} &= \\ &= y_2^2 F_2(T) - kT \ln(1 - y_2) - \Delta S_{tr} [T - (a - cy_2^2) T_{tr}^{\max}], \\ y_1(2 - y_1) F_2(T) - \frac{a^{(s)}}{4t^2} \eta_{eq}^2 F_2(T) + \\ - \frac{kT}{2t} [\ln n_1^{(d)} + (2t - 1) \ln n_2^{(d)}]_{\eta=\eta_{eq}} &= \\ &= y_2(2 - y_2) F_2(T) - kT \ln y_2 + \\ &+ \Delta S_{tr} [T - (a + b + 2cy_2 - cy_2^2) T_{tr}^{\max}]. \end{aligned} \quad (39)$$

In Eqns (39), the parameters  $n_1$ ,  $n_2$ ,  $t$ ,  $\eta_{eq}$  and  $a^{(s)}$  refer to the ordered phase  $V_6C_5$ .

The fragment of the phase diagram of the V–C system calculated without considering the homogeneity region of the phase  $V_8C_7$  is shown in Fig. 24, and the corresponding fragment, which was calculated taking into account this region, is presented in Fig. 25. Calculations<sup>27</sup> demonstrated that the homogeneity region of the phase  $V_8C_7$  is very narrow (the maximum size is observed at 1340 K and corresponds to the composition range from  $VC_{0.852}$  to  $VC_{0.875}$ ). A decrease in the temperature from 1340 K leads to a further narrowing of the homogeneity region of the phase  $V_8C_7$ . At 1340 K, the phases  $V_6C_5$  and  $V_8C_7$  form an eutectic with  $y_e \approx 0.8476$ . The  $V_6C_5 + V_8C_7$  two-phase region existing at  $T < 1340 \text{ K}$  is almost half as wide as that observed in the first case. Otherwise the phase diagram of the V–C system remains unchanged. It is necessary to perform thorough exper-

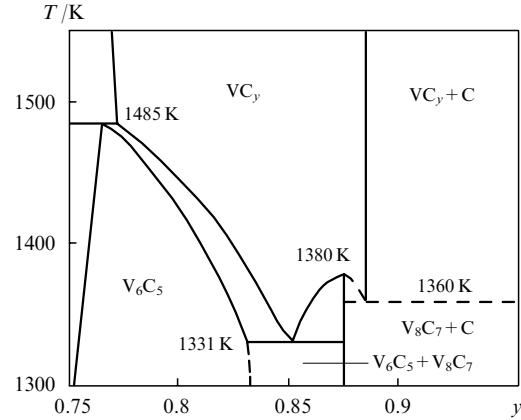


**Figure 24.** Fragment of the ordering region near the upper boundary of the homogeneity region of carbide  $VC_y$  (see Fig. 23). Calculated on the assumption of the absence of the homogeneity region of the phase  $V_8C_7$ .

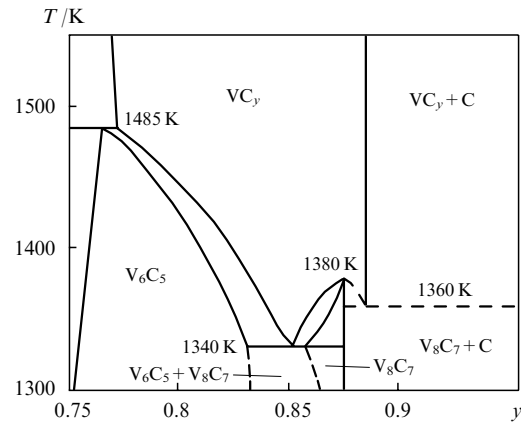


**Figure 25.** Fragment of the ordering region of carbide  $VC_y$  (see Fig. 23). Calculated on the assumption of the presence of a narrow homogeneity region of the phase  $V_8C_7$ .

imental investigations of the structure of vanadium carbide in the narrow composition range,  $VC_{0.85} - VC_{0.875}$ , to give an unambiguous answer to the question as to whether the phase  $V_8C_7$  has a homogeneity region.

On the whole, the calculations<sup>25–27, 32</sup> well reproduced the formation of the monoclinic (or trigonal) phase  $V_6C_5$  with the  $VC_{0.75} - VC_{0.83}$  homogeneity region (or 1100 K), the cubic phase  $V_8C_7$ , which can co-exist with  $V_6C_5$  in the two-phase region, and the ordered phase  $V_3C_2$ , which appears at  $T < 1150 \text{ K}$  and exhibits a very narrow homogeneity region, upon ordering of  $VC_y$ . The temperatures of the  $V_6C_5 \rightleftharpoons VC_y$  and  $V_8C_7 \rightleftharpoons VC_{0.875}$  transitions are 1400–1450 and 1360–1380 K, respectively.

## VI. Conclusion

Analysis of the results of investigations performed in the last 15 years demonstrated that a large number of compounds and phases are produced in the vanadium–carbon system. Their detection became possible due to the use of unconventional synthetic methods, studies of the phase equilibria in a low-temperature region and the use of highly sensitive diffraction and spectroscopic methods for analysing products of annealing and chemical reactions.

The phase  $V_6C_5$ , which can have monoclinic (space group  $C2/m$  and  $C2$ ) and trigonal (space group  $P3_1$ ) symmetry, and the cubic (space group  $P4_332$ ) phase  $V_8C_7$  are the most well-known ordered phases of vanadium carbide. The phase  $V_6C_5$  exists in the  $VC_{0.75-0.77}-C_{0.82-0.86}$  range. The phase  $V_8C_7$  was observed in vanadium carbide samples, whose compositions are close to the upper boundary of the homogeneity region of  $VC_y$  and was detected even in samples quenched from 1500 K.

Molecular clusters with compositions varying from  $V_{14}C_{13}$ , which, presumably, has a cubic structure, to  $V_8C_{12}$  with a dodecahedral structure and then to  $V_{11}C_{21}$  and  $V_{13}C_{22}$  were produced by the plasma-chemical synthesis using laser heating. Apparently, these compounds can be stabilised in the crystalline state in thin films by deposition of the molecular clusters onto supports.<sup>149</sup> A chemical modification of the support or thermal treatment of the deposited film provides additional possibilities of forming a particular structure of clusters.

X-Ray, neutron and electron diffraction techniques are the main experimental methods for the detection and investigation of new compounds and phases in the V–C system. The presence of model diffraction spectra for the phases under consideration in the V–C system substantially facilitates their identification and interpretation of experimental results.

Noteworthy is the applied aspect of investigations of non-stoichiometric carbides. Carbides of stoichiometric composition are generally used in the production of solid alloys with the aim of providing stability of their properties. However, interactions with matrix metal lead to complex chemical processes resulting in dissolution of matrix metal in carbide, depletion of the carbide phase in carbon and enrichment of matrix metal in metal from the carbide phase and (to a smaller degree) in carbon. Carbide grains in solid alloys have a ring structure with a non-uniform distribution of elements over the grain section. It is evident, even from this fact, that carbide phases in solid alloys are generally nonstoichiometric, and ordering and disordering processes can occur in these phases. Evidently, to provide stability of the properties of solid alloys during usage, i.e., at temperatures from 600 to 900 °C, it is necessary that the solid nonstoichiometric carbide phase be in a thermodynamically stable structural state and do not undergo transformations under these conditions. That is why ordering of nonstoichiometric carbides is of applied interest.

Investigations of high-alloy vanadium-containing steels performed in the last decades demonstrated that the resulting vanadium carbide phases are ordered  $V_6C_5$  phases and, more rarely,  $V_8C_7$  phases. An understanding of the conditions of formation and isolation of these phases requires a knowledge of the disorder–order transformations in nonstoichiometric carbides.

Finally, recent investigations showed that ordering of non-stoichiometric vanadium carbide can be used to form nanocrystalline structures. Apparently, disorder–order transformations can be used to construct other nanostructured nonstoichiometric compounds and solid solutions.

On the whole, investigations of ordering of vanadium carbides and properties of these compounds in different structural states contribute to fundamental knowledge of nonstoichiometry and provides the basis for their practical use.

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# Oxide ferroelectric thin films: synthesis from organometallic compounds and properties

V N Vertoprakhov, L D Nikulina, I K Igumenov

## Contents

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**Abstract.** Chemical methods for the preparation of oxide ferroelectric thin films from organometallic compounds published over the last 10–15 years are considered systematically and generalised. Layers of these films are promising for the creation of non-volatile memory elements and for use in nano- and microelectronic devices. The bibliography includes 318 references.

## I. Introduction

Progress in microelectronics requires novel materials for information storage and retrieval. Switches based on chalcogenide semiconductors containing transition metal oxides embedded into glassy matrices of phosphorus, barium, germanium and lead oxides are known. Memory elements based on them stand  $10^3$  recirculation cycles. However, these materials did not find further development.<sup>1</sup> Non-volatile memory elements that exist in two states corresponding to storage of either the logical zero or unity have been designed based on transistors with the structure metal–dielectric–floating gate semiconductor. Superlarge integrated circuits (SLIC) with high information capacities have been developed on their base.

In the course of intense investigations into the design of novel devices for information storage and processing it has been demonstrated that the effect of spontaneous polarisation in ferroelectrics (Fig. 1) can be exploited in the manufacture of non-volatile memory elements. In this case, the maximum number of recirculation cycles ( $Y$ ) reaches  $10^{10}$ – $10^{12}$ . A drawback of such materials consists of their fatigue, which is reflected in a decrease in the residual polarisation with an increase in the number of recirculation cycles. This fact impedes wide application of ferroelectrics in SLIC technology. With this regard, the search for novel materials with enhanced ferroelectric properties is urgently needed. In our opinion, the use of ferroelectrics in the form of thin films or layers with parameters approaching those of the bulk materials is highly promising. The energy consumption, levels of control, electrical and mechanical loads, and optical and acoustic

losses are relatively low for such films. Methods for the preparation of the films should be compatible with modern technology for the production of semiconducting microdevices. This issue has been the focus of several dedicated international symposia.<sup>2–6</sup> The relation between the structure of the films and their physical properties has been considered in monographs<sup>7,8</sup> and reviews.<sup>9–14</sup>

The methods for the preparation of ferroelectric thin films (FETF) can arbitrarily be classified into physical and chemical methods. For instance, thermal evaporation, high-vacuum sputtering induced by electron or ion beams, magnetron sputtering and laser ablation belong to the physical methods. Meanwhile, the sol–gel process, gas-phase deposition of layers from organometallic compounds [Metal-Organic Chemical Vapour Deposition (MOCVD)] or solid precursors (with or without the use of plasma), the hydrothermal method and the Langmuir–Blodgett method are classified as chemical methods. It is of note that the MOCVD method for the preparation of thin films is superior to other techniques for the following reasons:<sup>15</sup>

- it is compatible with the technology of SLIC production;
- it is applicable to the preparation of films in a wide range of thicknesses and areas;
- it yields films with high-quality surface morphologies suitable for further lithographic processing with the required spatial resolution.

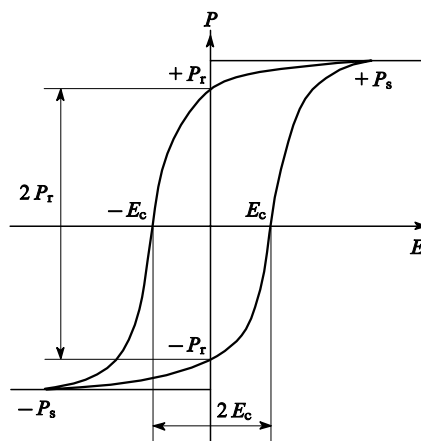


**Figure 1.** Polarisation curve of a ferroelectric film.  $\pm P_r$  is the residual polarisation at  $E = 0$ ,  $\pm P_s$  is the spontaneous polarisation,  $\pm E_c$  is the coercive force.

V N Vertoprakhov, L D Nikulina, I K Igumenov A V Nikolaev Institute of Inorganic Chemistry, Siberian Branch of the Russian Academy of Sciences, prosp. Acad. Lavrent'eva 3, 630090 Novosibirsk, Russian Federation. Fax (7-383) 334 44 89, tel. (7-383) 330 66 46, e-mail: verto@che.nsk.su (V N Vertoprakhov), Lnik@che.nsk.su (L D Nikulina), tel. (7-383) 330 94 87, e-mail: igumen@che.nsk.su (I K Igumenov)

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The typical required thickness of ferroelectric thin films lies in the range from nanometers to a few hundred nanometers. Since nearly all ferroelectrics are complex oxides or solid solutions thereof, it is the partial pressure and chemical state of oxygen in the gas phase that play a crucial role in the vacuum deposition of films. The application of MOCVD to the synthesis of films can be stipulated, for instance, by the technology of capacitor manufacturing, where the multistage process of formation of ferroelectric layers and electrical electrodes above them is replaced by a single operation. Other chemical methods have their own advantages.

The authors of the present review aspired to survey the state-of-the-art advances in the field of preparation of FETF by chemical methods from various classes of organometallic precursors. Only selected types of films are concerned. Compounds manifesting piezoelectric properties, the potential of which has not been explored in sufficient detail so far, are left beyond the scope of this paper. These include complex oxides, such as  $(\text{Pb,Ba})_2\text{Nb}_5\text{O}_{15}$ ,  $\text{Bi}_7\text{Ti}_4\text{Nb}_4\text{O}_{21}$ ,  $\text{ACu}_3\text{Ti}_4\text{O}_{12}$  [ $\text{A} = \text{Bi}^{3+}$  or  $\text{Ln}^{3+}$  ( $\text{Y}$ ,  $\text{La}$ ,  $\text{Sm}$ ,  $\text{Dy}$ )],  $\text{MBi}_4\text{Ti}_4\text{O}_{15}$  ( $\text{M} = \text{Pb}$ ,  $\text{Ca}$ ,  $\text{Sr}$ ),  $(\text{Ba,Sr})\text{Nb}_2\text{O}_6$  and  $\text{Sr}_2(\text{Nb,Ta})_2\text{O}_7$ .

## II. Methods for thin film preparation

### 1. A MOCVD technology of film preparation

The technology of FETF preparation by chemical vapour deposition (CVD) has been reviewed in detail.<sup>16</sup> Film deposition from the vapour of organometallic compounds represents a particular case of this process based on the use of volatile organometallic compounds as the starting material. Presently, the major regularities relating the volatility of a compound to its composition and structure are reliably established, which facilitates the selection of a proper compound among the wide assortment of alkoxides,  $\beta$ -diketonates and mixed ligand–metal complexes. A precursor to be used in the synthesis of a complex oxide film by the chemical vapour deposition process should comply with several requirements: first, the metal should be in the form of its oxide that is deposited on a support; second, it is desirable that all the volatile starting compounds belong to the same class. This will exclude transesterification reactions in the gas phase and violations of the stoichiometry of the resultant films.

Considerable reduction of temperatures for film preparation can be achieved by either modifying the entire technological process (which is not always possible) or substituting one class of volatile starting compounds for other classes. Metal alkoxides possess the lowest evaporation temperatures among all suitable starting compounds. Alkoxide ligands efficiently screen the central metal atom, which favours a significant increase in the volatility. Meanwhile, alkoxides of alkaline-earth metals are characterised by a rather low thermal stability, they are prone to polymerisation and are moisture-sensitive. In contrast, metal  $\beta$ -diketonates are evaporated and condensed from the gas phase at temperatures up to 300 °C. This temperature can be substantially lowered (to 100–150 °C) if mixed ligand–metal complexes or their adducts are employed. Among metal  $\beta$ -diketonates, compounds based on dipivaloylmethane (DPM) are used most often, these afford high-purity films. Only in two studies,<sup>17,18</sup> strontium hexafluoroacetylacetonate in combination with tetraglyme was used to yield films with fairly good ferroelectric properties.

The nature of the metal atom is of particular importance in the synthesis of ferroelectrics. As a rule, it is heavy metals, such as barium, lead or bismuth, that are used. As the chemistry of volatile compounds of alkaline-earth metals, zirconium and titanium is being developed, an increasing number of publications appear that describe new compounds with a broad set of interesting properties. The prevailing part of these studies is devoted to adducts of metal (primarily, zirconium or titanium)  $\beta$ -diketonate complexes with oxygen-containing organic ligands. The probability of the preparation of FETF with desirable properties is enhanced if the starting compound contains oxygen in an amount

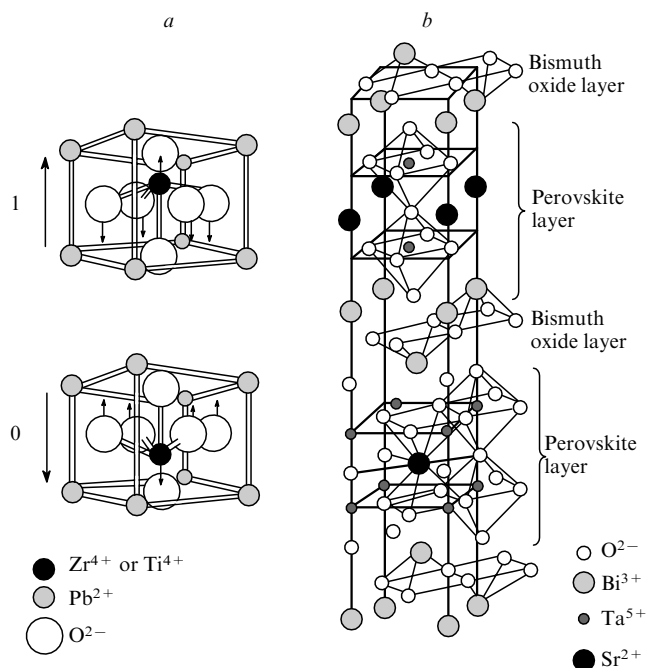


**Figure 2.** Unit cells of typical ferroelectric crystals.<sup>12</sup> (a) Cubic perovskite  $\text{Pb}(\text{Zr,Ti})\text{O}_3$ ; shifts of the  $\text{Zr}^{4+}$  or  $\text{Ti}^{4+}$  atoms upon polarisation are shown; vertical arrows to the left denote two states of the memory cell: the positive direction of polarisation is denoted as '1', the negative direction is denoted as '0'; (b) perovskite-like  $\text{SrBi}_2\text{Ta}_2\text{O}_9$  composed of alternating layers of perovskite and bismuth oxide.

sufficient for the formation of the target film with the perovskite stoichiometry (Fig. 2).<sup>12</sup> For this purpose, additional oxygen-containing ligands are often introduced into the adducts.

MOCVD has proven to be the method of choice for the synthesis of FETF from precursors belonging to these classes.

### 2. The sol–gel method for the preparation of films from solutions

The technology of the synthesis of films from solutions by the sol–gel method includes preparation of a sol followed by its conversion into a gel. In the first step, a highly disperse colloidal solution, *i.e.*, a sol, with a composition corresponding to that of the target film is formed. An increase in the concentration of the dispersed phase results in the formation of additional bonds between molecules in the solution, which favours gelation. Further increase in the volume concentration and surface area of the dispersed phase gradually changes the plastic properties of the gel. In order to deposit the compound in the form of a thin film, the gel is placed onto a rapidly spinning support for a few seconds. If a compound does not form a gel, its solution is just deposited on the support, which is further subject to annealing: first, to remove the solvent, then to decompose the organometallic starting compound, and finally to crystallise the target phase. Therefore, the method of decomposition of an organometallic precursor deposited from a solution (Metal–Organic Deposition, or MOD) represents a particular case of the sol–gel method as applied to thin film preparation.

In this method, metal hydroxides, salts of organic and inorganic acids and alkoxides are used as the starting compounds. Among salts of inorganic acids, chlorides are used most often. In the cases of metal alkoxides and carboxylates, the originally formed sol that is further annealed is highly homogeneous. It is advisable that hydrolysis of metal alkoxides and carboxylates be performed in aqueous and ethanolic solutions, respectively.

In a recently proposed method for the preparation of ferroelectric nanostructures with a crystallite size of 10 nm (see

Ref. 19), porous silicon produced by anodic etching in a 15% solution of HF in aqueous ethanol is used as a support. The porosity of the near-surface layer as high as 66% is reached at an etching rate of  $23 \text{ nm s}^{-1}$ . Wafers of porous silicon are immersed into a solution of starting compounds which enters the pores of the matrix. The material acquires ferroelectric properties after annealing.

### 3. Hydrothermal process

In the hydrothermal method, a support, starting compounds and a solvent are placed into an autoclave. The solubility of the starting compounds increases on heating under high pressures and a thin film of a metal oxide is deposited onto the support upon cooling of the mixture. It was shown that the resultant films possess poor ferroelectric properties, which limits the usage of this method.

Like in the sol–gel method, metal hydroxides, alkoxides and salts of inorganic and organic acids are used as the starting compounds in the hydrothermal method.

### 4. The Langmuir–Blodgett process

The Langmuir–Blodgett process includes three steps:

- creation of a monolayer of film-forming molecules on a water surface and formation of a compact floating film. The molecules within the film have a polar (or hydrophilic) group bound to a long hydrocarbon chain that is long enough to provide insolubility of the whole molecule in water (as in the case of, *e.g.*, stearic acid or octadecylaminomethyldehydrocarbotine,  $\text{n-C}_{18}\text{H}_{37}\text{NHCH}_2\text{C}_{26}\text{S}_2\text{H}_{11}$ );<sup>20</sup>
- formation of a layer of starting compounds (most often, salts of inorganic acids are used) on top of the monolayer film;
- transfer of the layer onto a support upon withdrawal of the latter from the solution.

The required thickness of the target film can be achieved by drying the film and repeating the procedure several times.

A distinctive feature of this method is the possibility to produce continuous films at extremely small thicknesses (tens of Å).

## III. Ferroelectric thin films for non-volatile memory elements

### 1. Tantalum pentaoxide films

Films of tantalum pentaoxide in the pure form are not used in non-volatile memory elements. A serious drawback of such films as compared to standard  $\text{SiO}_2$  films is larger leakage current. To correct for this, silicon supports are covered with a layer of silicon dioxide or silicon oxynitride prior to the deposition of a  $\text{Ta}_2\text{O}_5$  layer. The films can be produced using both sol–gel technology and the MOCVD method.<sup>21,22</sup> Metal alkoxides are used as the starting compounds in both cases (Table 1). The sol–gel technology is based on hydrolysis that is sometimes performed in the presence of an acidic catalyst, *e.g.*, HCl.<sup>30</sup> The sol is prepared at room temperature from a mixture of  $\text{Ta}(\text{OEt})_5$  and aqueous-ethanolic HCl. Titanium ethoxide  $\text{Ti}(\text{OEt})_4$  can be used as a dopant precursor in order to dope ferroelectric films of tantalum pentaoxide with titanium. The doping level is varied over the range from 8 mol.% to 46 mol.% with respect to  $\text{TiO}_2$ .<sup>30</sup> Following deposition, the film is annealed at 600–900 °C in an atmosphere of  $\text{N}_2\text{O}$ , which acts as an oxidant.

Typical conditions for the CVD deposition of  $\text{Ta}_2\text{O}_5$  films from organometallic precursors have been reported by Murawala *et al.*<sup>23</sup> by the example of tantalum pentaethoxide: the support temperature was 475 °C, the temperature of  $\text{Ta}(\text{OEt})_5$  deposition was 160–190 °C,  $\text{N}_2$  and  $\text{O}_2$  were used as a gas carrier and an oxidant, respectively, the rate of deposition was  $6.4 \text{ nm min}^{-1}$ . Rapid annealing at 700–900 °C afforded films with a specific electrical resistivity of  $10^{14}$ – $10^{15} \Omega \text{ cm}$ , a leakage current  $< 10^{-8} \text{ A cm}^{-2}$  at a voltage of 1.2 V and a break-down voltage not exceeding  $5 \text{ MV cm}^{-1}$ . These conditions allow preparation of films suitable for the manufacture of memory elements with a capacity of 256 MB.<sup>16,23,24</sup>

### 2. Films of yttrium–manganese double oxide ( $\text{YMnO}_3$ )

Films of  $\text{YMnO}_3$  can be synthesised both by the sol–gel and the CVD methods. In the former method, yttrium and manganese acetates were suggested as the most useful precursors.<sup>37–44</sup> Yttrium isopropoxide is also sometimes utilised. Ethanolic sol-

**Table 1.** Conditions of synthesis of ferroelectric thin films of  $\text{Ta}_2\text{O}_5$  and their properties.

| Starting compounds                                                                                           | Preparation method | Support                              | Process conditions     |                        |                        | Properties of FETF <sup>a</sup> |                                |           | Ref. |
|--------------------------------------------------------------------------------------------------------------|--------------------|--------------------------------------|------------------------|------------------------|------------------------|---------------------------------|--------------------------------|-----------|------|
|                                                                                                              |                    |                                      | $T_v / ^\circ\text{C}$ | $T_p / ^\circ\text{C}$ | $P / \text{Torr}$      | $\epsilon$                      | $I / \text{A cm}^{-2}$         | $n$       |      |
| $\text{Ta}(\text{OEt})_5$ , $\text{O}_2$                                                                     | CVD                | Si, $\text{Ta}_x\text{Si}_y\text{O}$ | —                      | 260, 700               | —                      | 38                              | —                              | —         | 22   |
| $\text{Ta}(\text{OEt})_5$ , $\text{O}_2$                                                                     | CVD                | n,p-Si                               | 160–190                | 475, 700, 900          | —                      | 25–38                           | —                              | —         | 23   |
| $\text{Ta}(\text{OEt})_5$ , $\text{O}_2$                                                                     | CVD                | p-Si(100)                            | —                      | 500, 700               | —                      | —                               | $10^{-10}$                     | —         | 24   |
| $\text{Ta}(\text{OEt})_5$ , $\text{N}_2$ , $\text{O}_2$ , $\text{O}_3$                                       | CVD                | Si, TiN                              | —                      | 400, 800               | —                      | 22–24                           | —                              | —         | 25   |
| $\text{Ta}(\text{OEt})_5$ , $\text{O}_2$                                                                     | CVD                | Pt/Ti/Si                             | 140–170                | 400                    | 0.4                    | 22–25                           | $2 \times 10^{-8}$             | —         | 26   |
| $\text{Ta}(\text{OEt})_5$ , AcOH, EtOH                                                                       | sol–gel            | quartz, glass                        | —                      | 150–450                | —                      | —                               | —                              | 1.78–1.97 | 27   |
| $\text{Ta}(\text{OEt})_5$ , $\text{O}_2$                                                                     | CVD                | Si                                   | —                      | —                      | —                      | 25 <sup>b</sup>                 | —                              | —         | 28   |
|                                                                                                              |                    |                                      |                        |                        |                        | 56–59 <sup>c</sup>              |                                |           |      |
| $\text{Ta}(\text{OEt})_5$ , $\text{O}_2$                                                                     | CVD                | Ru/Si                                | —                      | 400–700                | —                      | —                               | $10^{-8}$                      | —         | 29   |
| $\text{Ta}(\text{OEt})_5$ , HCl + $\text{H}_2\text{O}$ , $\text{Ti}(\text{OEt})_4$ (see <sup>d</sup> ), EtOH | sol–gel            | n-Si                                 | —                      | 600–900                | —                      | 25, 90                          | —                              | —         | 30   |
| $\text{Ta}(\text{OEt})_5$ , $\text{O}_2$ , $\text{O}_3$                                                      | CVD                | Si                                   | 130–240, 130–168       | 390, 800               | 1                      | 30.2                            | $10^{-8}$                      | —         | 31   |
| $\text{Ta}(\text{OEt})_5$ , $\text{O}_2$ , $\text{O}_3$                                                      | CVD                | Si                                   | —                      | 400                    | —                      | —                               | —                              | —         | 32   |
| $\text{Ta}(\text{OEt})_5$ , $\text{O}_2$ , $\text{O}_3$                                                      | CVD                | $\text{Si}_3\text{N}_4/\text{Si}$    | —                      | 300, 900               | —                      | —                               | —                              | —         | 33   |
| $\text{Ta}(\text{OEt})_5$ , Ar, $\text{O}_2$                                                                 | CVD                | $\text{Si}_3\text{N}_4/\text{Si}$    | —                      | 350, 600–800           | $(2–5) \times 10^{-3}$ | —                               | —                              | —         | 34   |
| $\text{Ta}(\text{OEt})_5$ , $\text{O}_2$ , $\text{N}_2\text{O}$                                              | CVD                | Si                                   | —                      | 400, 800               | —                      | —                               | —                              | —         | 35   |
| $\text{Ta}(\text{OEt})_5$ , $\text{N}_2$ , $\text{O}_2$                                                      | CVD                | Pt/Si                                | 140                    | 400, 550               | 3                      | 38                              | $8 \times 10^{-9}$ – $10^{-6}$ | —         | 36   |

<sup>a</sup>  $\epsilon$  is permittivity,  $I$  is the leakage current density,  $n$  is the refraction index. <sup>b</sup> Amorphous state. <sup>c</sup> Crystal. <sup>d</sup> Dopants.

utions of diethanolamine and 2-ethoxyethanol are typically used as solvents. The increase in the coordination number of yttrium upon introduction of an additional ligand (*i.e.*, diethanolamine) into the coordination sphere of the metal atom increases the solubility of the starting compounds in organic solvents. The preparation of the films from polymerised salts of organic acids is accompanied by intense gas evolution during thermolysis. With this regard, the temperature is typically raised stepwise, first to 300–400 °C, and then higher.<sup>40,42</sup> Platinum is normally used as the material of the top layer of the supports.

In the case of the CVD synthesis of  $\text{YMnO}_3$ , DPM-based organometallic compounds are used as the starting compounds. The temperature modes of the process are nearly the same.

Parameters of the methods for the preparation of thin films of  $\text{YMnO}_3$  and the physical properties of the resultant films are summarised in Table 2.

### 3. Films of barium and strontium titanates ( $\text{BaTiO}_3$ , $\text{SrTiO}_3$ ) and of their solid solutions

Different starting compounds are used for the synthesis of ferroelectric films of  $\text{BaTiO}_3$ ,  $\text{SrTiO}_3$  and of their solid solutions, depending on the method selected. Metal hydroxides and salts of various inorganic acids, *e.g.*, chlorides,<sup>57</sup> are employed in solution methods (Table 3). This approach excludes side chemical reactions yielding products with uncontrolled compositions during the synthesis of FETF. However, combination of different technologies for the preparation of oxide films with desired properties implies simultaneous use of several classes of compounds in a single process. Zeng *et al.*<sup>64</sup> proposed a new method based on titanium alkoxides and barium carboxylates which combines the sol–gel and hydrothermal methods. The gel employed for the preparation of a  $\text{BaTiO}_3$  film was then subjected to hydrothermal treatment. A solution was applied onto a support followed by

**Table 2.** Conditions of synthesis and properties of ferroelectric thin films of  $\text{YMnO}_3$ .

| Starting compounds                                                                                            | Method  | Solvent, oxidant                            | Support                                           | $T/^\circ\text{C}$    | $P/\text{Torr}$ | Properties of FETF |               |               |               |                       | Ref. |
|---------------------------------------------------------------------------------------------------------------|---------|---------------------------------------------|---------------------------------------------------|-----------------------|-----------------|--------------------|---------------|---------------|---------------|-----------------------|------|
|                                                                                                               |         |                                             |                                                   |                       |                 | $\varepsilon$      | $\tan \delta$ | $P_r$         | $E_c$         | $I$                   |      |
| $\text{Y}(\text{OAc})_3 \cdot 4 \text{H}_2\text{O}$ ,<br>$\text{Mn}(\text{OAc})_2 \cdot 4 \text{H}_2\text{O}$ | sol–gel | diethanolamine,<br>2-ethoxyethanol          | Pt/Ti/SiO <sub>2</sub> /Si                        | 125, 400,<br>700, 900 | —               | —                  | —             | —             | —             | —                     | 37   |
| $\text{Y}(\text{OAc})_3 \cdot 4 \text{H}_2\text{O}$ ,<br>$\text{Mn}(\text{OAc})_2 \cdot 4 \text{H}_2\text{O}$ | "       | diethanolamine,<br>2-ethoxyethanol,<br>EtOH | Pt/Ti/SiO <sub>2</sub> /Si                        | 125, 400,<br>700, 900 | —               | 20                 | 0.05          | —             | —             | —                     | 38   |
| $\text{Y}(\text{OAc})_3 \cdot 4 \text{H}_2\text{O}$ ,<br>$\text{Mn}(\text{OAc})_2 \cdot 4 \text{H}_2\text{O}$ | "       | MeOH                                        | Pt/Si                                             | 400,<br>450–800       | —               | 23(am),<br>30(cr)  | —             | 0.5,<br>6(cr) | 50,<br>20(cr) | —                     | 39   |
| $\text{Y}(\text{OAc})_3 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Mn}(\text{OAc})_2 \cdot 3 \text{H}_2\text{O}$ | "       | diethanolamine,<br>2-ethoxyethanol          | Pt/sapphire,<br>Y <sub>2</sub> O <sub>3</sub> /Si | 125, 150,<br>300, 800 | —               | —                  | —             | —             | —             | —                     | 40   |
| $\text{Y}(\text{C}_{10}\text{H}_{19}\text{CO}_2)_3$ ,<br>$\text{Mn}(\text{MeCp})(\text{CO})_3$                | CVD     | —                                           | p-Si(111)                                         | 165, 450,<br>600      | —               | 30                 | —             | —             | —             | —                     | 41   |
| $\text{Y}(\text{OAc})_3 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Mn}(\text{OAc})_2 \cdot 3 \text{H}_2\text{O}$ | sol–gel | diethanolamine,<br>2-ethoxyethanol          | Si                                                | 125, 150,<br>300, 700 | —               | —                  | —             | —             | —             | $10^{-7}$ – $10^{-6}$ | 42   |
| $\text{Y}(\text{OAc})_3 \cdot 4 \text{H}_2\text{O}$ ,<br>$\text{Mn}(\text{OAc})_2 \cdot 4 \text{H}_2\text{O}$ | "       | the same                                    | Pt/sapphire                                       | 125, 400,<br>800–900  | —               | —                  | —             | —             | —             | $10^{-6}$ – $10^{-2}$ | 43   |
| $\text{Y}(\text{C}_{10}\text{H}_{19}\text{CO}_2)_3$ ,<br>$\text{Mn}(\text{MeCp})(\text{CO})_3$                | CVD     | EtOH, O <sub>2</sub>                        | Y <sub>2</sub> O <sub>3</sub> /Si(100)            | 162, 500,<br>750, 850 | 3               | —                  | —             | —             | —             | $10^{-7}$ – $10^{-3}$ | 44   |

**Note.** Hereinafter,  $\tan \delta$  is the dielectric loss tangent,  $P_r$  is the residual polarisation ( $\mu\text{C cm}^{-2}$ ),  $E_c$  is the coercive force ( $\text{kV cm}^{-1}$ ),  $I$  is the leakage current density ( $\text{A cm}^{-2}$ ); the following notations are adopted: am is an amorphous layer, cr is a crystalline layer.

**Table 3.** Conditions of synthesis of ferroelectric thin films of  $\text{BaTiO}_3$ ,  $\text{SrTiO}_3$  and  $(\text{Ba},\text{Sr})\text{TiO}_3$  from metal hydroxides or salts of inorganic acids and their properties.

| Starting compounds                                                                                                | Method       | Solvent                                                | Support   | $T/^\circ\text{C}$           | Properties of FETF |               |       |       |     | Ref. |
|-------------------------------------------------------------------------------------------------------------------|--------------|--------------------------------------------------------|-----------|------------------------------|--------------------|---------------|-------|-------|-----|------|
|                                                                                                                   |              |                                                        |           |                              | $\varepsilon$      | $\tan \delta$ | $P_r$ | $E_c$ | $I$ |      |
| $\text{Ba}(\text{OH})_2 \cdot 8 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                              | sol–gel      | methanol                                               | —         | 600                          | —                  | —             | —     | —     | —   | 45   |
| $\text{Ba}(\text{OH})_2$ , Ti                                                                                     | hydrothermal | water                                                  | Ti/TiC/Si | 100–200                      | 450–500            | 0.04–0.1      | —     | —     | —   | 46   |
| $\text{SrCO}_3$ , $\text{Ti}(\text{OPr}^i)_4$                                                                     | MOD          | water, citric<br>acid, ethylene<br>glycol <sup>a</sup> | Si(111)   | 150,<br>250–455,<br>550–1000 | —                  | —             | —     | —     | —   | 47   |
| $\text{Ba}_2\text{Ti}_2\text{O}_5\text{CO}_3$ ,<br>$\text{Sr}_2\text{Ti}_2\text{O}_5\text{CO}_3$                  | MOD          | acetylacetone                                          | —         | —                            | —                  | —             | —     | —     | —   | 48   |
| $\text{Ba}(\text{OH})_2 \cdot 8 \text{H}_2\text{O}$ ,<br>$\text{Ba}(\text{AcO})_2$ ,<br>$\text{Ti}(\text{OEt})_4$ | hydrothermal | water, ethanol,<br>NH <sub>4</sub> OH                  | —         | 150                          | —                  | —             | —     | —     | —   | 49   |

Table 3 (continued).

| Starting compounds                                                                                                                                 | Method       | Solvent                                                         | Support                                                 | $T/^{\circ}\text{C}$ | Properties of FETF |               |       |       |           | Ref.      |
|----------------------------------------------------------------------------------------------------------------------------------------------------|--------------|-----------------------------------------------------------------|---------------------------------------------------------|----------------------|--------------------|---------------|-------|-------|-----------|-----------|
|                                                                                                                                                    |              |                                                                 |                                                         |                      | $\epsilon$         | $\tan \delta$ | $P_r$ | $E_c$ | $I$       |           |
| $\text{BaCl}_2 \cdot 2\text{H}_2\text{O}$ ,<br>$\text{NaOH}$ , Ti                                                                                  | hydrothermal | water                                                           | Ti                                                      | 240                  | 400–500            | —             | —     | —     | —         | 50        |
| $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ , Ti                                                                                            | "            | "                                                               | —                                                       | 110–200              | 200                | —             | —     | —     | —         | 51        |
| $\text{SrCO}_3$ , $\text{Ti}(\text{OPr}^i)_4$                                                                                                      | sol–gel      | water, citric acid,<br>ethylene glycol <sup>a</sup>             | Pt/Ti/SiO <sub>2</sub> /Si                              | 600                  | 250                | 0.01          | —     | 100   | $10^{-7}$ | 52,<br>53 |
| $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ ,<br>$\text{Sr}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{O}^n\text{Bu})_4$ | —            | water, acetic acid,<br>butanol, ethylene<br>glycol <sup>a</sup> | Pt/Si(100),<br>60/40                                    | 350,<br>600–800      | 492                | —             | 7.2   | 102.7 | —         | 54        |
| $\text{Ba}(\text{OH})_2$ ,<br>$\text{Sr}(\text{OH})_2$ , $\text{TiCl}_4$                                                                           | —            | water, NaOH                                                     | Pt/Si(100)<br>90/10                                     | 950                  | —                  | —             | —     | —     | —         | 55        |
| $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ ,<br>$\text{Sr}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OPr}^i)_4$        | —            | methanol                                                        | Pt/Ti/SiO <sub>2</sub> /Si,<br>70/30                    | 150, 650,<br>1275    | 600–800            | 0.04–0.07     | —     | —     | —         | 56        |
| $\text{BaCl}_2 \cdot 2\text{H}_2\text{O}$ ,<br>$\text{SrCl}_2 \cdot 2\text{H}_2\text{O}$ , $\text{TiCl}_4$                                         | —            | oxalic acid <sup>b</sup>                                        | —                                                       | 40–45                | —                  | —             | —     | —     | —         | 57        |
| $\text{BaCO}_3$ , $\text{SrCO}_3$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                                                                 | sol–gel      | citric acid <sup>b</sup>                                        | Pt/Ti/SiO <sub>2</sub> /Si                              | 700                  | —                  | —             | —     | —     | —         | 58        |
| $\text{Ba}(\text{OH})_2$ , $\text{Sr}(\text{OH})_2$ ,<br>$\text{TiO}_2$                                                                            | hydrothermal | water                                                           | Ti, Si/Ti,<br>Si/Pt/Ti, $\text{TiO}_2$                  | 100, 150,<br>200     | —                  | —             | —     | —     | —         | 59        |
| $\text{Ba}(\text{OH})_2$                                                                                                                           | "            | "                                                               | titanium<br>foil                                        | 100, 150,<br>215     | —                  | —             | —     | —     | —         | 60        |
| $\text{Ba}(\text{OH})_2$                                                                                                                           | "            | "                                                               | $\text{TiO}_2$                                          | 150, 200             | —                  | —             | —     | —     | —         | 61        |
| $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$                                                                                                 | "            | "                                                               | $\text{TiO}_2$ , $\text{SrTiO}_3$ ,<br>$\text{LaAlO}_3$ | 90, 150              | —                  | —             | —     | —     | —         | 62        |
| $\text{BaCO}_3$ , $\text{SrCO}_3$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                                                                 | sol–gel      | water, citric<br>acid, ethylene<br>glycol <sup>b</sup>          | Pt/Ti/SiO <sub>2</sub> /Si                              | 150, 600,<br>800     | —                  | —             | —     | —     | —         | 63        |

<sup>a</sup> It is used to initiate polycondensation. <sup>b</sup> Here and in other tables, saturated aqueous solution of acids.

annealing for 30 min at 150 °C, then the support with a film was placed in a teflon container, an aqueous solution of barium hydroxide was added and the container was loaded into an autoclave. Hydrothermal treatment lasted for 1–6 h at 100–200 °C. Crystalline films with a good surface morphology have been prepared by this procedure at such low temperatures.<sup>64</sup>

McKinley and Sandler<sup>25</sup> prepared thin films of nanocrystalline barium titanate on silicon supports from solutions of barium and titanium alkoxides using the sol–gel method. Hydrolysis was effected by water, whereas the polymerisation was carried out in a monoglyme solution. The process of gel formation proceeded very slowly at 20–22 °C. After deposition of the film onto the support, its polarisation curve was obtained and the stability of its dielectric properties over a temperature range from –85 to +200 °C was established.

McCormick and Slamovich<sup>65</sup> used titanium ethoxide for the preparation of barium titanate films. A mixture of titanium ethoxide, barium acetate and tetramethylammonium hydroxide in an alkaline medium (pH > 13) was heated in an autoclave to 150 °C at a rate of 3 °C min<sup>–1</sup>, at which temperature the hydrothermal synthesis lasted for 2 h. However, in addition to the films, an appreciable amount of powder was formed, which negatively affected the properties of the films.

Films with good dielectric properties were obtained<sup>47, 52, 53, 58</sup> by dissolving  $\text{SrCO}_3$  and  $\text{Ti}(\text{OPr}^i)_4$  in a mixture of citric acid and ethylene glycol (see Table 3) and annealing at 550–1000 °C following the solution deposition onto a support.

Thin films of  $\text{BaTiO}_3$ ,  $\text{SrTiO}_3$  and  $(\text{Ba,Sr})\text{TiO}_3$  were also prepared from the respective metal carboxylates (Tables 4 and 5). They were grown on titanium supports using barium acetate solutions. Films with grain sizes of ~50–340 nm were obtained in the temperature range 120–200 °C and a solution flow rate of 1–50 cm<sup>3</sup> min<sup>–1</sup>. The design of the reactor made it possible to supply the solution in a cyclic manner, which facilitated control over the process.<sup>45</sup> Films of  $\text{BaTiO}_3$  with high permittivities were prepared from organometallic precursors by spin-coating with subsequent annealing. Xu *et al.*<sup>66</sup> employed titanium alkoxide-carboxylate  $(\text{MeO})_2\text{Ti}(\text{n-C}_9\text{H}_{19}\text{CO}_2)_2$  and barium carboxylate  $\text{Ba}(\text{n-C}_9\text{H}_{19}\text{CO}_2)_2$  and xylene as a solvent. First, a layer with a thickness of 350 nm was deposited onto a silicon support that was spinning with a velocity of 1500 rpm and the coated support was then annealed at 500–800 °C for 1 h. The thickness of the film was increased to 4–8 µm by repeating the procedure. The resultant films with grain sizes of 0.034, 0.1 and 0.2 µm manifested permittivities of 200, 500 and 1200, respectively. The spontaneous polarisation of the films with grain size of 0.2 µm was 3 µC cm<sup>–2</sup> and  $\tan \delta = 0.1$  (at 1 MHz).

An interesting new modification of the sol–gel–hydrothermal technique for the preparation of thin films of  $\text{BaTiO}_3$  on silicon supports developed by Zeng *et al.*<sup>64</sup> has already been mentioned above. The gel used for the preparation of the film served as a precursor that was subjected to hydrothermal treatment,  $\text{Ba}(\text{AcO})_2$  and  $\text{Ti}(\text{O}^n\text{Bu})_4$  being the starting compounds (see Table 4).

**Table 4.** Conditions of synthesis of ferroelectric thin films of BaTiO<sub>3</sub>, SrTiO<sub>3</sub> and (Ba,Sr)TiO<sub>3</sub> from salts of carboxylic acids and their properties.

| Starting compounds                                                                                                                                                                 | Method            | Solvent                                            | Support                                                                                 | T / °C                       | Properties of FETF |               |       |       |                  | Ref. |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------------------------------------------|-----------------------------------------------------------------------------------------|------------------------------|--------------------|---------------|-------|-------|------------------|------|
|                                                                                                                                                                                    |                   |                                                    |                                                                                         |                              | $\epsilon$         | $\tan \delta$ | $P_r$ | $E_c$ | $I$              |      |
| Ba(n-C <sub>9</sub> H <sub>19</sub> CO <sub>2</sub> ) <sub>2</sub> ,<br>Ti(n-C <sub>9</sub> H <sub>19</sub> CO <sub>2</sub> ) <sub>2</sub> (MeO) <sub>2</sub>                      | sol–gel           | xylene                                             | —                                                                                       | 500–800                      | 200–1200           | —             | —     | —     | —                | 66   |
| Sr(AaO) <sub>2</sub> , Ti(OBu <sup>n</sup> ) <sub>4</sub>                                                                                                                          | MOD               | acetic acid,<br>propanol,<br>acetylacetone         | Pt/Ti/SiO <sub>2</sub> /Si                                                              | 750–800                      | —                  | —             | —     | —     | —                | 67   |
| Ba(AcO) <sub>2</sub> , Ti(AcO) <sub>4</sub>                                                                                                                                        | MOD               | —                                                  | t/Si, SiO <sub>2</sub>                                                                  | 550–700                      | 255                | 0.025         | 2.2   | 25    | —                | 68   |
| Ba(AcO) <sub>2</sub> , Ti(OPr <sup>i</sup> ) <sub>4</sub>                                                                                                                          | sol–gel           | acetic acid,<br>2-methoxyethanol                   | Pt/Ti/SiO <sub>2</sub> /Si                                                              | 350, 700                     | 370                | —             | 3.2   | 30    | —                | 69   |
| Ba(AcO) <sub>2</sub> , Ti(AcO) <sub>4</sub>                                                                                                                                        | hydro-<br>thermal | water                                              | Ti                                                                                      | 120–200                      | —                  | —             | —     | —     | —                | 70   |
| Ba(OH) <sub>2</sub> · 8 H <sub>2</sub> O,<br>Ba(AcO) <sub>2</sub> , Ti(OEt) <sub>4</sub>                                                                                           | "                 | water, ethanol,<br>NH <sub>4</sub> OH              | —                                                                                       | 150                          | —                  | —             | —     | —     | —                | 49   |
| Ba(AcO) <sub>2</sub> , Ti(OBu <sup>n</sup> ) <sub>4</sub>                                                                                                                          | "                 | water                                              | —                                                                                       | 100–200                      | —                  | —             | —     | —     | —                | 64   |
| Ba, Ti naphthenates                                                                                                                                                                | MOD               | toluene                                            | SrTiO <sub>3</sub>                                                                      | 470, 850                     | 230                | —             | —     | —     | —                | 71   |
| Ba(n-C <sub>7</sub> H <sub>15</sub> CO <sub>2</sub> ) <sub>2</sub> ,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub>                                                                         |                   | ethanol,<br>acetylacetone                          | Si                                                                                      | 400                          | 16–17              | 0.015         | —     | —     | —                | 72   |
| Sr(AcO) <sub>2</sub> , Ti(OBu <sup>n</sup> ) <sub>4</sub>                                                                                                                          | MOD               | acetylacetone,<br>acetic acid,<br>2-methoxyethanol | LaNiO <sub>3</sub> /<br>(La,Sr)CoO <sub>3</sub> ,<br>(La,Sr)MnO <sub>3</sub> /<br>Pt/Si | 350, 750                     | —                  | —             | —     | —     | —                | 73   |
| Sr(AcO) <sub>2</sub> , Ti(OEt) <sub>4</sub>                                                                                                                                        | sol–gel           | acetic acid,<br>2-methoxyethanol                   | Au/BaTiO <sub>3</sub> /<br>InP                                                          | —                            | —                  | —             | —     | —     | —                | 74   |
| Ba, Ti naphthenates                                                                                                                                                                | MOD               | toluene                                            | LaAlO <sub>3</sub>                                                                      | 470, 950                     | —                  | —             | —     | —     | —                | 75   |
| Ba(n-C <sub>7</sub> H <sub>15</sub> CO <sub>2</sub> ) <sub>2</sub> ,<br>Ti(DPM) <sub>2</sub> (OMe) <sub>2</sub>                                                                    | CVD               | —                                                  | —                                                                                       | —                            | —                  | —             | —     | —     | —                | 76   |
| Ba(n-C <sub>7</sub> H <sub>15</sub> CO <sub>2</sub> ) <sub>2</sub> ,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub>                                                                         | CVD               | —                                                  | p-Si(100)                                                                               | 500, 550                     | 250                | 0.1           | —     | —     | 10 <sup>−5</sup> | 77   |
| Ba(AcO) <sub>2</sub> ,<br>Sr(AcO) <sub>2</sub> · 0.5 H <sub>2</sub> O,<br>Ti(OBu <sup>n</sup> ) <sub>4</sub>                                                                       | sol–gel           | acetic acid,<br>methanol                           | Pt/Ti/SiO <sub>2</sub> /Si                                                              | 250,<br>390–450,<br>600, 730 | —                  | —             | —     | —     | —                | 78   |
| Ba(AcO) <sub>2</sub> ,<br>Sr(AcO) <sub>2</sub> ,<br>Ti(OBu <sup>n</sup> ) <sub>4</sub>                                                                                             | "                 | acetic acid,<br>2-methoxyethanol                   | LaAlO <sub>3</sub>                                                                      | 750, 1100                    | —                  | —             | —     | —     | —                | 79   |
| Ba(n-C <sub>7</sub> H <sub>15</sub> CO <sub>2</sub> ) <sub>2</sub> ,<br>Sr(n-C <sub>7</sub> H <sub>15</sub> CO <sub>2</sub> ) <sub>2</sub> ,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub> | "                 | ethanol,<br>acetylacetone                          | Pt/SiO <sub>2</sub> /Si                                                                 | 150, 350,<br>450–700         | 592                | 0.028         | —     | —     | —                | 80   |
| Ba(AcO) <sub>2</sub> ,<br>Sr(AcO) <sub>2</sub> ,<br>Ti(OBu <sup>n</sup> ) <sub>4</sub>                                                                                             | "                 | acetylacetone                                      | Pt/Ti/SiO <sub>2</sub> /Si                                                              | 750                          | —                  | —             | —     | —     | —                | 81   |
| Ba(AcO) <sub>2</sub> ,<br>Ti(OAlk) <sub>4</sub>                                                                                                                                    | "                 | acetic acid,<br>propan-2-ol,<br>ethanol            | Pt                                                                                      | 600, 800,<br>1000            | 167–500            | 0.015–0.06    | 3.2   | 14    | —                | 82   |

Cole *et al.*<sup>87</sup> reported the following physical characteristics of the films prepared in this way:  $\epsilon = 205–450$ ,  $\tan \delta = 0.09–0.013$ ,  $I = 2 \times 10^{-11}–10^{-10}$  A cm<sup>−2</sup> (see Table 5).

Thin films of BaTiO<sub>3</sub> and SrTiO<sub>3</sub> can also be prepared from the gas phase.<sup>93,94</sup> In this case, volatile metal  $\beta$ -diketonates or adducts based on them are used as starting compounds. This approach is also applicable for solid solutions (Ba,Sr)TiO<sub>3</sub>. The starting compounds are evaporated and condensed onto a support at temperatures up to 300 °C. For the (Ba,Sr)TiO<sub>3</sub> films, the deposition temperature was significantly (by almost 100–150 °C) reduced, which did not deteriorate the properties of the resultant films (Table 6). The best results were achieved by Fitsilis *et al.*<sup>114</sup>

#### 4. Films of lead titanate (PbTiO<sub>3</sub>)

Films of PbTiO<sub>3</sub> with good ferroelectric properties were synthesised by solution methods from lead and titanium naphthenates (Table 7). The films grown on a TiSi<sub>2</sub> support possessed high electroconductivity, which made possible their use as bottom plate electrodes in capacitors.<sup>121</sup>

Preparation of PbTiO<sub>3</sub> from lead carboxylates using diols HOC<sub>n</sub>H<sub>2n</sub>OH ( $n = 3–5$ ), *i.e.*, propane-1,3-diol, butane-1,4-diol and pentane-1,5-diol, as solvents was reported by Pardo *et al.*<sup>123</sup> Exothermic effects at temperature ranges of 255–261 °C, 311–326 °C, 449–467 °C and 500–525 °C were detected by complex thermal analysis. These effects are due to oxidative

**Table 5.** Parameters of the solution synthesis and properties of ferroelectric thin films of (Ba,Sr)TiO<sub>3</sub>.

| Starting compounds                                                                                                                                                                                                    | Solvent                                                | Support                                   | $T/^{\circ}\text{C}$ | Properties of FETF |               |       |       |                                | Ref. |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|-------------------------------------------|----------------------|--------------------|---------------|-------|-------|--------------------------------|------|
|                                                                                                                                                                                                                       |                                                        |                                           |                      | $\varepsilon$      | $\tan \delta$ | $P_r$ | $E_c$ | $I$                            |      |
| Ba(AcO) <sub>2</sub> ,<br>Sr(AcO) <sub>2</sub> ,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub>                                                                                                                                | ethanol, water,<br>acetic acid,<br>pentane-2,4-dione   | Ba/Sr                                     | —                    | 198–224            | 0.04          | —     | —     | —                              | 83   |
| Ba(n-C <sub>7</sub> H <sub>15</sub> CO <sub>2</sub> ) <sub>2</sub> ,<br>Sr(n-C <sub>7</sub> H <sub>15</sub> CO <sub>2</sub> ) <sub>2</sub> ,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub> Zr(OPr <sup>i</sup> ) <sub>4</sub> | xylene                                                 | Pt/Ti/SiO <sub>2</sub> /Si                | 750                  | 1000               | —             | —     | 300   | $3.47 \times 10^{-7}$          | 84   |
| Ba(AcO) <sub>2</sub> , Sr(AcO) <sub>2</sub> ,<br>Ti(OBu <sup>n</sup> ) <sub>4</sub>                                                                                                                                   | acetic acid,<br>2-methoxyethanol                       | Pt/Si, 70/30                              | 300, 750             | 100–280,<br>563    | 0.02–0.04     | —     | —     | —                              | 85   |
| Ba(AcO) <sub>2</sub> , Sr(AcO) <sub>2</sub> ,<br>Ti(OBu <sup>n</sup> ) <sub>4</sub>                                                                                                                                   | acetic acid,<br>acetylacetone                          | Pt/Ti/SiO <sub>2</sub> /Si                | 350, 750             | —                  | —             | 3.5   | 86    | —                              | 86   |
| Ba(AcO) <sub>2</sub> , Sr(AcO) <sub>2</sub> ,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub>                                                                                                                                   | —                                                      | Pt                                        | 350, 750             | 205–450            | 0.09–0.013    | —     | —     | $2 \times 10^{-11} - 10^{-10}$ | 87   |
| Ba(AcO) <sub>2</sub> , Sr(AcO) <sub>2</sub> ,<br>Ti(OBu <sup>n</sup> ) <sub>4</sub>                                                                                                                                   | 2-methoxyethanol,<br>acetylacetone                     | Pt/Ti/SiO <sub>2</sub> /Si                | 400, 750             | —                  | —             | —     | —     | —                              | 88   |
| BaCl <sub>2</sub> · 2 H <sub>2</sub> O,<br>SrCl <sub>2</sub> · 2 H <sub>2</sub> O, TiCl <sub>4</sub>                                                                                                                  | water                                                  | —                                         | 40–45                | —                  | —             | —     | —     | —                              | 57   |
| Ba(AcO) <sub>2</sub> , Sr(AcO) <sub>2</sub> ,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub>                                                                                                                                   | ethylene glycol                                        | Pt/TiO <sub>2</sub> /SiO <sub>2</sub> /Si | 400,<br>550–750      | —                  | —             | —     | —     | —                              | 89   |
| Ba(n-C <sub>7</sub> H <sub>15</sub> CO <sub>2</sub> ) <sub>2</sub> ,<br>Sr(n-C <sub>7</sub> H <sub>15</sub> CO <sub>2</sub> ) <sub>2</sub> ,<br>Ti(n-C <sub>7</sub> H <sub>15</sub> CO <sub>2</sub> ) <sub>2</sub>    | 2-ethylhexanoic<br>acid, 2-methoxy-<br>ethanol, xylene | Pt/TiO <sub>2</sub> /SiO <sub>2</sub> /Si | 700                  | —                  | —             | —     | —     | —                              | 90   |
| Ba(n-C <sub>7</sub> H <sub>15</sub> CO <sub>2</sub> ) <sub>2</sub> ,<br>Sr(n-C <sub>7</sub> H <sub>15</sub> CO <sub>2</sub> ) <sub>2</sub> ,<br>Ti(OBu <sup>n</sup> ) <sub>2</sub> (acac) <sub>2</sub>                | 2-ethylhexanoic<br>acid                                | Pt/Si                                     | 250–800              | —                  | —             | —     | —     | —                              | 91   |
| Ba(AcO) <sub>2</sub> ,<br>Zr(OPr <sup>i</sup> ) <sub>4</sub> , Ti(OPr <sup>i</sup> ) <sub>4</sub>                                                                                                                     | acetic acid,<br>ethylene glycol                        | LaAlO <sub>3</sub>                        | 600, 1000            | —                  | —             | —     | —     | —                              | 92   |

**Table 6.** Conditions of MOCVD synthesis of ferroelectric thin films of (Ba,Sr)TiO<sub>3</sub> solid solutions from metal β-diketonates with various ligands and their properties.

| Starting compounds                                                                                                                                                                                                     | Support                                       | Process conditions      |                        |                 | Properties of FETF |               |                      | Ref. |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-------------------------|------------------------|-----------------|--------------------|---------------|----------------------|------|
|                                                                                                                                                                                                                        |                                               | $T_v/^{\circ}\text{C}$  | $T_p/^{\circ}\text{C}$ | $P/\text{Torr}$ | $\varepsilon$      | $\tan \delta$ | $I$                  |      |
| Ba(DPM) <sub>2</sub> , Sr(DPM) <sub>2</sub> ,<br>TiO(DPM) <sub>2</sub> , THF                                                                                                                                           | Pt/SiO <sub>2</sub> /Si                       | 250                     | 480                    | 10              | 230                | 0.013         | $6.7 \times 10^{-6}$ | 95   |
| Ba(DPM) <sub>2</sub> , Sr(DPM) <sub>2</sub> ,<br>TiO(DPM) <sub>2</sub> , THF                                                                                                                                           | RuO <sub>2</sub> /Si, Pt/SiO <sub>2</sub> /Si | 250                     | 420                    | 1.5             | 190                | 0.018         | $4.6 \times 10^{-8}$ | 96   |
| Ba(DPM) <sub>2</sub> , Sr(DPM) <sub>2</sub> ,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub>                                                                                                                                    | Pt/Ti/SiO <sub>2</sub> /Si                    | 186–204,<br>174–188, 36 | 450, 500               | 7               | —                  | —             | $4.6 \times 10^{-7}$ | 97   |
| Ba(DPM) <sub>2</sub> , Sr(DPM) <sub>2</sub> ,<br>TiO(DPM) <sub>2</sub> , THF                                                                                                                                           | Ru/Si, Ru/TiN/Ti/Si                           | 250                     | 420                    | 1.5             | —                  | —             | —                    | 98   |
| Ba(DPM) <sub>2</sub> · (C <sub>8</sub> H <sub>12</sub> N <sub>5</sub> ) <sub>2</sub> ,<br>Sr(DPM) <sub>2</sub> · (C <sub>6</sub> H <sub>18</sub> N <sub>4</sub> ) <sub>2</sub> ,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub> | SrTiO <sub>3</sub> , MgO                      | —                       | 750–800                | —               | —                  | —             | —                    | 99   |
| Ba(DPM) <sub>2</sub> · TG,<br>Sr(DPM) <sub>2</sub> · TG,<br>Ti(DPM) <sub>2</sub> (OPr <sup>i</sup> ) <sub>2</sub> ,<br>Bu <sup>n</sup> OAc                                                                             | Pt/SiO <sub>2</sub> /Si                       | —                       | 420–570                | —               | —                  | —             | —                    | 100  |
| Ba(DPM) <sub>2</sub> · (phen) <sub>2</sub> ,<br>Sr(DPM) <sub>2</sub> · (phen) <sub>2</sub> , Ti(OPr <sup>i</sup> ) <sub>4</sub>                                                                                        | Pt/MgO                                        | 215–220,<br>200–205, 35 | 650                    | —               | 400–590            | —             | $10^{-8} - 10^{-7}$  | 101  |
| Ba(DPM) <sub>2</sub> , Sr(DPM) <sub>2</sub> ,<br>TiO(DPM) <sub>2</sub>                                                                                                                                                 | —                                             | —                       | 420                    | 1.5             | 200                | —             | $2 \times 10^{-7}$   | 102  |

**Table 6** (continued).

| Starting compounds                                                                                                                                                                                                                | Support                                              | Process conditions              |                        |                   | Properties of FETF |               |                      | Ref.        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|---------------------------------|------------------------|-------------------|--------------------|---------------|----------------------|-------------|
|                                                                                                                                                                                                                                   |                                                      | $T_v / ^\circ\text{C}$          | $T_p / ^\circ\text{C}$ | $P / \text{Torr}$ | $\varepsilon$      | $\tan \delta$ | $I$                  |             |
| Ba(DPM) <sub>2</sub> , Sr(DPM) <sub>2</sub> ,<br>Ti(DPM) <sub>2</sub> (OPr <sup>i</sup> ) <sub>2</sub>                                                                                                                            | Pt/Si                                                | 215–250,<br>215–230,<br>130–200 | 400–500                | 200               | —                  | —             | —                    | 103         |
| Ba(HFA) <sub>2</sub> ·TG,<br>Sr(HFA) <sub>2</sub> ·TG, Ti(OPr <sup>i</sup> ) <sub>4</sub>                                                                                                                                         | —                                                    | —                               | 650–800                | —                 | —                  | —             | —                    | 104         |
| Ba(DPM) <sub>2</sub> , Sr(DPM) <sub>2</sub> ,<br>Ti(DPM) <sub>2</sub> (OPr <sup>i</sup> ) <sub>2</sub>                                                                                                                            | —                                                    | —                               | 480–580                | —                 | 260–290            | —             | —                    | 105,<br>106 |
| Ba(DPM) <sub>2</sub> ·TG,<br>Sr(DPM) <sub>2</sub> ·TG, Ti(OPr <sup>i</sup> ) <sub>4</sub>                                                                                                                                         | Pt/RuO <sub>2</sub> /Ta/<br>/Si/SiO <sub>2</sub> /Si | 190,<br>190, 20                 | 550                    | 2                 | 240                | 0.01          | $4.0 \times 10^{-7}$ | 107         |
| Ba(DPM) <sub>2</sub> ·(phen) <sub>2</sub> ,<br>Sr(DPM) <sub>2</sub> ·(phen) <sub>2</sub> , Ti(OPr <sup>i</sup> ) <sub>4</sub>                                                                                                     | Pt/MgO                                               | 210–220,<br>195–205, 35         | 650                    | 130–670           | 1000               | —             | $2.3 \times 10^{-9}$ | 108         |
| Ba(DPM) <sub>2</sub> ·COT,<br>Sr(DPM) <sub>2</sub> ·COT,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub>                                                                                                                                    | SrTiO <sub>3</sub>                                   | 115, 138, 20                    | 620                    | 1.3–1.4           | 400                | 0.02          | —                    | 109         |
| Ba(DPM) <sub>2</sub> , Sr(DPM) <sub>2</sub> ,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub>                                                                                                                                               | RuO <sub>2</sub> /Ru                                 | 175–205<br>175–205,<br>20–36    | 550                    | —                 | 80–170             | —             | —                    | 110         |
| Ba(DPM) <sub>2</sub> ·(TEP) <sub>2</sub> ,<br>Sr(DPM) <sub>2</sub> ·(TEP) <sub>2</sub> ,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub>                                                                                                    | Pt/MgO                                               | 135,<br>105–110, 40             | 650                    | 1.33              | 600–1200           | —             | —                    | 111         |
| Ba(DPM) <sub>2</sub> , Sr(DPM) <sub>2</sub> ,<br>Ti(DPM) <sub>2</sub> (OBu <sup>t</sup> ) <sub>2</sub> , THF                                                                                                                      | —                                                    | —                               | 250–650                | —                 | —                  | —             | —                    | 112         |
| Ba(DPM) <sub>2</sub> ·TG,<br>Sr(HFA) <sub>2</sub> ·TG,<br>Ti(DPM) <sub>2</sub> (OPr <sup>i</sup> ) <sub>2</sub>                                                                                                                   | —                                                    | —                               | 440                    | 1.3               | —                  | —             | —                    | 113         |
| Ba(DPM) <sub>2</sub> , Sr(DPM) <sub>2</sub> ,<br>Ti(DPM) <sub>2</sub> (OPr <sup>i</sup> ) <sub>2</sub>                                                                                                                            | Pt/Si                                                | —                               | 565–655                | —                 | 185–208            | 0.002         | $10^{-10}$           | 114         |
| Ba(DPM) <sub>2</sub> , Sr(DPM) <sub>2</sub> ,<br>Ti(DPM) <sub>2</sub> (OBu <sup>t</sup> ) <sub>2</sub> , THF                                                                                                                      | —                                                    | —                               | 250–640                | 10                | —                  | —             | —                    | 115         |
| Ba(DPM) <sub>2</sub> ·PA,<br>Sr(DPM) <sub>2</sub> ·PA,<br>Ti(DPM) <sub>2</sub> (OPr <sup>i</sup> ) <sub>2</sub>                                                                                                                   | —                                                    | 250<br>250                      | 600                    | 1.4               | 260                | 0.003         | —                    | 116         |
| Ba[(R <sup>1</sup> R <sup>2</sup> )C(OX)COHCOR <sup>3</sup> ] <sub>2</sub> (see <sup>a</sup> ),<br>Ti(DPM) <sub>2</sub> (OPr <sup>i</sup> ) <sub>2</sub> , Sr(DPM) <sub>2</sub> ,<br>TiO(DPM) <sub>2</sub> , Sr(DPM) <sub>2</sub> | SiO <sub>2</sub>                                     | 100, 250,<br>160, 250           | 127, 550,<br>650       | —                 | —                  | —             | —                    | 117         |
| Ba(DPM) <sub>2</sub> ·(PMDT),<br>Sr(DPM) <sub>2</sub> ·(PMDT),<br>Ti(DPM) <sub>2</sub> (OPr <sup>i</sup> ) <sub>2</sub>                                                                                                           | Ru/SiO <sub>2</sub> /Si                              | —                               | 700                    | 2                 | —                  | 0.006         | $2 \times 10^{-8}$   | 118         |

**Note.** The following notations are adopted: COT is cyclooctatetraene, TEP is tetraethylenepentamine, HFA is hexafluoroacetylacetone, TG is tetraglyme, PA is a polyamine, PMDT is pentamethyldiethylenetriamine.

<sup>a</sup> X = OMe, R<sup>1</sup> = Me, R<sup>2</sup> = Me, Bu<sup>i</sup>, Bu<sup>t</sup>, n-C<sub>6</sub>H<sub>13</sub>, R<sup>3</sup> = Pr<sup>i</sup>, Bu<sup>t</sup>, hexan-2-yl; R<sup>1</sup> = R<sup>2</sup> = —(CH<sub>2</sub>)<sub>5</sub>—, R<sup>3</sup> = Ph; X = H, R<sup>1</sup> = Pr<sup>i</sup>, R<sup>2</sup> = H, R<sup>3</sup> = Bu<sup>t</sup>; R<sup>1</sup> = R<sup>2</sup> = Me, R<sup>3</sup> = Ph; R<sup>1</sup> = R<sup>2</sup> = H, R<sup>3</sup> = Ph; R<sup>1</sup> = Bu<sup>t</sup>, R<sup>2</sup> = H, R<sup>3</sup> = Bu<sup>t</sup>.

**Table 7.** Conditions of synthesis of ferroelectric thin films of PbTiO<sub>3</sub> from metal carboxylates and their properties.

| Starting compounds                                                              | Method   | Solvent          | Support                                                          | $T / ^\circ\text{C}$ | Properties of FETF |               |       |       | Ref. |
|---------------------------------------------------------------------------------|----------|------------------|------------------------------------------------------------------|----------------------|--------------------|---------------|-------|-------|------|
|                                                                                 |          |                  |                                                                  |                      | $\varepsilon$      | $\tan \delta$ | $P_r$ | $E_c$ |      |
| Pb(AcO) <sub>2</sub> ·3 H <sub>2</sub> O,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub> | sol–gel  | 2-methoxyethanol | Pt/SiO <sub>2</sub> /Si, Al <sub>2</sub> O <sub>3</sub> ,<br>MgO | 750–800              | 250–300            | —             | —     | —     | 119  |
| Pb(AcO) <sub>2</sub> ·3 H <sub>2</sub> O<br>Ti(OPr <sup>i</sup> ) <sub>4</sub>  | the same | 2-methoxyethanol | SiO <sub>2</sub> , SrTiO <sub>3</sub>                            | 125, 330,<br>550     | —                  | —             | 3.5   | 50    | 120  |
| Pb,Ti naphthenates                                                              | "        | naphthenic acid  | TiSi <sub>2</sub> /Si                                            | —                    | —                  | —             | 16.0  | 52.9  | 121  |

Table 7 (continued).

| Starting compounds                                                                                                      | Method                | Solvent                                             | Support                                                          | $T/^{\circ}\text{C}$    | Properties of FETF |               |       |        | Ref.        |
|-------------------------------------------------------------------------------------------------------------------------|-----------------------|-----------------------------------------------------|------------------------------------------------------------------|-------------------------|--------------------|---------------|-------|--------|-------------|
|                                                                                                                         |                       |                                                     |                                                                  |                         | $\epsilon$         | $\tan \delta$ | $P_r$ | $E_c$  |             |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                   | sol–gel               | propan-2-ol,<br>diethanolamine                      | $\text{In}_2\text{O}_3/\text{Sn}/\text{SiO}_2$                   | 110,<br>600–700         | —                  | —             | —     | —      | 122         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OPr}^i)_2(\text{acac})_2$                    | the same              | propane-1,3-diol                                    | $\text{Si}(100)$                                                 | 350–600                 | —                  | —             | —     | —      | 123         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OPr}^i)_4$ , $\text{Al}(\text{OPr}^n)_3$     | "                     | 2-methoxyethanol                                    | Si                                                               | 520,<br>550–700         | 356                | —             | 9     | 84     | 124         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                   | "                     | 2-methoxyethanol,<br>acetylacetone                  | $\text{Pt}/\text{MgO}$ , $\text{Si}(100)$                        | 360, 575                | —                  | —             | —     | —      | 125         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OPr}^i)_2(\text{acac})_2$                    | "                     | propane-1,3-diol                                    | $\text{TiO}_2/\text{SiO}_2/\text{Si}$ ,<br>$\text{Pt}/\text{Si}$ | 350, 650                | —                  | —             | —     | —      | 126,<br>127 |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OBu})_4$                                     | "                     | 2-methoxyethanol                                    | $\text{Pt}/\text{Ti}/\text{Si}$                                  | 70, 120,<br>300, 600    | —                  | —             | —     | —      | 128         |
| $\text{PbCl}_2$ , $n\text{-C}_{17}\text{H}_{35}\text{CO}_2\text{H}$ ,<br>$\text{Ti}(\text{OH})_2(\text{AmL})_2$         | Langmuir–<br>Blodgett | stearic acid,<br>chloroform                         | —                                                                | —                       | —                  | —             | —     | —      | 129         |
| $\text{PbCl}_2$ , $n\text{-C}_{17}\text{H}_{35}\text{CO}_2\text{H}$ ,<br>$\text{K}_2\text{TiO}(\text{C}_2\text{O}_4)_2$ | the same              | stearic acid,<br>chloroform, $\text{NH}_4\text{OH}$ | —                                                                | 500, 700                | —                  | —             | —     | —      | 130         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OBu})_4$                                     | MOD                   | 2-methoxyethanol                                    | $\text{Pt}/\text{TiO}_2/\text{Si}$                               | 350, 600                | —                  | —             | —     | —      | 131         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                   | sol–gel               | acetic acid                                         | $\text{Pt}/\text{TiO}_x/\text{SiO}_2/\text{Si}$                  | 110, 450,<br>650        | 109                | —             | —     | —      | 132         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ , $\text{PbO}$                                                     | the same              | 2-methoxyethanol                                    | —                                                                | 550, 600                | —                  | —             | —     | —      | 133         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                   | "                     | 2-methoxyethanol,<br>ethylene glycol                | —                                                                | 600                     | 90–120             | —             | —     | —      | 134         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                   | "                     | citric acid, ethylene<br>glycol                     | $\text{Pt}/\text{Ti}/\text{SiO}_2/\text{Si}$                     | 60–70, 150,<br>350, 500 | 570                | —             | 13.62 | 121.43 | 135         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                   | "                     | the same                                            | $\text{Pt}/\text{Ti}/\text{SiO}_2/\text{Si}$                     | 80–90, 150,<br>400, 700 | 457                | 0.03          | 17    | 75     | 136         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OBu})_4$ , $\text{Ba}(\text{AcO})_2$         | "                     | acetic acid,<br>2-methoxyethanol                    | $\text{Pt}/\text{Si}$ , quartz                                   | 300, 650                | 118                | —             | 12    | 65     | 137         |

**Note.** The following notations are adopted: AmL is  $\text{MeCH}(\text{O})\text{CO}_2\text{NH}_4$ , EDTA is ethylenediaminetetraacetate.

processes and thermodestruction of the starting compounds. The films prepared from solutions in the diol with  $n = 3$  revealed a homogeneous microstructure, whereas those prepared from solutions in higher diols ( $n = 4$  and 5) were heterogeneous. With a decrease in the thickness of the  $\text{PbTiO}_3$  films, their ferroelectric properties degraded. This was related to the oxygen vacancies that diffuse from the film surface along the grain boundaries into the bulk. In order to compensate for this process, Iijma and Sanada<sup>124</sup> replaced part of titanium ions in  $\text{PbTiO}_3$  by aluminium. Films with the composition  $\text{Pb}(\text{Ti}_{0.85}\text{Al}_{0.15})\text{O}_{3-x}$  and a thickness of 0.14  $\mu\text{m}$  were prepared in air by the sol–gel method (the annealing temperature was  $\sim 700^{\circ}\text{C}$ ) from solutions of lead acetate trihydrate, titanium tetraisopropoxide and aluminium triisopropoxide in 2-methoxyethanol. The ferroelectric properties of the resultant films as a function of the annealing temperature were investigated.

Low temperature of the hydrothermal method for the synthesis of  $\text{PbTiO}_3$  films makes it attractive.<sup>138–140</sup> However, no high-quality films suitable for use in devices with non-volatile memory elements have been produced so far by this method. Sugai *et al.*<sup>129, 130</sup> have attempted to prepare ferroelectric ultrathin layers of  $\text{PbTiO}_3$  by the Langmuir–Blodgett method (see Table 7) using lead dichloride and titanium bis(ammonium lactate) or potassium titanium oxalate as starting compounds and a solution of stearic acid in chloroform as a solvent. Monolayer films were prepared,

which were irradiated with UV light and then annealed. As a result, a dense film with a thickness of 0.2 nm was obtained. Ferroelectric films with thicknesses of 30–50 nm possessing a perovskite-like structure dominantly exposing (111), (101) or (110) crystal faces were produced by repeating this procedure 250–300 times.

## 5. Films of solid solutions $\text{Pb}(\text{Zr},\text{Ti})\text{O}_3$ and $\text{Pb}(\text{Sr},\text{Ti})\text{O}_3$

Lead carboxylates are most commonly used as starting compounds in the preparation of FETF based on solid solutions  $\text{Pb}(\text{Zr},\text{Ti})\text{O}_3$  and  $\text{Pb}(\text{Sr},\text{Ti})\text{O}_3$  (also referred to as PZT and PST, respectively) by solution methods (Table 8). Lead carboxylates are well soluble in organic solvents, such as propan-2-ol or 2-methoxyethanol. Zirconium, titanium and strontium alkoxides are also soluble in these solvents, which favours the formation of high-quality films with uniform thicknesses. It should be taken into account that it is preferable to use starting compounds belonging to the same class, but this is not always possible (see Table 8).

More complex processes (as regards both the synthetic method and the starting compounds used) are also applied to prepare FETF of PZT solid solutions (Table 9). This may be exemplified by syntheses from metal alkoxides and chelate complexes as well as the hydrothermal synthesis envisaging two consecutive steps, *viz.*, generation of growth nuclei and film



**Table 8** Conditions of synthesis of ferroelectric thin films of  $\text{Pb}(\text{Zr,Ti})\text{O}_3$  and  $\text{Pb}(\text{Sr,Ti})\text{O}_3$  and their properties.

| Starting compounds                                                                                                                             | Method          | Solvents                                                              | Composition<br>Zr/Ti      | Support                                   | $T / ^\circ\text{C}$          | Properties of FETF    |               |                |       | Ref.          |
|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------------------------------------------------------------|---------------------------|-------------------------------------------|-------------------------------|-----------------------|---------------|----------------|-------|---------------|
|                                                                                                                                                |                 |                                                                       |                           |                                           |                               | $\varepsilon$         | $\tan \delta$ | $P_r$          | $E_c$ |               |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{OPr}^i)_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                         | sol–gel         | acetic acid, ethylene glycol, water                                   | 40/60<br>60/40            | Al                                        | 600                           | 260                   | —             | 6.6            | 26.7  | 141           |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{OBu})_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                           | "               | 2-methoxyethanol, diethanolamine                                      | 50/50                     | Pt/Ti/SiO <sub>2</sub> /Si, Ir            | 480, 650                      | 730                   | —             | 20.7           | —     | 142, 143, 144 |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{OBu})_4$ , $\text{Ti}(\text{OPr}^i)_4$                              | "               | 2-methoxyethanol                                                      | 52/48                     | Pt/Ti/SiO <sub>2</sub> /Si                | 600                           | —                     | —             | —              | —     | 145           |
| $\text{Pb}(\text{AcO})_2$ ,<br>$\text{Zr}(\text{OPr}^i)_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                                    | "               | "                                                                     | 40/60,<br>52/48,<br>70/30 | Pt/Ti/SiO <sub>2</sub> /Si,               | 150, 400,<br>550, 600,<br>700 | 66–75<br>1010–1300    | —             | 41–45<br>38–66 | —     | 146, 147      |
| $\text{Pb}(\text{AcO})_2$ , $\text{Zr}(\text{OPr}^i)_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                                       | "               | "                                                                     | 52/48                     | SrTiO <sub>3</sub> , MgO                  | 650–700                       | 448                   | —             | 15             | —     | 148           |
| $\text{Pb}(\text{AcO})_2$ ,<br>$\text{Zr,Ti}$ methyl-<br>cellosolvates                                                                         | "               | 2-methoxyethanol, acetic anhydride                                    | 52/48                     | Pt/Ti/SiO <sub>2</sub> /Si                | 600, 650                      | —                     | —             | —              | —     | 149           |
| $\text{Pb,Zr,Ti}$ naphthenates                                                                                                                 | "               | naphthenic acid                                                       | 52/48                     | SrTiO <sub>2</sub> /Nb                    | 600–750                       | —                     | —             | —              | —     | 150           |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{OPr}^i)_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                         | "               | ethanol, acetone, propanol, propane-1,2-diol                          | 52/48                     | Al <sub>2</sub> O <sub>3</sub>            | —                             | —                     | —             | —              | —     | 151           |
| $\text{Pb}(\text{AcO})_2$ ,<br>$\text{ZrO}(\text{AcO})_2$ ,<br>$\text{Ti}(\text{OBu})_4$                                                       | "               | 2-methoxyethanol                                                      | 52/48                     | Pt/Ti                                     | 300–600,<br>700               | 1000–1100,<br>500–700 | —             | —              | —     | 152           |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{OPr}^i)_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                         | "               | 2-methoxyethanol, acetylacetone                                       | 50/50                     | Pt/Ti/SiO <sub>2</sub> /Si                | 150                           | 1000                  | —             | —              | —     | 153           |
| $\text{Pb}(\text{AcO}) \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{OPr}^i)_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                           | "               | 2-methoxyethanol                                                      | 53/47                     | —                                         | 350–420                       | —                     | —             | —              | —     | 154           |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{OPr}^i)_4$ ,<br>$\text{Ti}(\text{OPr}^i)_2(\text{acac})_2$          | "               | propane-1,3-diol, pentane-2,4-dione, 1,1,1-tris(hydroxy-methyl)ethane | 53/47                     | Pt/GaAs                                   | 600, 650                      | 950                   | —             | 24             | 32    | 155           |
| $\text{Pb}(\text{AcO}) \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{OPr}^i)_4$ , $\text{Ti}(\text{OPr}^i)_4$                              | "               | propane-2-ol                                                          | —                         | ITO/glass                                 | 300, 350,<br>450, 500         | 532                   | —             | 49.58          | —     | 156           |
| $\text{Pb}(\text{OR})_2$ , $\text{Zr}(\text{OR})_4$ ,<br>$\text{Ti}(\text{OEt})_2(\text{OR})_2$<br>(R is neodecanoate)                         | MOD             | xylene                                                                | 52/48                     | Si <sub>3</sub> N <sub>4</sub> /Si, Pt/Si | 400–600,<br>600–700,<br>800   | —                     | —             | 11.8           | 76.0  | 157           |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{OBu})_4$ , $\text{Ti}(\text{OPr}^i)_4$                              | sol–gel         | 2-methoxyethanol, propan-2-ol                                         | 20/80                     | Pt/Ti/SiO <sub>2</sub> /Si                | 95, 350,<br>600               | —                     | —             | 31.9           | 120.8 | 158           |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{OBu})_4$ , $\text{Ti}(\text{OPr}^i)_4$                              | "               | 2-methoxyethanol                                                      | 40/60                     | Pt/Ti/SiO <sub>2</sub> /Si                | 200, 400,<br>650              | —                     | —             | 30             | —     | 159           |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{OPr}^i)_4$ , $\text{Ti}(\text{OPr}^i)_4$                            | "               | —                                                                     | 53/47                     | Pt/Si                                     | 600–700                       | 930–990               | —             | 20–25          | 38    | 160           |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{NO}_3)_4 \cdot 5 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OBu})_4$ | "               | 2-methoxyethanol                                                      | 50/50                     | Pt/Ti/SiO <sub>2</sub> /S                 | —                             | —                     | —             | —              | —     | 161           |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{acac})_4$ , $\text{Ti}(\text{OPr}^i)_4$                             | MOD             | acetic acid, water                                                    | 53/47                     | Pt/Ti/SiO <sub>2</sub>                    | 100                           | 1040                  | —             | 26             | 39    | 162           |
| $\text{Pb}(\text{AcO})_2$ ,<br>$\text{Zr}(\text{OPr}^i)_4$ , $\text{Ti}(\text{OPr}^i)_4$                                                       | sol–gel,<br>MOD | propan-2-ol                                                           | 53/47                     | Pt/Ti/SiO <sub>2</sub> /Si                | 350–550                       | 1600                  | —             | 34.8           | 41.7  | 163           |
| $\text{Pb}(\text{AcO})_2$ ,<br>$\text{ZrO}(\text{NO}_3)_2$ , $\text{Ti}(\text{OBu})_4$                                                         | sol–gel         | —                                                                     | 52/48                     | Pt/diamond                                | 300,<br>500–700               | —                     | —             | 5.1            | 300   | 164           |

**Table 8** (continued).

| Starting compounds                                                                                                                                                    | Method  | Solvents                           | Composition<br>Zr/Ti | Support                    | $T/^{\circ}\text{C}$          | Properties of FETF |               |       |       | Ref.        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|------------------------------------|----------------------|----------------------------|-------------------------------|--------------------|---------------|-------|-------|-------------|
|                                                                                                                                                                       |         |                                    |                      |                            |                               | $\varepsilon$      | $\tan \delta$ | $P_r$ | $E_c$ |             |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{NO}_3)_4 \cdot 5 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OBu})_4$                        | sol–gel | 2-methoxyethanol,<br>acetylacetone | 50/50                | Pt/Ti/SiO <sub>2</sub> /Si | 550                           | 520                | —             | 11    | 45    | 165,<br>166 |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{acac})_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$ ,<br>$\text{Ti}(\text{OPr}^i)_2(\text{acac})_2$ | "       | 2-methoxyethanol                   | 30/70                | Pt/Ti/SiO <sub>2</sub> /Si | 124, 500                      | —                  | —             | —     | —     | 167         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{OPr}^i)_4$ , $\text{Ti}(\text{OPr}^i)_4$                                                   | "       | 2-methoxyethanol                   | 10/90,<br>90/10      | Pt/Ti/SiO <sub>2</sub> /Si | 300, 600                      | —                  | —             | —     | —     | 168         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{NO}_3)_4 \cdot 5 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OBu})_4$                        | "       | 2-methoxyethanol,<br>acetylacetone | 50/50                | Pt/Ti/SiO <sub>2</sub> /Si | 125, 450,<br>500, 550,<br>600 | 730–1020           | —             | 11.2  | —     | 169         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{OPr}^i)_4$ , $\text{Ti}(\text{OPr}^i)_4$                                                   | MOD     | propan-2-ol                        | —                    | Pt/Ti/SiO <sub>2</sub> /Si | 350–550                       | —                  | —             | —     | —     | 170         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{OPr}^i)_4$ , $\text{Ti}(\text{OPr}^i)_4$                                                   | sol–gel | ethanol                            | —                    | Pt/SiO <sub>2</sub> /Si    | 110, 350,<br>400–600          | —                  | —             | —     | —     | 171         |

**Table 9.** Conditions of MOCVD synthesis of ferroelectric thin films of  $\text{Pb}(\text{Zr,Ti})\text{O}_3$  from the gas phase and their properties.

| Starting compounds                                                                                                     | Support                                                            | Zr/Ti           | Process conditions          |                        |                 | Properties of FETF |       |       | Ref. |
|------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|-----------------|-----------------------------|------------------------|-----------------|--------------------|-------|-------|------|
|                                                                                                                        |                                                                    |                 | $T_v/^{\circ}\text{C}$      | $T_p/^{\circ}\text{C}$ | $P/\text{Torr}$ | $\varepsilon$      | $P_r$ | $E_c$ |      |
| $\text{PbEt}_4$ , $\text{Zr}(\text{DPM})_4$ , $\text{Ti}(\text{OPr}^i)_4$                                              | Pb/MgO                                                             | 52/48           | 10, 180, 25                 | 600, 700               | 660             | 200–350            | 30–40 | 40–65 | 172  |
| $\text{PbEt}_4$ , $\text{Zr}(\text{DPM})_4$ , $\text{Ti}(\text{OPr}^i)_4$                                              | $\text{Al}_2\text{O}_3$ (see <sup>a</sup> )                        | —               | 182–208, 45–80              | 630                    | 10              | 5000               | —     | —     | 173  |
| $\text{Pb}(\text{DPM})_2$ , $\text{Zr}(\text{DPM})_4$ ,<br>$\text{Ti}(\text{OEt})_4$                                   | Pt/Si, SiO <sub>2</sub> /Si,<br>$\text{RuO}_x/\text{SiO}_2$        | 82/18           | 145–165,<br>210–230, 90–115 | 550–600                | 6.0             | —                  | 23.3  | 64.5  | 174  |
| $\text{Pb}(\text{DPM})_2$ , $\text{Zr}(\text{DPM})_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                 | Pt/SiO <sub>2</sub> /Si                                            | 55/45           | 140, 155, 35                | 550                    | 5.0             | —                  | 6–10  | —     | 175  |
| $\text{PbEt}_4$ , $\text{Zr}(\text{DPM})_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                           | Pt/MgO, $\text{RuO}_2$ /<br>$\text{MgO}$ , Pt/SiO <sub>2</sub> /Si | 15/85,<br>50/50 | —                           | 650                    | 5.0             | —                  | —     | —     | 176  |
| $\text{Pb}(\text{DPM})_2$ , $\text{Zr}(\text{DPM})_4$ ,<br>$\text{Ti}(\text{OPr}^i)_2(\text{DPM})_2$                   | Pt/Si, Pt/MgO                                                      | 39/61           | 133, 165, 56.4              | 600–700                | —               | 480                | —     | —     | 177  |
| $\text{Pb}(\text{DPM})_2$ , $\text{Zr}(\text{OBu}^t)_4$ , $\text{Ti}(\text{OPr}^i)_4$                                  | Pt/MgO                                                             | 49/51           | —                           | 700                    | 10              | 425                | 50    | 33    | 178  |
| $\text{Pb}(\text{DPM})_2$ , $\text{Zr}_2(\text{OPr}^i)_6(\text{DPM})_2$ ,<br>$\text{Ti}(\text{OPr}^i)_2(\text{DPM})_2$ | —                                                                  | —               | —                           | 250–600                | —               | —                  | —     | —     | 179  |
| $\text{Pb}(\text{DPM})_2$ , $\text{Zr}(\text{OBu}^t)_4$ , $\text{Ti}(\text{OPr}^i)_4$                                  | MgO                                                                | 39/61           | 141, 31, 41                 | 650                    | 670             | —                  | —     | —     | 180  |

<sup>a</sup> A solid solution with a variable composition  $\text{Pb}(\text{Zr}_{1-x}\text{Ti}_x)\text{O}_3$ , where  $x = 0-1$ , is formed on  $\text{Al}_2\text{O}_3$  supports.

growth. Properties of the resultant films strongly depend on the first step. The procedure for the hydrothermal synthesis of PZT films is as follows. A titanium support is immersed into an aqueous solution of lead nitrate, zirconium oxychloride and potassium hydroxide to initiate nucleation; the lead:zirconium ratio should be equal to 2.29 and the concentrations of lead nitrate and potassium hydroxide should be 0.33 and 8.0 mol litre<sup>-1</sup>, respectively. The solution and the support are slowly heated in an autoclave for 6–96 h. Heating at 120 °C for 48 h affords thin polycrystalline films.<sup>181</sup> However, this method is of low potential since it does not yield high-quality films.

A primary requirement of starting compounds to be used in the synthesis of complex oxide films by the CVD method is that the element is deposited as an oxide. Starting from the 1990s, lead, zirconium and titanium alkoxides have been commonly used for the preparation of films of  $\text{Pb}(\text{Zr,Ti})\text{O}_3$  solid solutions. The

evaporation temperatures of these compounds are very low (below 35 °C), which constitutes their major advantage over other classes of compounds. Parameters of the CVD method used to grow PZT films on various supports are summarised in Table 10. Among the alkoxides, zirconium derivatives are the least studied. Actually, the choice of suitable starting compounds is limited to two types, *viz.*, propoxy- and butoxy-derivatives (see below). Both types of compounds are employed for the preparation of  $\text{Pb}(\text{Zr,Ti})\text{O}_3$  thin films (doped with  $\text{La}^{3+}$ ,  $\text{Pb}^{3+}$ ,  $\text{Bi}^{3+}$  and  $\text{Nb}^{5+}$ ) from both solutions and the vapour phase. The first application of volatile complexes and adducts of metal  $\beta$ -diketonates dates back to the late 1980s.<sup>172, 194</sup> More recently, zirconium and titanium mixed-ligand complexes, such as metal alkoxy- $\beta$ -diketonates came in use (see Tables 6, 9 and 11).<sup>95</sup> Thin films of  $\text{Pb}(\text{Zr,Ti})\text{O}_3$  synthesised from mixed-ligand metal  $\beta$ -diketonates (see Tables 9 and 12) acquired the greatest practical importance

**Table 10.** Conditions of MOCVD synthesis of ferroelectric thin films of  $\text{Pb}(\text{Zr,Ti})\text{O}_3$  from metal alkoxides and their properties.

| Starting compounds                                                                                                | Support                                  | Zr/Ti          | Process conditions     |                        |                   | Properties of FETF |       |       | Ref.        |
|-------------------------------------------------------------------------------------------------------------------|------------------------------------------|----------------|------------------------|------------------------|-------------------|--------------------|-------|-------|-------------|
|                                                                                                                   |                                          |                | $T_v / ^\circ\text{C}$ | $T_p / ^\circ\text{C}$ | $P / \text{Torr}$ | $\varepsilon$      | $P_r$ | $E_c$ |             |
| $\text{PbEt}_4$ ,<br>$\text{Zr}(\text{OBu}^t)_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                 | —                                        | —              | 0<br>35<br>35          | 605                    | 6.0               | —                  | —     | —     | 182         |
| $\text{PbEt}_4$ ,<br>$\text{Zr}(\text{OBu}^t)_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                 | Pt/SiO <sub>2</sub> /Si                  | —              | 0<br>35<br>35          | 535–625                | 6.0               | —                  | —     | —     | 183         |
| $\text{PbEt}_4$ ,<br>$\text{Zr}(\text{OBu}^t)_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                 | Pt/SiO <sub>2</sub> /Si                  | 50/50          | 0<br>30<br>35          | 500–625                | 5                 | 1200<br>220–240    | 1–20  | —     | 184,<br>185 |
| $\text{PbEt}_4$ ,<br>$\text{Zr}(\text{OBu}^t)_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                 | Pt/SiO <sub>2</sub> /Si                  | —              | 0<br>35<br>30          | 550–600                | 5.0               | —                  | —     | —     | 186         |
| $\text{Et}_3\text{Pb}(\text{OCH}_2\text{Bu}^t)$ ,<br>$\text{Zr}(\text{OBu}^t)_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$ | Pt/Si<br>Au/PZT/Pt/Si                    | —              | 60<br>60<br>60         | 650                    | 5                 | —                  | —     | —     | 187         |
| $\text{PbEt}_4$ , $\text{Zr}(\text{OBu}^t)_4$ ,<br>$\text{Ti}(\text{OBu}^t)_4$                                    | Pt                                       | —              | —                      | 550–775                | —                 | 750–1130           | 30    | 45–80 | 188         |
| $\text{PbEt}_4$ ,<br>$\text{Zr}(\text{OBi}^t)_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                 | SrRuO <sub>3</sub> /SrTiO <sub>3</sub>   | 35/65<br>52/48 | 32<br>32<br>28.5       | 700                    | 5–6               | 225–650            | 30–55 | 20    | 189         |
| $\text{PbEt}_4$ ,<br>$\text{Zr}(\text{OBu}^t)_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                 | Pt/MgO<br>Pt/SiO <sub>2</sub> /Si        | —              | 0<br>35<br>35          | 530–670                | 5.0               | —                  | —     | —     | 190         |
| $\text{PbEt}_4$ ,<br>$\text{Zr}(\text{OBu}^t)_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                 | Pt/SiO <sub>2</sub> /Si                  | —              | 0<br>30<br>30          | 600                    | 5.0               | —                  | —     | —     | 191         |
| $\text{PbEt}_4$ ,<br>$\text{Zr}(\text{OBu}^t)_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$                                 | SrRuO <sub>3</sub><br>SrTiO <sub>3</sub> | 80/20<br>65/35 | 28.5<br>32<br>32       | 700                    | —                 | —                  | —     | —     | 192         |
| $\text{PbEt}_4$ ,<br>$\text{Zr}(\text{OBu}^t)_4$ , $\text{Ti}(\text{OPr}^i)_4$                                    | RuO <sub>2</sub><br>SiO <sub>2</sub> /Si | 50/50          | —                      | —                      | —                 | —                  | 20–45 | 35–40 | 193         |

**Table 11.** Conditions of MOCVD synthesis of ferroelectric thin films of  $\text{PbTiO}_3$  from the gas phase and their properties.

| Starting compounds                                         | Support                 | Process conditions     |                        |                   | Properties of FETF |       |       | Ref. |
|------------------------------------------------------------|-------------------------|------------------------|------------------------|-------------------|--------------------|-------|-------|------|
|                                                            |                         | $T_v / ^\circ\text{C}$ | $T_p / ^\circ\text{C}$ | $P / \text{Torr}$ | $\varepsilon$      | $P_r$ | $E_c$ |      |
| $\text{PbEt}_4$ , $\text{Ti}(\text{OPr}^i)_4$              | SiO <sub>2</sub>        | —                      | 500                    | 0.37              | 180                | —     | —     | 194  |
| $\text{PbEt}_4$ , $\text{Ti}(\text{OPr}^i)_4$              | MgO                     | —                      | 500–650                | 6                 | 100–130            | —     | —     | 195  |
| $\text{PbEt}_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$           | SrTiO <sub>3</sub>      | 16.0<br>33.0           | 700                    | 18                | —                  | —     | —     | 196  |
| $\text{Pb}(\text{DPM})_2$ ,<br>$\text{Ti}(\text{OPr}^i)_4$ | p-Si(100)               | 125<br>15              | 400–600                | 1                 | —                  | —     | —     | 197  |
| $\text{Pb}(\text{DPM})_2$ , $\text{Ti}(\text{OPr}^i)_4$    | Pt/SiO <sub>2</sub> /Si | —                      | 570                    | 5                 | 50–200             | —     | —     | 198  |
| $\text{PbEt}_4$ , $\text{Ti}(\text{OPr}^i)_4$              | MgO                     | —                      | 510                    | —                 | —                  | —     | —     | 199  |
| $\text{PbEt}_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$           | Si, MgO                 | 1<br>30                | 510                    | 1                 | —                  | —     | —     | 200  |
| $\text{PbEt}_4$ ,<br>$\text{Ti}(\text{OPr}^i)_4$           | CeO <sub>2</sub> /Si    | 1<br>30                | —                      | 900               | 10 <sup>–6</sup>   | 26    | —     | 201  |
| $\text{Pb}(\text{DPM})_2$ ,<br>$\text{Ti}(\text{OPr}^i)_4$ | p-Si                    | 125<br>15              | 500, 800               | 1                 | —                  | —     | —     | 202  |
| $\text{PbEt}_4$ , $\text{Ti}(\text{OPr}^i)_4$              | Pt/MgO                  | —                      | —                      | —                 | —                  | —     | —     | 203  |

**Table 11** (continued).

| Starting compounds                                           | Support                                          | Process conditions     |                        |                   | Properties of FETF |       |       | Ref. |
|--------------------------------------------------------------|--------------------------------------------------|------------------------|------------------------|-------------------|--------------------|-------|-------|------|
|                                                              |                                                  | $T_v / ^\circ\text{C}$ | $T_p / ^\circ\text{C}$ | $P / \text{Torr}$ | $\varepsilon$      | $P_r$ | $E_c$ |      |
| PbEt <sub>4</sub> ,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub>    | Pt/SiO <sub>2</sub> /Si,<br>Pt/MgO               | 0<br>30                | 530–670                | 5                 | —                  | —     | —     | 190  |
| PbEt <sub>4</sub> , Ti(OPr <sup>i</sup> ) <sub>4</sub>       | Pt/SiO <sub>2</sub> /Si                          | —                      | 450, 650               | —                 | —                  | 21    | 70    | 204  |
| Pb(DPM) <sub>2</sub> , Ti(OPr <sup>i</sup> ) <sub>4</sub>    | Pt/Ti/SiO <sub>2</sub> /Si                       | —                      | —                      | —                 | 52–200             | 8     | —     | 205  |
| Pb(DPM) <sub>2</sub> ,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub> | LaAlO <sub>3</sub>                               | 120<br>34              | 550–700                | 10                | —                  | —     | —     | 206  |
| PbEt <sub>4</sub> ,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub>    | Pt/SrTiO <sub>3</sub> ,<br>Pt/LaAlO <sub>3</sub> | 35<br>65               | 650                    | 13.3              | —                  | —     | —     | 207  |
| PbEt <sub>4</sub> ,<br>TiCl <sub>4</sub>                     | Si                                               | –11<br>–21             | 170                    | 0.004             | —                  | —     | —     | 208  |
| Pb(DPM) <sub>2</sub> ,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub> | Pt/SiO <sub>2</sub> /Si                          | 130<br>45              | 350–400                | —                 | —                  | —     | —     | 209  |

**Table 12.** Conditions of synthesis of ferroelectric thin films of PbTiO<sub>3</sub> and Pb(Zr,Ti)O<sub>3</sub> doped with La, Mg, Nb, Ca, Al and Bi and their properties.

| Starting compounds                                                                                                                                                                   | Method  | Dopant | Solvents                                                   | Support                                   | $T / ^\circ\text{C}$  | Properties of FETF |          |          | Ref.        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------|------------------------------------------------------------|-------------------------------------------|-----------------------|--------------------|----------|----------|-------------|
|                                                                                                                                                                                      |         |        |                                                            |                                           |                       | $\varepsilon$      | $P_r$    | $E_c$    |             |
| Pb(AcO) <sub>4</sub> · 3 H <sub>2</sub> O,<br>Ti(OPr <sup>i</sup> ) <sub>2</sub> (acac) <sub>2</sub> ,<br>Sm(AcO) <sub>4</sub> · 3 H <sub>2</sub> O                                  | sol–gel | Sm     | propane-1,3-diol,<br>acetylacetone                         | Pt/TiO <sub>2</sub> /SiO <sub>2</sub> /Si | 350, 550,<br>650–700  | —                  | —        | —        | 210         |
| Pb(AcO) <sub>4</sub> · 3 H <sub>2</sub> O,<br>Ti(OBu) <sub>4</sub> ,<br>La(NO <sub>3</sub> ) <sub>3</sub>                                                                            | "       | La     | —                                                          | Pt/Ti/SiO <sub>2</sub> /Si                | 410–600               | 210                | 16.5     | 60       | 211         |
| Pb(AcO) <sub>2</sub> · 3 H <sub>2</sub> O,<br>Zr(OPr <sup>i</sup> ) <sub>4</sub> ,<br>La(acac) <sub>3</sub> · 3 H <sub>2</sub> O                                                     | "       | Pb     | 2-methoxyethanol                                           | Pt/Ti/SiO <sub>2</sub> /Si                | —                     | —                  | —        | —        | 212         |
| Pb(AcO) <sub>2</sub> ,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub> , Nb(OEt) <sub>5</sub> ,<br>Mg(AcO) <sub>2</sub> · 4 H <sub>2</sub> O                                                   | "       | Mg, Nb | 2-methoxyethanol                                           | Pt/sapphire                               | 300, 840              | 2400,<br>3100      | —        | —        | 213         |
| Pb(AcO) <sub>2</sub> · 3 H <sub>2</sub> O,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub> , Nb(OEt) <sub>5</sub> ,<br>La(AcO) <sub>3</sub> · <i>n</i> H <sub>2</sub> O                        | "       | La, Nb | 2-methoxyethanol,<br>HNO <sub>3</sub> , ethylene<br>glycol | Pt/Ti/SiO <sub>2</sub> /Si                | 350, 600              | 611–619            | —        | —        | 214         |
| Pb(AcO) <sub>2</sub> · 3 H <sub>2</sub> O,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub> , CaCl <sub>2</sub>                                                                                 | "       | Ca     | 2-methoxyethanol,<br>HNO <sub>3</sub>                      | Pt/MgO, Si                                | 126, 142,<br>360, 550 | —                  | —        | —        | 215         |
| Pb(AcO) <sub>2</sub> · 3 H <sub>2</sub> O,<br>Ti(OPr <sup>i</sup> ) <sub>2</sub> (acac) <sub>2</sub> ,<br>Ca(AcO) <sub>2</sub> , Sm(AcO) <sub>3</sub>                                | "       | Ca, Sm | propane-1,3-diol                                           | Pt/TiO <sub>2</sub> /Si                   | 85,<br>350–650        | —                  | 8.6–20.7 | 11, 9–73 | 216,<br>217 |
| Pb(AcO) <sub>2</sub> · 3 H <sub>2</sub> O,<br>Ti(OPr <sup>i</sup> ) <sub>2</sub> (acac) <sub>2</sub> ,<br>Sm(AcO) <sub>3</sub> , Sm(acac) <sub>3</sub>                               | "       | Sm     | propane-1,3-diol                                           | Pt/TiO <sub>2</sub> /Si                   | 350, 650              | —                  | —        | —        | 218         |
| Pb(AcO) <sub>2</sub> · 3 H <sub>2</sub> O,<br>Ti(OBu) <sub>4</sub> , La(NO <sub>3</sub> ) <sub>3</sub>                                                                               | "       | La     | 2-methoxyethanol,<br>xylene                                | LaNiO <sub>3</sub> , Si                   | 650–700               | 110                | 13       | 50       | 219         |
| Pb(AcO) <sub>2</sub> · 3 H <sub>2</sub> O,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub> , Al(OPr <sup>i</sup> ) <sub>3</sub>                                                                | "       | Al     | 2-methoxyethanol                                           | —                                         | —                     | 365                | 15       | 86       | 220         |
| Pb(AcO) <sub>2</sub> · 3 H <sub>2</sub> O,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub> ,<br>Ca(AcO) <sub>2</sub> · <i>n</i> H <sub>2</sub> O,<br>Mn(AcO) <sub>2</sub> · 4 H <sub>2</sub> O | "       | Ca, Mn | propane-1,2-diol                                           | —                                         | 800                   | —                  | —        | —        | 221         |
| Pb(AcO) <sub>2</sub> · 3 H <sub>2</sub> O,<br>Ti(OPr <sup>i</sup> ) <sub>4</sub> , Zr(OPr <sup>n</sup> ) <sub>4</sub> ,<br>Bi(NO <sub>3</sub> ) <sub>3</sub>                         | "       | Bi     | 2-methoxyethanol,<br>acetic acid,<br>propan-2-ol           | Pt/Ti/SiO <sub>2</sub> /Si                | —                     | —                  | —        | —        | 222         |

**Table 12** (continued).

| Starting compounds                                                                                                                                                                                        | Method  | Dopant | Solvents                                        | Support                                   | $T/^{\circ}\text{C}$  | Properties of FETF |       |       | Ref.        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------|-------------------------------------------------|-------------------------------------------|-----------------------|--------------------|-------|-------|-------------|
|                                                                                                                                                                                                           |         |        |                                                 |                                           |                       | $\varepsilon$      | $P_r$ | $E_c$ |             |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OBu})_4$ ,<br>$\text{Ca}(\text{NO}_3)_2 \cdot n \text{H}_2\text{O}$ ,<br>$\text{La}(\text{NO}_3)_3 \cdot n \text{H}_2\text{O}$ | MOD     | Ca, La | 2-butoxyethanol,<br>$\text{HNO}_3$              | Pt/Si                                     | 180, 400,<br>500–800  | 375                | —     | —     | 223         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{OPr})_4$ , $\text{Ti}(\text{OPr}^i)_4$ ,<br>$\text{La}(\text{AcO})_3$                                                          | sol–gel | La     | 2-methoxyethanol                                | $\text{In}_2\text{O}_3$                   | 130–500               | —                  | —     | —     | 224         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Zr}(\text{OBu})_4$ , $\text{Ti}(\text{OPr}^i)_4$ ,<br>$\text{Nb}(\text{OEt})_5$ , $\text{La}(\text{OPr}^i)_3$                            | "       | La, Nb | —                                               | Pt/Ti/SiO <sub>2</sub> /Si                | 200, 400,<br>650      | —                  | 30    | —     | 111         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OBu})_4$ , $\text{Ca}(\text{NO}_3)_2$ ,<br>$\text{La}(\text{NO}_3)_3$                                                          | "       | Ca, La | 2-methoxyethanol                                | Pt/Ti/SiO <sub>2</sub> /Si                | 120, 350,<br>500, 600 | —                  | —     | —     | 225         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OBu})_4$ , $\text{Ca}(\text{NO}_3)_2$                                                                                          | "       | Ca     | methanol,<br>ethanolamine                       | Pt/Ti/Si                                  | 400, 550,<br>600      | 280                | 37.7  | 60.4  | 226         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OBu})_4$ , $\text{Ca}(\text{NO}_3)_2$ ,<br>$\text{La}(\text{NO}_3)_3$                                                          | MOD     | Ca, La | 2-butoxyethanol                                 | Pt/Ti/SiO <sub>2</sub> /Si                | 500–800               | —                  | —     | —     | 227         |
| $\text{Pb}(\text{AcO})_2 \cdot 3 \text{H}_2\text{O}$ ,<br>$\text{Ti}(\text{OPr}^i)_4$ ,<br>$\text{La}(\text{AcO})_3 \cdot 1.5 \text{H}_2\text{O}$                                                         | sol–gel | La     | —                                               | Pt/TiO <sub>x</sub> /SiO <sub>2</sub> /Si | 110, 450,<br>650      | 428–761            | —     | —     | 132         |
| $\text{Pb}(\text{AcO})_2$ ,<br>$\text{Zr}(\text{OPr}^i)_4$ , $\text{Ti}(\text{OPr}^i)_4$ ,<br>$\text{La}(\text{CO}_3)_3 \cdot \text{H}_2\text{O}$                                                         | MOD     | La     | ethylene glycol,<br>acetic acid, citric<br>acid | Si(100)                                   | 90,<br>450–700        | —                  | —     | —     | 228,<br>229 |

due to their high permittivities. As has been mentioned above, film structures play a crucial role in the preparation of ferroelectric layers. A film can undergo polarisation as a result of mutual shifts of atoms. The introduction of additional oxygen-containing ligands into metal  $\beta$ -diketonate complexes makes it possible to control the structure of the target films and, consequently, obtain films with the desired properties (see Tables 9 and 12).

FETF can be doped with various elements to improve their physical properties, in particular permittivity (see Table 12). As precursors of dopants enhancing the ferroelectric properties, either metal carboxylates (from 0 mol.% to 25 mol.%)<sup>216, 217</sup> or volatile thermally stable  $\beta$ -diketonates of alkaline-earth and rare-earth metals or of such metals as Nb, Al and Bi are used.<sup>212, 214, 218, 220, 222</sup>

## 6. Films based on strontium/bismuth/tantalum and strontium/bismuth/niobium complex oxides

Films of ternary oxides  $\text{SrBi}_2\text{Ta}_2\text{O}_9$  and  $\text{SrBi}_2\text{Nb}_2\text{O}_9$  (also referred to as SBT and SBN, respectively) can be prepared by both the MOCVD and solution methods. It is the hydrothermal technique that is most common among the solution methods. Published data on the preparation of films from bismuth and strontium carboxylates are summarised in Table 13. As for tantalum and niobium, the respective metal alkoxides are used most often. The sol–gel method is less common but it is also in use for the synthesis of SBT- and SBN-based FETF. Acetylacetone is sometimes added to the solution in the preparation of SBT films by the sol–gel method since it promotes growth of films oriented along the crystallographic  $c$  axis. The degree of the orientational ordering in

**Table 13.** Conditions of synthesis of ferroelectric thin films of  $\text{SrBi}_2\text{Ta}_2\text{O}_9$  and  $\text{SrBi}_2\text{Nb}_2\text{O}_9$  from metal carboxylates and their properties.

| Starting compounds                                                                                                                                                      | Method  | Solvent                               | Support                                                   | $T/^{\circ}\text{C}$ | Properties of FETF |       |       |                         | Ref. |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|---------------------------------------|-----------------------------------------------------------|----------------------|--------------------|-------|-------|-------------------------|------|
|                                                                                                                                                                         |         |                                       |                                                           |                      | $\varepsilon$      | $P_r$ | $E_c$ | $Y$ (see <sup>a</sup> ) |      |
| $\text{Sr}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_2$ ,<br>$\text{Bi}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_3$ ,<br>$\text{Ta}(\text{OEt})_5$                             | sol–gel | 2-methoxyethanol,<br>isopentylacetate | Pt/Ta/SiO <sub>2</sub> /Si,<br>Pt/Ti/SiO <sub>2</sub> /Si | 800                  | —                  | —     | —     | —                       | 230  |
| $\text{Sr}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_2$ ,<br>$\text{Bi}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_3$ ,<br>$\text{Ta}(\text{OEt})_5$                             | "       | 2-methoxyethanol,<br>acetic acid      | —                                                         | 120, 600             | —                  | —     | —     | —                       | 231  |
| $\text{Sr}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_2$ ,<br>$\text{Bi}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_3$ ,<br>$\text{Ta}(\text{OEt})_5$                             | "       | —                                     | Pt/Ti/SiO <sub>2</sub> /Si                                | 450, 700,<br>800     | —                  | 5     | —     | —                       | 232  |
| $\text{Sr}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_2$ ,<br>$\text{Bi}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_3$ ,<br>$\text{Bi}(\text{OEt})_3$ , $\text{Ta}(\text{OEt})_5$ | MOD     | 2-ethylhexanoic acid,<br>toluene      | —                                                         | 700–750              | —                  | 3–4   | 1.5   | —                       | 233  |

Table 13 (continued).

| Starting compounds                                                                                                                                                                                                             | Method  | Solvent                                                     | Support                                                                               | $T/^{\circ}\text{C}$  | Properties of FETF |          |            |                         | Ref.        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------|--------------------|----------|------------|-------------------------|-------------|
|                                                                                                                                                                                                                                |         |                                                             |                                                                                       |                       | $\varepsilon$      | $P_r$    | $E_c$      | $Y$ (see <sup>a</sup> ) |             |
| $\text{Sr}(\text{AcO})_2$ ,<br>$\text{Bi}(\text{NO}_3)_3 \cdot 5 \text{H}_2\text{O}$ ,<br>$\text{Ta}(\text{OEt})_5$                                                                                                            | MOD     | acetic acid,<br>methanol,<br>aminoalcohols                  | $\text{Pt}/\text{ZrO}_2/\text{SiO}_2/\text{Si}$                                       | 260, 450,<br>700, 800 | —                  | 8–10     | —          | —                       | 234         |
| $\text{Sr}(\text{AcO})_2$ ,<br>$\text{Bi}(\text{NO}_3)_3 \cdot 5 \text{H}_2\text{O}$ ,<br>$\text{Ta}(\text{OEt})_5$                                                                                                            | MOD     | acetic acid,<br>methanol                                    | $\text{Pt}/\text{ZrO}_2/\text{SiO}_2/\text{Si}$                                       | 260, 450,<br>700, 800 | —                  | 8–10     | —          | $10^{10}$               | 235         |
| $\text{Sr}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_2$ ,<br>$\text{Bi}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_3$ ,<br>$\text{Ta}(\text{OEt})_5$                                                                                    | MOD     | xylene                                                      | $\text{Si}_3\text{N}_4/\text{SiO}_2/\text{Si}$ ,<br>$\text{Al}_2\text{O}_3/\text{Si}$ | 400, 600,<br>750–900  | —                  | —        | —          | —                       | 236         |
| $\text{Sr}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_2$ ,<br>$\text{Bi}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_3$ ,<br>$\text{Nb}(\text{OEt})_5$                                                                                    | sol–gel | 2-ethylhexanoic<br>acid, ethanol                            | $\text{SrTiO}_3$                                                                      | 120, 550,<br>600, 700 | —                  | —        | —          | —                       | 237         |
| $\text{Sr}(\text{AcO})_2$ ,<br>$\text{Bi}(\text{C}_7\text{H}_{15}\text{CO}_2)_3$ ,<br>$\text{Ti}(\text{OPr}^i)_4$ , $\text{Ta}(\text{OEt})_5$                                                                                  | MOD     | 2-methoxyethanol,<br>acetic acid, 2-ethyl-<br>hexanoic acid | $\text{Pt}-\text{RhO}_x/\text{Si}$                                                    | 650, 750              | 180–225            | 6.2–13.9 | 80         | $10^{10}$               | 238         |
| $\text{Sr}(\text{AcO})_2$ ,<br>$\text{Bi}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_3$ ,<br>$\text{Ta}(\text{OEt})_5$                                                                                                              | MOD     | —                                                           | $\text{Pt}-\text{Rh}/\text{Pt}-\text{Rh}-\text{O}_x$                                  | 650                   | 150–170            | —        | —          | $10^{11}$               | 239         |
| $\text{Sr}(\text{EDTA})_2$ ,<br>$\text{Bi}(\text{EDTA})_3$ ,<br>$\text{Bi}(\text{NO}_3)_3 \cdot 5 \text{H}_2\text{O}$ ,<br>Nb citrate                                                                                          | MOD     | ethylenediamine-<br>tetraacetic acid                        | —                                                                                     | 300, 650              | —                  | —        | —          | —                       | 240         |
| $\text{Bi}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_3$ ,<br>$\text{Sr}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_2$ ,<br>$\text{Ta}(\text{OEt})_5$                                                                                    | MOD     | 2-methoxyethanol,<br>xylene                                 | $\text{Pt}/\text{Ti}/\text{SiO}_2/\text{Si}$                                          | 250, 340,<br>800      | —                  | —        | —          | —                       | 241         |
| $\text{Bi}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_3$ ,<br>$\text{Sr}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_2$ ,<br>$\text{Bi}(\text{AcO})_3$                                                                                    | MOD     | 2-ethylhexanoic<br>acid                                     | $\text{Pt}/\text{TiO}_x/\text{SiO}_2/\text{Si}$                                       | 400, 750              | —                  | —        | —          | —                       | 242         |
| $(\text{Sr},\text{Ba})(\text{n-C}_7\text{H}_{15}\text{CO}_2)_2$ ,<br>$\text{Bi}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_3$ ,<br>$\text{Ta}(\text{OEt})_5$                                                                        | MOD     | toluene                                                     | $\text{Pt}/\text{Ti}/\text{SiO}_2/\text{Si}$                                          | 150, 400,<br>700–750  | —                  | 0.7–1.2  | 37         | —                       | 243         |
| $\text{Sr}(\text{OH})_2 \cdot 8 \text{H}_2\text{O}$ ,<br>$\text{Bi}(\text{AcO})_3$ , $\text{Ta}(\text{OEt})_5$ ,<br>$\text{Ba}(\text{OH})_2 \cdot \text{H}_2\text{O}$                                                          | MOD     | 2-methoxyethanol,<br>2-ethylhexanoic acid,<br>acetic acid   | $\text{Pt}/\text{Ti}/\text{SiO}_2/\text{Si}$                                          | 650, 700              | —                  | —        | —          | —                       | 244         |
| $\text{Sr}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_2$ ,<br>$\text{Bi}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_3$ ,<br>$\text{Ta}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_5$                                                          | MOD     | toluene                                                     | $\text{SrTiO}_3$                                                                      | 800                   | —                  | —        | —          | —                       | 245         |
| $\text{Sr}(\text{AcO})_2$ ,<br>$\text{Bi}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_3$ ,<br>$\text{Ta}(\text{OEt})_5$                                                                                                              | MOD     | 2-ethylhexanoic acid,<br>acetic acid,<br>2-methoxyethanol   | $\text{Pt}/\text{Ti}/\text{SiO}_2/\text{Si}$                                          | 400, 750              | —                  | —        | —          | —                       | 246,<br>247 |
| $\text{Sr}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_2$ ,<br>$\text{Bi}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_3$ ,<br>$\text{Ta}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_5$                                                          | MOD     | n-butyl acetate                                             | $\text{Pt}/\text{Ti}/\text{SiO}_2/\text{Si}$                                          | 150, 400,<br>800      | —                  | 6.75     | 63         | $10^{12}$               | 248         |
| $\text{Sr}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_2$ ,<br>$\text{Bi}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_3$ ,<br>$\text{Ta}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_5$ ,<br>$\text{Nb}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_5$ | MOD     | 2-ethylhexanoic acid                                        | $\text{Pt}/\text{Ti}/\text{SiO}_2/\text{Si}$                                          | 400, 800              | —                  | 5.6–8.5  | 24.94–39.6 | —                       | 249         |
| $\text{Sr}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_2$ ,<br>$\text{Bi}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_3$ ,<br>$\text{Ta}(\text{OEt})_5$                                                                                    | MOD     | xylene, $\text{CF}_4/\text{Ar}$ (plasma)                    | $\text{Pt}/\text{SiO}_2$                                                              | 400, 800              | —                  | —        | —          | —                       | 250         |
| $\text{Sr}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_2$ ,<br>$\text{Bi}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_3$ ,<br>$\text{Ta}(\text{OEt})_5$                                                                                    | sol–gel | propane-1,3-diol,<br>2-ethylhexanoic acid                   | $\text{Pt}/\text{TiO}_2/\text{Si}$                                                    | 225, 550,<br>650      | —                  | 11       | 60         | $10^{10}$               | 251         |

<sup>a</sup> Hereinafter, the polarisation fatigue expressed in the number of cycles.

**Table 14.** Conditions of MOCVD synthesis of ferroelectric thin films of  $\text{SrBi}_2\text{Ta}_2\text{O}_9$  from the gas phase and their properties.

| Starting compounds                                                                                                                                                                                                        | Gases and solvents                                         | Support                              | $T/^\circ\text{C}$ | $P/\text{Torr}$ | Properties of FETF |       |       |           | Ref. |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|--------------------------------------|--------------------|-----------------|--------------------|-------|-------|-----------|------|
|                                                                                                                                                                                                                           |                                                            |                                      |                    |                 | $\varepsilon$      | $P_r$ | $E_c$ | $Y$       |      |
| $\text{Sr}(\text{DPM})_2$ , $\text{BiPh}_3$ , $\text{Ta}(\text{OEt})_5$                                                                                                                                                   | $\text{N}_2$ , $\text{O}_2$ , THF, propan-2-ol, tetraglyme | Pt/Ti/SiO <sub>2</sub> /Si, sapphire | 500–700            | 4–10            | —                  | 4.15  | 60    | $10^{10}$ | 253  |
| $\text{Sr}(\text{HFA})_2 \cdot \text{TG}$ , $\text{BiPh}_3$ , $\text{Ta}(\text{OEt})_5$                                                                                                                                   | Ar, $\text{O}_2$                                           | Pt/Ti/SiO <sub>2</sub> /Si           | 500–600            | —               | 320                | 15    | 50    | $10^{11}$ | 254  |
| $\text{Sr}[\text{Ta}(\text{OEt})_6]_2$ , $\text{BiMe}_3$                                                                                                                                                                  | $\text{O}_2$                                               | Pt/Ti/SiO <sub>2</sub> /Si           | 500–750, 800       | —               | —                  | 6.1   | 87    | —         | 255  |
| $\text{Sr}(\text{DPM})_2 \cdot \text{TG}$ , $\text{BiPh}_3$ , $\text{Ta}(\text{OPr}^i)_4(\text{DPM})$ , $\text{Sr}(\text{DPM})_2 \cdot \text{PMDT}$ , $\text{Bi}(\text{DPM})_3$ , $\text{Ta}(\text{DPM})(\text{OPr}^i)_4$ | $\text{O}_2$                                               | Pt/Ti/Si                             | 330–600            | 2–10            | —                  | 12    | —     | $10^{11}$ | 256  |
| $\text{Sr}[\text{Ta}(\text{OEt})_6]_2$ , $\text{BiPh}_3$                                                                                                                                                                  | Ar, $\text{O}_2$                                           | Pt/SiO <sub>2</sub> /Si              | 300–800            | 3–6             | —                  | —     | —     | —         | 257  |

the films strongly affects the residual polarisation and the coercive field. Oriented films exhibit improved ferroelectric properties. In particular, for the films prepared in the absence of acetylacetone and annealed at 750 °C, the permittivity ( $\varepsilon$ ), residual polarisation ( $P_r$ ) and coercive field ( $E_c$ ) were equal to 119, 3.1  $\mu\text{C cm}^{-2}$  and 65.1  $\text{kV cm}^{-1}$ , respectively. For the similarly prepared film in the presence of acetylacetone, the following values of these parameters were obtained:<sup>252</sup>  $\varepsilon = 205$ ,  $P_r = 7.2 \mu\text{C cm}^{-2}$  and  $E_c = 53.3 \text{ kV cm}^{-1}$ .

Legrand *et al.*<sup>237</sup> prepared 30 nm-thick SBN films by the sol–gel method [deposition on a support of double oxide  $\text{SrTiO}_3(001)$ ]. The films often crystallise in the temperature range 500–700 °C. As a rule, this occurs at a lower temperature, between 500 °C and 550 °C. As a result, epitaxial layers (001)SBN/(001)SrTiO<sub>3</sub> and (100)SBN/(110)SrTiO<sub>3</sub> are formed.<sup>202</sup> The mechanism of crystallisation of the SBN films was studied in detail by Shimizu *et al.*<sup>184</sup>. However, SBN films with the composition 1:2:2:9 can hardly be applied in non-volatile memory elements.

In addition to metal carboxylates and  $\beta$ -diketonates, aryl derivatives and preformed bimetallic alkoxides are used in the preparation of SBT films by the MOCVD method (Table 14). Multilayer composites with the composition Pt/Ti/SiO<sub>2</sub>/Si are typically used as supports. The temperature of the process is typically varied from 300 to 800 °C and the residual pressure, from 1 to 10 Torr. Alkyl, aryl and dipivaloylmethane bismuth derivatives deposited at 500 °C,<sup>255</sup> 470 °C<sup>256</sup> and 330 °C, respectively. The use of aryl derivatives complicates the control over the

preparation of films with required compositions.<sup>256</sup> Final characteristics of the films are largely determined by the temperature regime of annealing; some of them are listed in Table 14.

## 7. Films of $\text{Bi}_4\text{Ti}_3\text{O}_{12}$

Films of  $\text{Bi}_4\text{Ti}_3\text{O}_{12}$  (also referred to as BTO) are synthesised most often by the sol–gel and CVD methods (Tables 15 and 16). In the former method, metal alkoxides and carboxylates (primarily, acetates and naphthenates) are typically used. In the latter method, the available starting compounds are employed, *e.g.*, alkoxy or aryl derivatives or metal  $\beta$ -diketonates. Crackless films are produced from  $\text{Bi}(\text{NO}_3)_3$ ,  $\text{Ti}(\text{OPr}^i)_4$  and  $\text{Ti}(\text{OBu}^n)_4$  dissolved in glacial acetic acid or monoglyme. This was achieved by applying solutions of the starting compounds onto platinum-coated silicon or  $\text{SrTiO}_3(100)$  supports using spin-coating followed by annealing at 500 °C or 600 °C, respectively. This resulted in well-ordered films which consequently possessed good dielectric and ferroelectric properties. The films synthesised by the MOD method were additionally annealed at 700 °C and manifested the following characteristics: permittivity, 184 at a signal frequency of 100 kHz; dielectric loss tangent, 0.039; residual polarisation, 4.4  $\mu\text{C cm}^{-2}$ ; coercive force, 84  $\text{kV cm}^{-1}$ ; resistivity,  $10^8 \Omega \text{ cm}$  at room temperature; mean leakage current density,  $10^{-7} \text{ A cm}^{-2}$  at a film thickness of 0.5  $\mu\text{m}$  under an applied field of 100  $\text{kV cm}^{-1}$ . The hysteresis loop on the polarisation curve remained unchanged over  $10^{10}$  cycles of repolarisation.<sup>274</sup>

**Table 15.** Conditions of synthesis of ferroelectric thin films of  $\text{Bi}_4\text{Ti}_3\text{O}_{12}$  from metal carboxylates and their properties.

| Starting compounds                                                                                                                                                                         | Method  | Solvents                                   | Support                                   | $T/^\circ\text{C}$ | $P/\text{Torr}$ | Properties of FETF |       |       |        | Ref. |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------------------------------------------|-------------------------------------------|--------------------|-----------------|--------------------|-------|-------|--------|------|
|                                                                                                                                                                                            |         |                                            |                                           |                    |                 | $\varepsilon$      | $P_r$ | $E_c$ | $Y$    |      |
| $\text{Bi}(\text{AcO})_3$ , $\text{Ti}(\text{OPr}^i)_4$ , $\text{Ti}(\text{OCH}_2\text{CH}_2\text{OMe})_4$                                                                                 | sol–gel | acetic acid, 2-methoxyethanol              | Pt/Ti/SiO <sub>2</sub> /Si                | 128–135, 200, 700  | —               | 120, 132           | 4     | 1.8   | —      | 258  |
| $\text{Bi}, \text{Ti}$ naphthenates, $\text{O}_2$                                                                                                                                          | MOD     | —                                          | —                                         | —                  | $4 \times 10^5$ | 45                 | 1.9   | 23    | $10^7$ | 259  |
| $\text{Bi}(\text{NO}_3)_3 \cdot 5 \text{H}_2\text{O}$ , $\text{Bi}(\text{AcO})_3$ , $\text{Ti}(\text{OPr}^i)_4$                                                                            | sol–gel | 2-methoxyethanol, acetic acid, propan-2-ol | —                                         | 124, 300, 750      | —               | —                  | —     | —     | —      | 260  |
| $\text{Bi}(\text{NO}_3)_3 \cdot 5 \text{H}_2\text{O}$ , $\text{Bi}(\text{AcO})_3$ , $\text{Bi}(\text{n-C}_7\text{H}_{15}\text{CO}_2)_3$ , $\text{Ti}(\text{OCH}_2\text{CH}_2\text{OMe})_4$ | "       | —                                          | Pt/Ti/SiO <sub>2</sub> /Si                | 550                | —               | 105                | 13.5  | 60    | —      | 261  |
| $\text{Bi}(\text{AcO})_3$ , $\text{Ti}(\text{OMe})_4$                                                                                                                                      | "       | 2-ethylhexanoic acid, ethanol              | Pt/TiO <sub>x</sub> /SiO <sub>2</sub> /Si | 250, 550–700       | —               | —                  | —     | —     | —      | 262  |

**Table 16.** Conditions of MOCVD synthesis of ferroelectric thin films of  $\text{Bi}_4\text{Ti}_3\text{O}_{12}$  and their properties.

| Starting compounds                                                               | Support                                                                         | Process conditions     |                        |                   | Properties of FETF |         |        |           | Ref.     |
|----------------------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------|------------------------|-------------------|--------------------|---------|--------|-----------|----------|
|                                                                                  |                                                                                 | $T_v / ^\circ\text{C}$ | $T_p / ^\circ\text{C}$ | $P / \text{Torr}$ | $\epsilon$         | $P_r$   | $E_c$  | $Y$       |          |
| $\text{BiPh}_3$ , $\text{Ti(OPr}^i)_4$                                           | Pt/Ti/SiO <sub>2</sub> /Si, sapphire                                            | 120–150, 35            | 500–750                | 1–5               | 180                | 0.6     | 13     | —         | 263      |
| $\text{BiPh}_3$ , $\text{Ti(OEt)}_4$                                             | Pt/Ti/SiO <sub>2</sub> /Si, sapphire                                            | 165–170, 75–127        | 450–500                | 6                 | —                  | 19.6    | 244.3  | —         | 264      |
| $\text{BiPh}_3$ , $\text{Ti(OBu)}_4$                                             | Si                                                                              | 130–140, 150–170       | 550                    | —                 | 93                 | 38      | 45     | —         | 265      |
| $\text{BiPh}_3$ , $\text{Ti(OPr}^i)_4$                                           | Pt/SiO <sub>2</sub> /Si                                                         | 140, 30                | 480–650                | 5                 | 130                | 1.3     | 25     | —         | 266      |
| $\text{BiPh}_3$ , $\text{Ti(OBu)}_4$                                             | Si(100)                                                                         | 150–170, 130–140       | 450–750, 600–800       | —                 | —                  | —       | —      | —         | 267      |
| $\text{Bi}(o\text{-C}_7\text{H}_7)_3$ , $\text{Ti(OPr}^i)_4$                     | Pt/Ta/SiO <sub>2</sub> /Si, p-Si, $\text{Bi}_2\text{SiO}_5/\text{Si}/\text{Al}$ | 160, 50                | 400, 500               | 2–10              | 30                 | 9–11    | 120–90 | $10^{12}$ | 268, 269 |
| $\text{Bi}(o\text{-C}_7\text{H}_7)_3$ , $\text{Ti(OPr}^i)_4$                     | Pt/Ta/SiO <sub>2</sub> /Si, $\text{BiO}_x$ -buffer                              | —                      | 400                    | 5                 | —                  | 1.9–8.2 | 55–90  | —         | 270      |
| $\text{BiPh}_3$ , $\text{Ti(OMe)}_4$                                             | Pt/SiO <sub>2</sub> /Si                                                         | 270                    | 640                    | 6                 | 132                | 38      | 45     | —         | 271      |
| $\text{BiMe}_3$ , $\text{Ti(OPr}^i)_4$ , $\text{La(DPM)}_3$ , $\text{VO(OEt)}_3$ | Ir/TiO <sub>2</sub> /SiO <sub>2</sub> /Si, Pt/Ti/SiO <sub>2</sub> /Si           | —                      | 600                    | —                 | —                  | —       | —      | —         | 272, 273 |

Jones *et al.*<sup>179</sup> accomplished deposition of films onto multi-layer composite supports Pt/Ti/SiO<sub>2</sub>/Si from vapour of organometallic precursors. The  $\text{Bi}_4\text{Ti}_3\text{O}_{12}$  phase proved sensitive to pyrolysis and annealing due to diffusion of titanium into bismuth titanate to yield the  $\text{Bi}_2\text{Ti}_2\text{O}_7$  phase. Nevertheless, the ferroelectric properties of the resultant film were satisfactory: residual polarisation of  $8.2 \mu\text{C cm}^{-2}$  and coercive force of  $7 \text{ kV cm}^{-1}$ . Malik *et al.*<sup>275</sup> prepared thin films of BTO on Si(100) supports from vapour of  $\text{BiPh}_3$  and  $\text{Ti(OBu)}_4$  at  $550^\circ\text{C}$  and atmospheric pressure using  $\text{N}_2$  as a carrier gas and  $\text{O}_2$  as an oxidant. According to the X-ray diffraction study, the single-crystal films exclusively exposed (100) crystal faces. The residual polarisation and coercive force were  $38 \mu\text{C cm}^{-2}$  and  $45 \text{ kV cm}^{-1}$ , respectively. Desu *et al.*<sup>276</sup> also used  $\text{BiPh}_3$  and  $\text{Ti(OBu)}_4$  for the same purpose; they studied the film growth as a function of the oxidant concentration. The films were deposited at  $600^\circ\text{C}$  on composite supports Pt(111)/SiO<sub>2</sub>/Si(100) with buffer layers of  $\text{Bi}_2\text{Ti}_2\text{O}_7$ . The final films were characterised by a residual polarisation of  $1.3 \mu\text{C cm}^{-2}$ , coercive force of  $25 \text{ kV cm}^{-1}$ , permittivity of 130 and leakage current density of  $10^{-8} - 10^{-7} \text{ A cm}^{-2}$ .

The possibility of growing thin films of BTO from metal alkoxides by the MOCVD method at a temperature below  $400^\circ\text{C}$  has been demonstrated.<sup>268–270</sup> The films with a thickness of 100 nm manifested good surface morphology and good ferroelectric properties: residual polarisation of  $11 \mu\text{C cm}^{-2}$ , coercive force of  $90 \text{ kV cm}^{-1}$  and leakage current density of  $7 \times 10^{-9} \text{ A cm}^{-2}$  at 3 V. The ferroelectric properties of the films with a thickness of 50 nm were satisfactory:  $P = 9 \mu\text{C cm}^{-2}$  and  $E_c = 120 \text{ kV cm}^{-1}$ . No polarisation fatigue of the film was observed after  $10^{12}$  switches.

#### IV. Metal and metal oxide electrodes, prepared from organometallic precursors, for thin-film capacitors

Thin films of ferroelectrics can be used as electrode-separating dielectric layers in the manufacture of capacitors for the memory elements of SLIC. With this regard, the issue of polarisation fatigue of the capacitors due to ageing of the ferroelectric material becomes of key importance.

Both metals, such as platinum, gold, ruthenium, iridium and titanium, and highly conductive metal oxides, such as  $\text{RuO}_2$ ,  $\text{IrO}_2$ ,  $\text{SrRuO}_3$ ,  $\text{CaRuO}_3$ ,  $\text{LaNiO}_3$  and  $(\text{La,Sr})\text{CoO}_3$ , are used as

the electrode materials. These can be produced by vapour deposition from the following organometallic precursors:  $\text{Pt}(\text{acac})_2$ ,<sup>277, 278</sup>  $\text{MeCpPtMe}_3$ ,<sup>279–284</sup>  $\text{Au}(\text{HFA})\text{Me}_2$ ,<sup>285, 286</sup>  $\text{Me}_2\text{Au}(\text{TFA})$  (TFA is 1,1,1-trifluoropentane-2,4-dione),  $\text{Me}_2\text{Au}(\text{HFA})$ ,  $\text{Me}_2\text{Au}(\text{acac})$ ,<sup>287</sup>  $\text{AuR}(\text{CN})\text{R}'$  ( $\text{R} = \text{Me}$ ,  $\text{Ph}$ , vinyl, prop-1-ynyl, 3,3-dimethylbutyl;  $\text{R}' = \text{Me}$ ,  $\text{Et}$ ,  $\text{Pr}^i$ ,  $\text{Bu}^i$ ,  $\text{Ph}$ ),<sup>288</sup>  $\text{Ru}(\text{EtCp})_2$ ,  $[\text{RuC}_5\text{H}_5(\text{CO})_2]_2$ ,<sup>289</sup>  $\text{Ru}_3(\text{CO})_{12}$ ,<sup>282</sup>  $\text{Ir}(\text{acac})_3$ ,  $\text{Ir}(\text{acac})\text{Cl}_2$ ,<sup>290</sup>  $(\text{EtCp})\text{Ir}(\text{COD})_2$  (COD is cyclooctadiene).<sup>291, 292</sup>

The starting compounds and selected technological parameters of the film deposition on supports are given in Table 17. For the preparation of  $\text{RuO}_2$  films,  $\text{RuCp}_2$ ,  $\text{Ru}(\text{DPM})_2$  and  $\text{Ru}(\text{EtCp})_2$  are most commonly utilised, whereas iridium cyclopentadienyl complexes and their derivatives are applied to the synthesis of  $\text{IrO}_2$ . Double oxides  $\text{SrRuO}_3$  and  $\text{LaNiO}_3$  can be prepared from  $\beta$ -diketonates of the respective metals, *e.g.*,  $\text{Sr}(\text{DPM})_2 \cdot (\text{C}_8\text{H}_{23}\text{N}_5)_x$ ,  $\text{La}(\text{DPM})_3$ ,  $\text{Ni}(\text{DPM})_2$  or  $\text{Ni}(\text{acac})_2$ . Films of  $\text{YBa}_2\text{Cu}_3\text{O}_7$  prepared from yttrium, barium and copper dipivaloylmethanates are sometimes employed.<sup>313, 314</sup>

\* \* \*

Studies conducted over the last 15 years have clearly demonstrated the possibility of using the effect of spontaneous polarisation in ferroelectric materials for the creation of the non-volatile memory elements. The requirements to such materials have been formulated.

Among chemical methods used for the preparation of ferroelectric thin films, the MOCVD method has become the most popular. Over the last few years, this method has been widely applied, in particular, for high-temperature coatings and superconductors.<sup>318</sup> Ferroelectric thin films manifesting the lowest polarisation fatigue have been synthesised, for which the maximum number of recirculation cycles reaches  $10^{11} - 10^{12}$ . Among the oxide films considered above, the following materials that are promising as ferroelectrics can be distinguished:  $\text{Ta}_2\text{O}_5$ ,  $\text{YMnO}_3$ ,  $\text{BaTiO}_3$ ,  $\text{SrTiO}_3$ ,  $(\text{Ba,Sr})\text{TiO}_3$ ,  $\text{PbTiO}_3$ ,  $\text{Pb}(\text{Zr,Ti})\text{O}_3$ ,  $\text{Pb}(\text{Sr,Ti})\text{O}_3$ ,  $\text{Bi}_4\text{Ti}_3\text{O}_{12}$ ,  $\text{SrBi}_2\text{Ta}_2\text{O}_9$ . An analysis of the temperature regimes of the preparation of oxide films shows that it is the annealing step that is of key importance. Control over this step can enable preparation of films with a layered perovskite-type structure. A systematic consideration of the methods for the synthesis of ferroelectric thin films with the emphasis placed on diverse chemical methods suggests the priority of the CVD



**Table 17.** Characteristics of oxides used as electrodes for ferroelectric thin films.

| Conductive oxide                                | Synthesis method | Starting compounds                                                                                                                                                                                                             | Solvents, oxidant gases                                            | Support                                 | Process conditions       |                  | $\rho$ / $\mu\Omega$ cm | Ref.     |
|-------------------------------------------------|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|-----------------------------------------|--------------------------|------------------|-------------------------|----------|
|                                                 |                  |                                                                                                                                                                                                                                |                                                                    |                                         | $T$ / $^{\circ}\text{C}$ | $P$ /Torr        |                         |          |
| RuO <sub>2</sub>                                | CVD              | Ru(DPM) <sub>3</sub>                                                                                                                                                                                                           | O <sub>2</sub> , N <sub>2</sub>                                    | Pt/Ti/SiO <sub>2</sub> /Si              | 450                      | 4                | 34–40                   | 293      |
|                                                 | CVD              | RuCp <sub>2</sub>                                                                                                                                                                                                              | O <sub>2</sub>                                                     | SiO <sub>2</sub> /Si                    | 200–350                  | 3                | 75–138                  | 294      |
|                                                 | CVD              | Ru <sub>3</sub> (CO) <sub>12</sub>                                                                                                                                                                                             | O <sub>2</sub>                                                     | Ru/SiO <sub>2</sub> /Si                 | 250                      | 2                | —                       | 295      |
|                                                 | CVD              | RuCp <sub>2</sub>                                                                                                                                                                                                              | O <sub>2</sub>                                                     | LaAlO <sub>3</sub> , MgO                | —                        | —                | 40–50                   | 296      |
|                                                 | MOD              | Ru(OC <sub>8</sub> H <sub>17–n</sub> ) <sub>4</sub>                                                                                                                                                                            | xylene, pentanol                                                   | Si(100)                                 | 300, 550                 | —                | —                       | 297      |
|                                                 | CVD              | RuCp <sub>2</sub>                                                                                                                                                                                                              | —                                                                  | Si                                      | 500–600                  | 10 <sup>–2</sup> | —                       | 298      |
|                                                 | CVD              | Ru(DPM) <sub>2</sub> (CO) <sub>2</sub>                                                                                                                                                                                         | —                                                                  | Si                                      | 450                      | 4.5              | —                       | 299      |
|                                                 | CVD              | Ru(DPM) <sub>2</sub> (COD)                                                                                                                                                                                                     | O <sub>2</sub>                                                     | Si                                      | 250–500                  | 1–10             | 200                     | 300      |
|                                                 | CVD              | Ru(EtCp) <sub>2</sub>                                                                                                                                                                                                          | O <sub>2</sub> , N <sub>2</sub>                                    | Ru/SiO <sub>2</sub> /Si                 | 120, 355                 | —                | 17–120                  | 301, 302 |
|                                                 | CVD              | Ru(DPM) <sub>3</sub>                                                                                                                                                                                                           | —                                                                  | Si                                      | 250–450                  | —                | 45–60                   | 303      |
|                                                 | sol–gel          | Ru(NO)(NO <sub>3</sub> ) <sub>3</sub>                                                                                                                                                                                          | Me <sub>4</sub> NOBu <sup>a</sup> , ethanol, Pr <sup>o</sup> OH    | Si                                      | 600                      | —                | —                       | 304      |
|                                                 | "                | RuCl <sub>3</sub> · <i>x</i> H <sub>2</sub> O                                                                                                                                                                                  | propan-2-ol, citric acid, ethylene glycol                          | Si                                      | 130, 250, 450            | —                | —                       | 305      |
| IrO <sub>2</sub>                                | CVD              | Ir(MeCp)(COD)                                                                                                                                                                                                                  | —                                                                  | Si                                      | 350–450                  | 0.005            | —                       | 298      |
| SrRuO <sub>3</sub>                              | MOD              | Ru(n-C <sub>7</sub> H <sub>15</sub> CO <sub>2</sub> ) <sub>4</sub><br>Sr(n-C <sub>8</sub> H <sub>17</sub> ) <sub>2</sub>                                                                                                       | xylene, butanol                                                    | SrTiO <sub>3</sub>                      | 300–750                  | —                | —                       | 297      |
| SrRuO <sub>3</sub> , CaRuO <sub>3</sub>         | CVD              | Sr(DPM) <sub>2</sub> ·(C <sub>8</sub> H <sub>23</sub> N <sub>5</sub> ) <sub>x</sub> ,<br>Ca(DPM) <sub>2</sub> ·(C <sub>8</sub> H <sub>23</sub> N <sub>5</sub> ) <sub>x</sub> ,<br>Ru(DPM) <sub>3</sub>                         | —                                                                  | SrTiO <sub>3</sub>                      | 750                      | —                | 300, 200                | 306, 307 |
| LaNiO <sub>3</sub>                              | CVD              | La(DPM) <sub>3</sub> , Ni(DPM) <sub>2</sub>                                                                                                                                                                                    | —                                                                  | MgO                                     | 750–850                  | 8–10             | —                       | 308      |
|                                                 | MOD              | La(NO <sub>3</sub> ) <sub>3</sub> ,<br>Ni(C <sub>4</sub> H <sub>5</sub> O <sub>2</sub> ) <sub>2</sub>                                                                                                                          | citric acid                                                        | —                                       | 300–800                  | —                | —                       | 309      |
|                                                 | sol–gel          | La(NO <sub>3</sub> ) <sub>3</sub> ,<br>Ni(AcO) <sub>2</sub> ·3 H <sub>2</sub> O                                                                                                                                                | —                                                                  | SrTiO <sub>3</sub> , LaAlO <sub>3</sub> | —                        | —                | —                       | 310      |
|                                                 | MOD              | La(NO <sub>3</sub> ) <sub>3</sub> ,<br>La(n-C <sub>7</sub> H <sub>15</sub> CO <sub>2</sub> ) <sub>3</sub> ,<br>Ni(AcO) <sub>2</sub> ·4 H <sub>2</sub> O,<br>Ni(n-C <sub>7</sub> H <sub>15</sub> CO <sub>2</sub> ) <sub>2</sub> | water, acetic acid                                                 | Si(100)                                 | 450–650                  | —                | 760                     | 311      |
| YBa <sub>2</sub> Cu <sub>3</sub> O <sub>7</sub> | CVD              | Y(DPM) <sub>3</sub> ,<br>Ba(DPM) <sub>2</sub> ,<br>Cu(DPM) <sub>2</sub>                                                                                                                                                        | O <sub>2</sub> /N <sub>2</sub> O                                   | SrTiO <sub>3</sub>                      | 150, 270                 | 3.5              | —                       | 312, 313 |
| (La,Sr)CoO <sub>3</sub>                         | sol–gel          | La <sub>2</sub> O <sub>3</sub> ,<br>Co(NO <sub>3</sub> ) <sub>2</sub> ·6 H <sub>2</sub> O,<br>Sr(NO <sub>3</sub> ) <sub>2</sub>                                                                                                | citric acid, ethylenediamine                                       | —                                       | —                        | —                | —                       | 314      |
|                                                 | MOD              | La(NO <sub>3</sub> ) <sub>3</sub> ·6 H <sub>2</sub> O<br>SrCl <sub>2</sub> ·6 H <sub>2</sub> O,<br>Co(NO <sub>3</sub> ) <sub>2</sub> ·6 H <sub>2</sub> O                                                                       | 2-methoxyethanol                                                   | SrTiO <sub>3</sub>                      | 110, 500, 800            | —                | 10–13                   | 315      |
|                                                 | MOD              | La(NO <sub>3</sub> ) <sub>3</sub> ·6 H <sub>2</sub> O,<br>Sr(NO <sub>3</sub> ) <sub>3</sub> ,<br>Co(NO <sub>3</sub> ) <sub>2</sub> ·6 H <sub>2</sub> O                                                                         | glycine, citric acid, C <sub>2</sub> H <sub>6</sub> O <sub>2</sub> | CeO <sub>2</sub> , MgO                  | 80                       | —                | —                       | 316      |
|                                                 | CVD              | La(DPM) <sub>3</sub> ,<br>Sr(DPM) <sub>2</sub> ,<br>Co(DPM) <sub>2</sub>                                                                                                                                                       | —                                                                  | LaAlO <sub>3</sub> , MgO                | —                        | —                | 0.85 × 10 <sup>3</sup>  | 317      |

processes. Mixed-ligand complexes based on metal  $\beta$ -diketonates as are mainly used as the starting compounds. Metal and conductive oxide layers have been proposed for the manufacture of capacitors based on ferroelectric thin films and their effects on polarisation fatigue properties have been studied.

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<sup>a</sup> — *Phys. Solid. State (Engl. Transl.)*

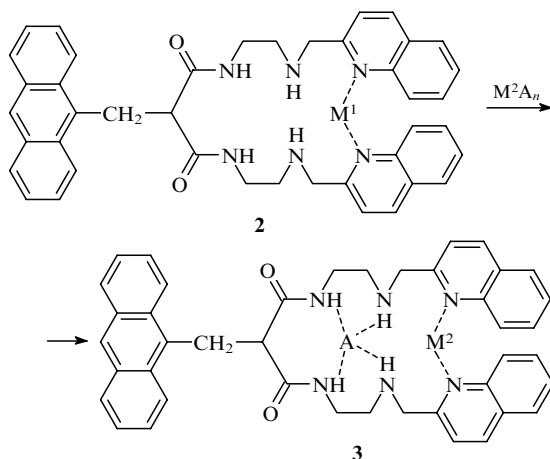
<sup>b</sup> — *J. Exp. Theor. Phys. (Engl. Transl.)*

<sup>c</sup> — *J. Techn. Phys. (Engl. Transl.)*

<sup>d</sup> — *Inorg. Chem. (Engl. Transl.)*

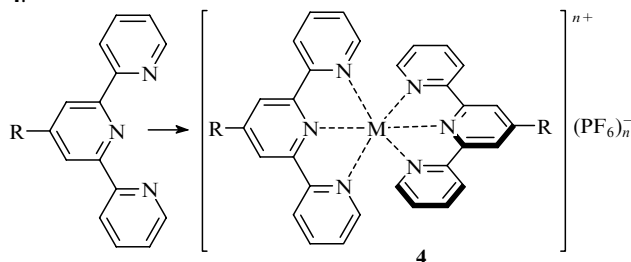
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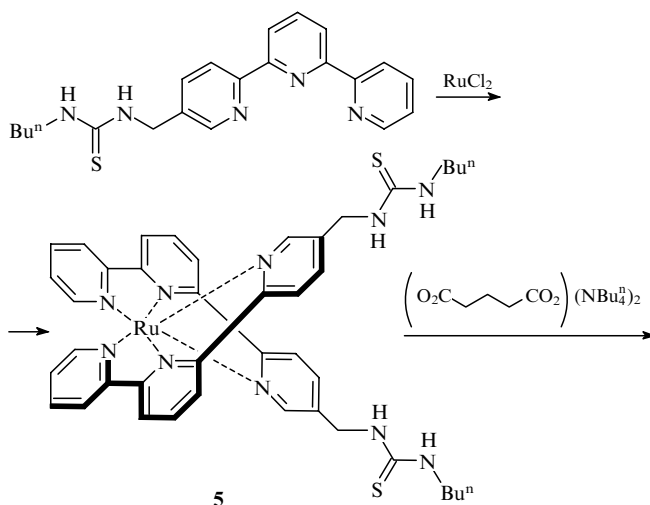
$M^1$  and  $M^2$  are metal cations,  $A$  is an anion.

Terpyridyl ligands are involved in the formation of inclusion compounds with transition metal cations and the  $PF_6^-$  anion, which occurs in the outer sphere. The reaction of polypyridyl-containing receptors with  $FeCl_2$ ,  $RuCl_3$  and  $CoAc_2$  in the presence of  $NH_4PF_6$  results in the isolation of stable hexafluorophosphates **4**,<sup>6,7</sup>

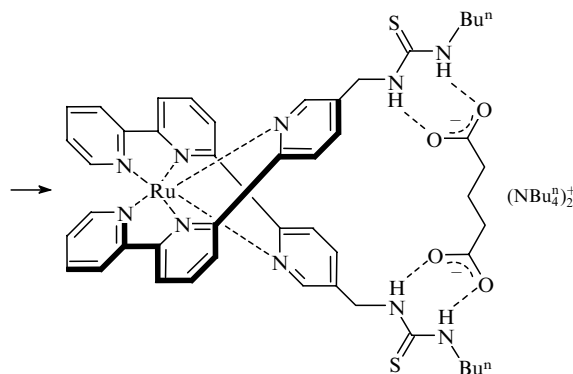


$R = Ph_2P, Ph_2PO$ .

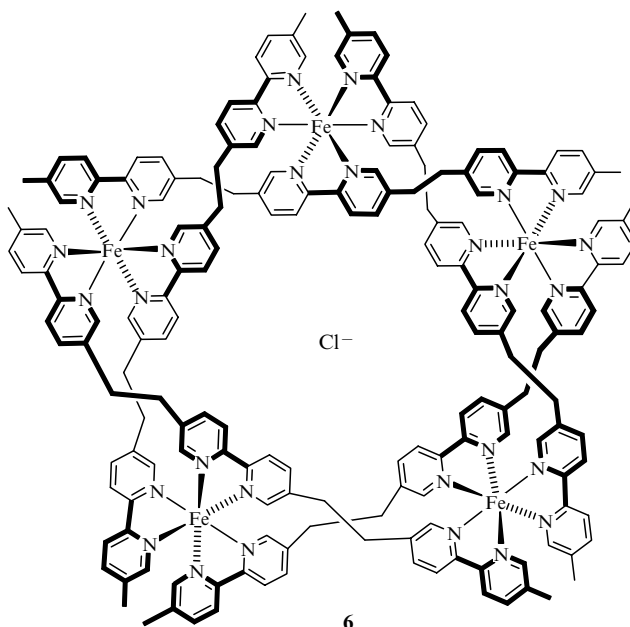
The combination of pyridyl fragments and (thio)urea residues within one molecule enables the use of these compounds for the simultaneous binding of transition metal cations and dicarboxylic acid anions. In particular, upon the formation of a  $Ru(II)$  complex with two terpyridyl fragments, the urea residues are arranged in space in such a way that they can interact with dicarboxylic acids. For example, compound **5** (based on terpyridyl-substituted thio-



urea) selectively extracts the glutarate anion [ $K_{ass} = 8300 \text{ mol litre}^{-1}$  (see<sup>†</sup>)].



The replacement of the thiourea fragment by the urethane residue results in non-covalent binding of the acetate.<sup>8</sup> An interesting case of the construction of supramolecular structures with simultaneous complexation of  $Fe^{3+}$  and  $Cl^-$  ions has been discovered.<sup>9</sup> Ensemble **6** was obtained upon the template reaction between five tris(bipyridyl) ligands and  $FeCl_3$ .



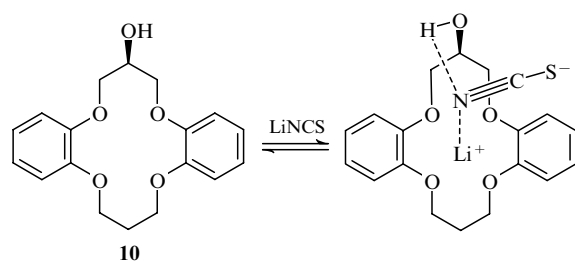
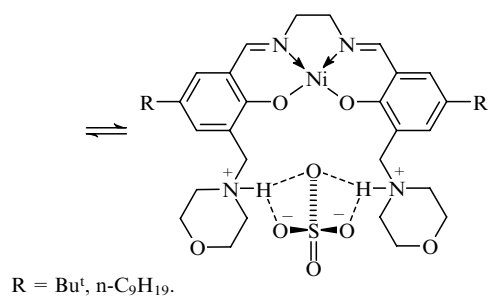
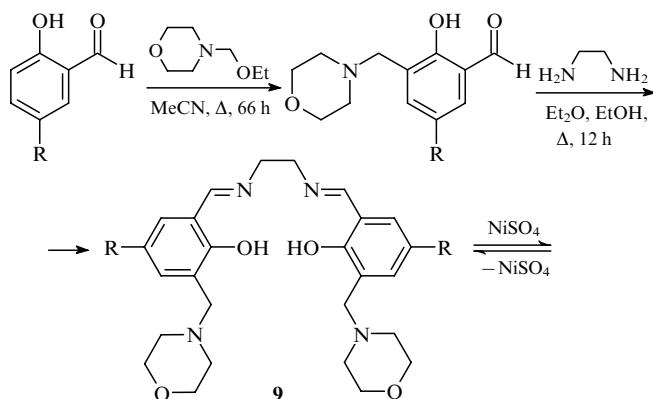
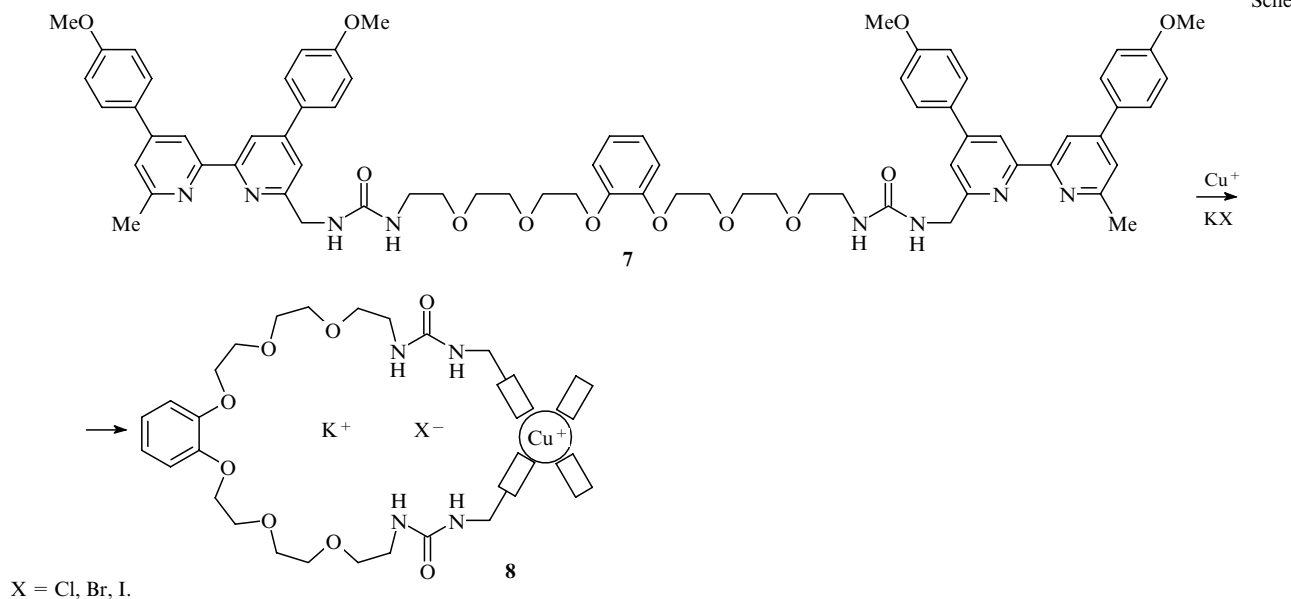
Recently,<sup>10</sup> an ion pair receptor has been prepared on the basis of a pseudocrown ether modified by urea and a bipyridyl fragment. The resulting compound **7** is complexed with  $Cu(I)$  through bipyridyl groups to form closed structure **8**, whose cavity is suitable for the complexation of a potassium cation. Due to the presence of anion-binding sites, this compound can be used for the recognition of ion pairs, the receptor ability decreasing in the sequence  $Cl^- \gg Br^- > I^-$  (Scheme 1).

A few examples of heteroditopic receptors devoid of pyridyl and ureide fragments have been reported. It was shown that monodendate pyrazole and 3(5)-*tert*-butylpyrazole as solutions in methanol form stable complexes  $[ZnX(Het)_3]X$ , where  $X = Cl, Br, I$ , with zinc halides either in the solid state or as solutions in non-polar solvents.<sup>11</sup>

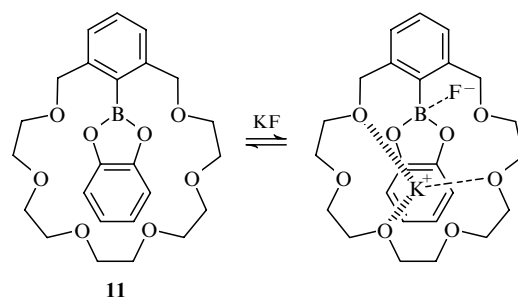
Compound **9** in the zwitter-ionic form is capable of the separate extraction of cations and anions.<sup>12,13</sup>

<sup>†</sup> Here and below, the binding constant is given in  $\text{mol litre}^{-1}$ .

Scheme 1



Crown ethers linked with Lewis acid fragments by covalent bonds represent another example of heteroditopic receptors. It was found that the oxygen atoms of the crown ether ring in compound **11** coordinate the potassium cation, the fluoride anion being bound simultaneously by the boron atom.



### III. The design of heteroditopic receptors based on crown ethers and calixarenes

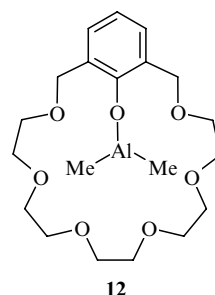
Crown ethers and calixarenes are selective extractants for metals and therefore they are often used for the design of heteroditopic complexing agents as cation-binding sites.

#### 1. Crown-containing ligands

Crown ether **10**, containing a free hydroxy group, is among the first examples of heteroditopic receptors based on a macrocyclic matrix. This compound as a suspension in THF binds simultaneously a Li<sup>+</sup> cation and a thiocyanate anion.<sup>14</sup> The cation is retained by the macrocyclic cavity, while the thiocyanate anion is coordinated to the hydroxy group due to the formation of an intermolecular hydrogen bond.

However, in an attempt to trap KCl or KBr in the same way, compound **11** acts only as a cation acceptor.

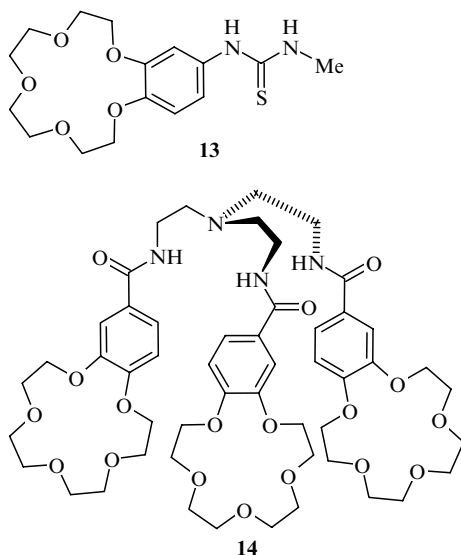
Related compound **12**, prepared by the reaction of the corresponding alcohol with Me<sub>3</sub>Al, forms a complex with lithium chloride both in solution and in a suspension in THF.<sup>15–17</sup>



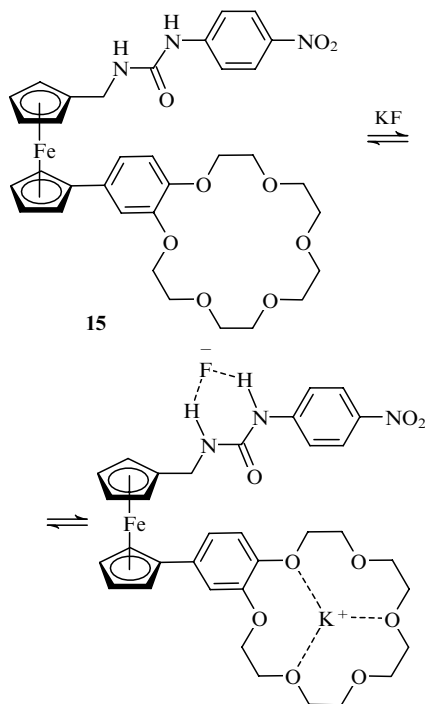


The introduction of urea fragments or amide groups, which tend to bind anions, into crown ether molecules allows one to use these compounds as bifunctional receptors.

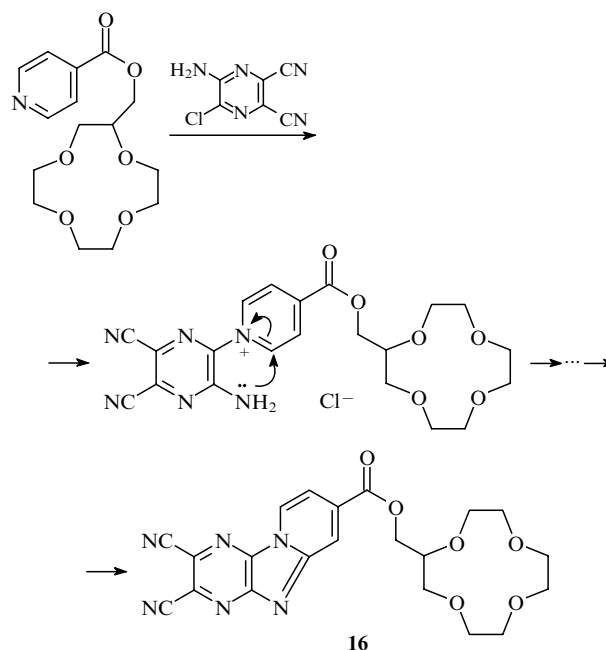
A study of the binding of benzo-15-crown-5 ether, modified by a thiourea residue, to a series of anions has shown that upon the addition of two equivalents of  $\text{NaBPh}_4$ , ligand **13** captures the  $\text{NO}_3^-$  ( $K_{\text{ass}} = 66$ )  $\text{Br}^-$  ( $K_{\text{ass}} = 260$ ), and  $\text{I}^-$  ( $K_{\text{ass}} = 20$ ) anions.<sup>18</sup> Compound **14** forms complexes with the  $\text{Cl}^-$ ,  $\text{I}^-$  and  $\text{ReO}_4^-$  anions upon the introduction of one equivalent of sodium picrate.<sup>19</sup>



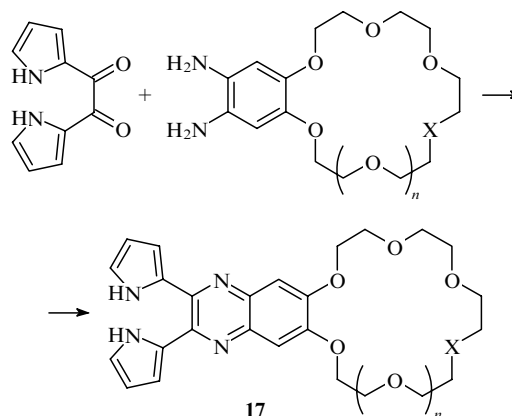
Nitrophenyl-substituted ureas are known to extract anions. Hence, one can expect that the introduction of such a residue into a benzocrown ether molecule would afford a heteroditopic receptor. However, it was found that for simultaneous binding of a cation and an anion, the molecule requires an additional modification with a fragment that would fix the complexation sites in space in an effective manner. Ferrocene proved to be the most appropriate spacer; this was used to synthesise the selective receptor for potassium fluoride **15**.<sup>20</sup>



Subsequently, examples of using hetaryl derivatives of crown ethers as bifunctional complexing agents have appeared in the literature. For example, a crown ether containing diaminopyridyl residues has been synthesised.<sup>21</sup> This molecule is capable of recognising monopotassium salts of dicarboxylic acids due to the formation of a hydrogen bond between the carboxyl group and the diaminopyridyl fragment, and the coordination of the potassium cation by the crown-ether oxygen atoms. 12-Crown-4 ether **16** modified with pyrido[1',2':1,2]imidazo[4,5-*b*]pyrazine exhibits complexing properties unusual for a compound with this size of molecular cavity. It was found by UV spectroscopy that compound **16** effectively reacts with  $\text{Ba}(\text{SCN})_2$  giving rise to a stable complex ( $\log K_{\text{ass}} = 3.98$ ).<sup>22</sup>

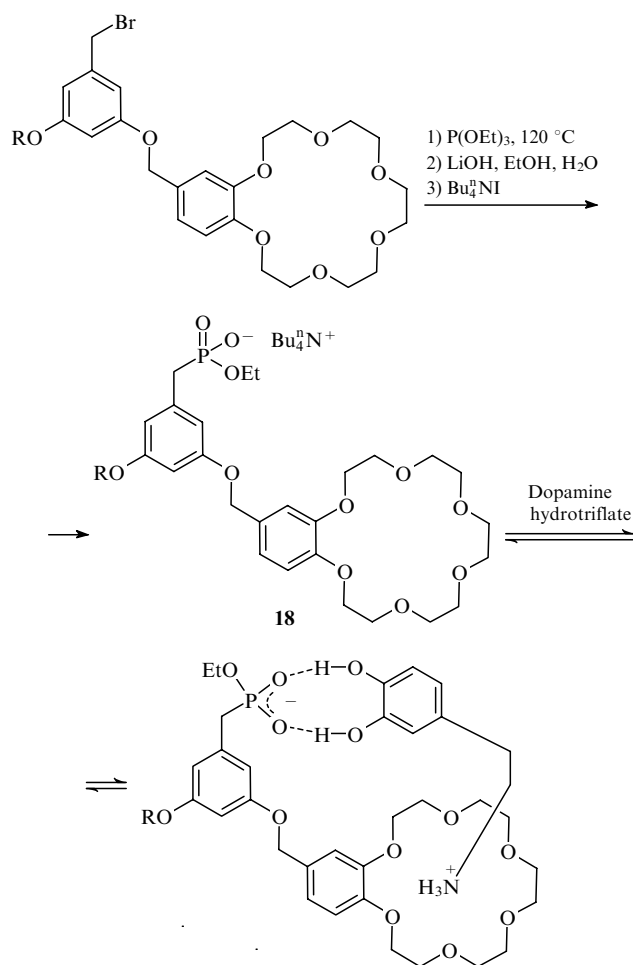


Recently, ditopic receptors **17** of a new class based on dipyrrolylquinoxaline have been prepared by the reaction of 1,2-diaminobenzocrown ethers with 1,2-dipyrrolylethane-1,2-dione.<sup>23</sup> Using NMR spectroscopy, it was shown that these compounds form complexes with the sodium cation and the fluoride anion.



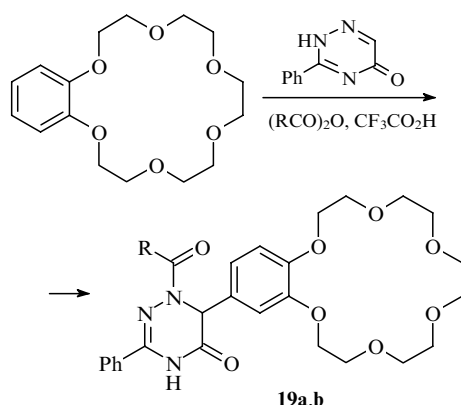
X = O, NH;  $n = 0, 1$ .

Heteroditopic receptors are used not only for binding inorganic ions but also for complex formation with bipolar organic molecules. The combination, within one crown-ether host molecule, of a fragment capable of forming complexes with the  $\text{NH}_3^+$  group and an organophosphorus residue able to capture anions accounts for the use of compound **18** for dopamine transport.<sup>24</sup>



$\text{R} = n\text{-C}_{18}\text{H}_{37}$ .

Direct, metal-noncatalysed C–C coupling of 1,2,4-triazin-5-one and benzo-18-crown-6 ether has furnished triazine-containing benzocrown ethers **19a,b**,<sup>25</sup> which form complexes with amino acids. According to  $^1\text{H}$  NMR spectroscopy, compound **19b** selectively extracts  $\beta$ -phenylalanine due to binding of the  $\text{NH}_3^+$  group by the crown ether fragment and hydrogen bonding between the NH group of the triazine ring and the carboxyl group of the amino acid.

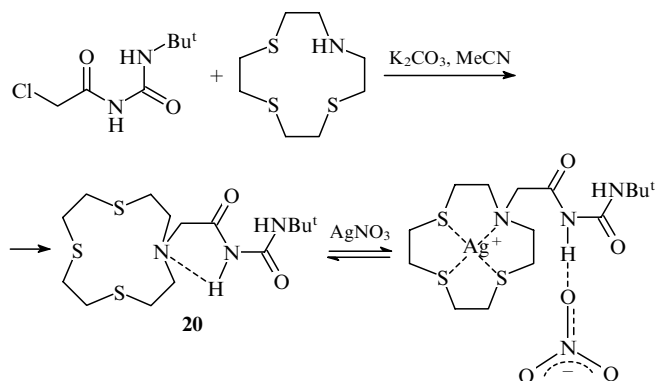


$\text{R} = \text{Me}$  (a),  $\text{CF}_3$  (b).

The formation of the complex is indicated by the upfield shift (by 0.07 ppm) of the  $^1\text{H}$  NMR signals of the methylene groups of the crown ether ring.<sup>26</sup>

Thiaazacrown compounds are the most vivid representatives of heteroditopic receptors. They are used most often to capture ion pairs formed from transition metal cations and anions of

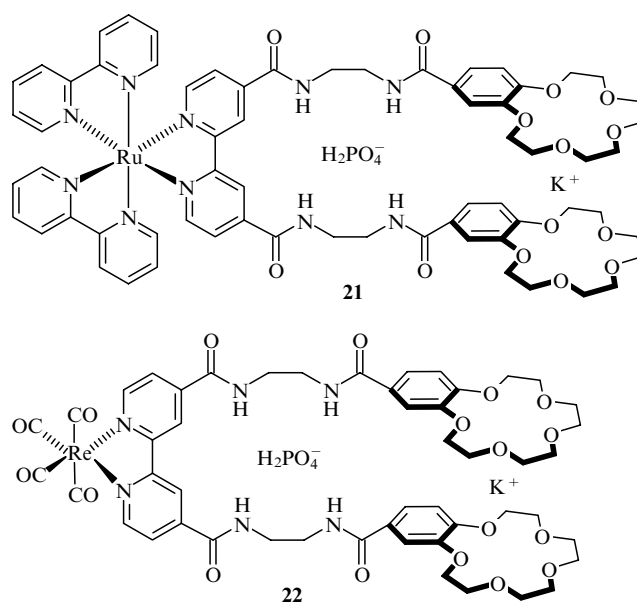
various natures. Compounds such as macrocycle **20** selectively bind  $\text{PdCl}_2$ ,  $\text{CuCl}_2$  and  $\text{AgNO}_3$ .



When  $\text{AgNO}_3$  is added to a solution of ligand **20** in acetonitrile, the signals for the NH protons in the  $^1\text{H}$  NMR spectrum shift upfield by 0.4 ppm. This shift is due to rupturing of the intramolecular hydrogen bonds upon the complex formation with  $\text{Ag}(\text{I})$ . Further addition of silver nitrate induces the formation of an intermolecular hydrogen bond with the nitrate anion, which is manifested as a downfield shift of the NH-proton signals. Thus, binding of the anion can take place only after the initial interaction of the ligand with the silver cation, resulting in cleavage of the intramolecular hydrogen bond.<sup>27</sup>

When cryptands are used as heteroditopic ligands, their interaction with anionic substrates such as 1- and 2-naphthalenemonosulfonates and 1,5-, 2,6- and 2,7-naphthalenedisulfonates can be observed.<sup>28</sup>

The introduction of pyridyl fragments into an azacrown ether, both as additional ligand groups and as binding sites, results in new complexing centres in azacrown ether molecules, *i.e.*, the binding properties of the molecule change. Heteroditopic ruthenium(II)- and rhenium(I)-bipyridylbis(benzocrown ether) receptors **21** and **22** (see Ref. 29) selectively bind  $\text{KH}_2\text{PO}_4$  ( $K_{\text{ass}} = 205$ ) in the presence of chloride anions ( $K_{\text{ass}} = 55$ ).

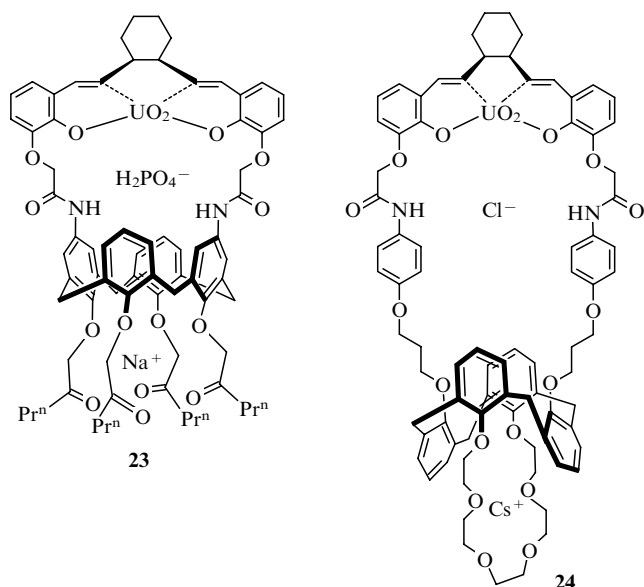


## 2. Heteroditopic receptors on a calixarene matrix

The cation-binding properties of calixarenes are well-known. For the design of a heteroditopic ligand, it is necessary to introduce anion receptors into the calixarene structure.

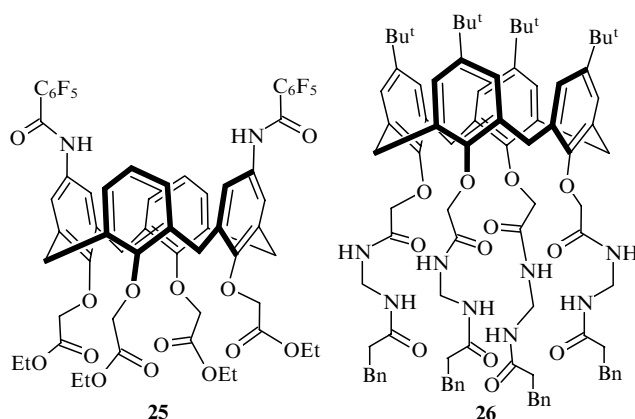
Binding of  $\text{NaH}_2\text{PO}_4$  and  $\text{CsCl}$  by calixarene complexes containing  $\text{UO}_2$  has been described.<sup>30, 31</sup> In these cases, the cation

interacts either with the functional groups grafted to the lower rim (compound **23**) or with the crown-ether fragment which cross-links the lower rim of the calixarene matrix (compound **24**). In both examples, the anions are bound by the amide groups immobilised on the calixarene matrix.



Heteroditopic receptors based on calixarenes containing amide functional groups in both the upper and lower rims are known. In the former case (compound **25**), the anion and the cation are separated in space, *i.e.*, they are bound at the upper and lower rims, respectively. The latter case (compound **26**) is of interest for the fact that both the cation- and anion-binding sites are located in the lower rim of the calixarene matrix. A study of the receptor ability of these ligands was carried out by NMR titration. It was found that compound **25** in  $\text{CD}_3\text{COCD}_3$  is suitable for the selective binding of  $\text{NaBr}$  to give a complex with the stoichiometric ratio ligand:anion = 1:2 ( $K_{\text{ass}} = 738$ ). Compound **26** can selectively bind  $\text{NaHSO}_4$  ( $K_{\text{ass}} = 1197$ ).

Potassium acetate selectively reacts with the heteroditopic calixarene receptor **27**, existing in the 1,3-alternate conformation and containing two pentafluorophenylamide groups (for complex formation with the anion) and a crown-ether fragment (to capture the cation) (Scheme 2).<sup>32</sup>

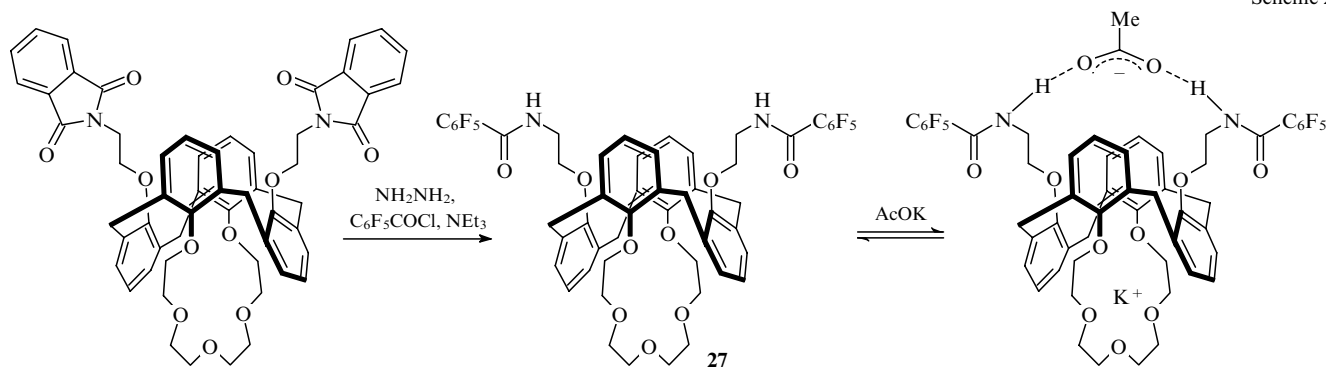


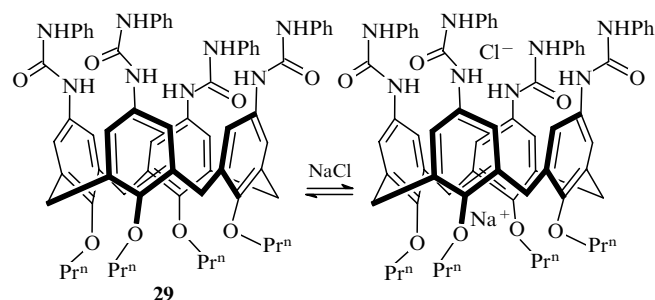
Apart from compound **27**, rhenium and ruthenium complexes **28a,b** may be applicable for the simultaneous transfer of cations and anions through the membrane (Scheme 3).<sup>33</sup> These heteroditopic ligands, containing  $\text{Re(I)}$ - and  $\text{Ru(III)}$ -bipyridylamide fragments connected by a flexible spacer to the calixarene lower rim, proved to be specific for ion pairs containing  $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{Br}^-$  and  $\text{I}^-$  ions. NMR titration showed selective binding of lithium bromide ( $K_{\text{ass}} = 1260$ ).<sup>34</sup>

The introduction of  $\text{Re(I)}$ -bipyridyl fragments into the upper rim gives rise to selective receptor behaviour with respect to sodium iodide ( $K_{\text{ass}} = 392$ ),<sup>35</sup> while the calixarene modified with a  $\text{Ru(II)}$ -bipyridyl fragment at the upper rim can be used for binding  $\text{NaH}_2\text{PO}_4$ .<sup>36</sup>

It was found that the combination of urea fragments (as anion-binding sites) and ester groups grafted to the lower rim within the same calixarene molecule results in the formation of selective extractants for alkali metal halides.<sup>37–39</sup> This was confirmed by NMR data obtained for mixtures of the bifunctional ligands and alkali metal halides. The extraction of sodium halides with biureide-substituted calixarene involves non-selective binding of the cations and the anions. The attempt to prepare an inclusion compound with caesium salts did not lead to the desired outcome, which may be due to the mismatch between the size of the complexing cavity and the radius of the metal cation. However, this compound can be used for the selective binding of potassium iodide.<sup>40,41</sup> The introduction of four urea fragments into the upper rim (compound **29**) brings about complexing properties with respect to sodium chloride. This is due to a higher affinity of urea for chloride anions (compared to other halide anions) as a result of the formation of strong hydrogen bonds.<sup>42</sup>

Scheme 2

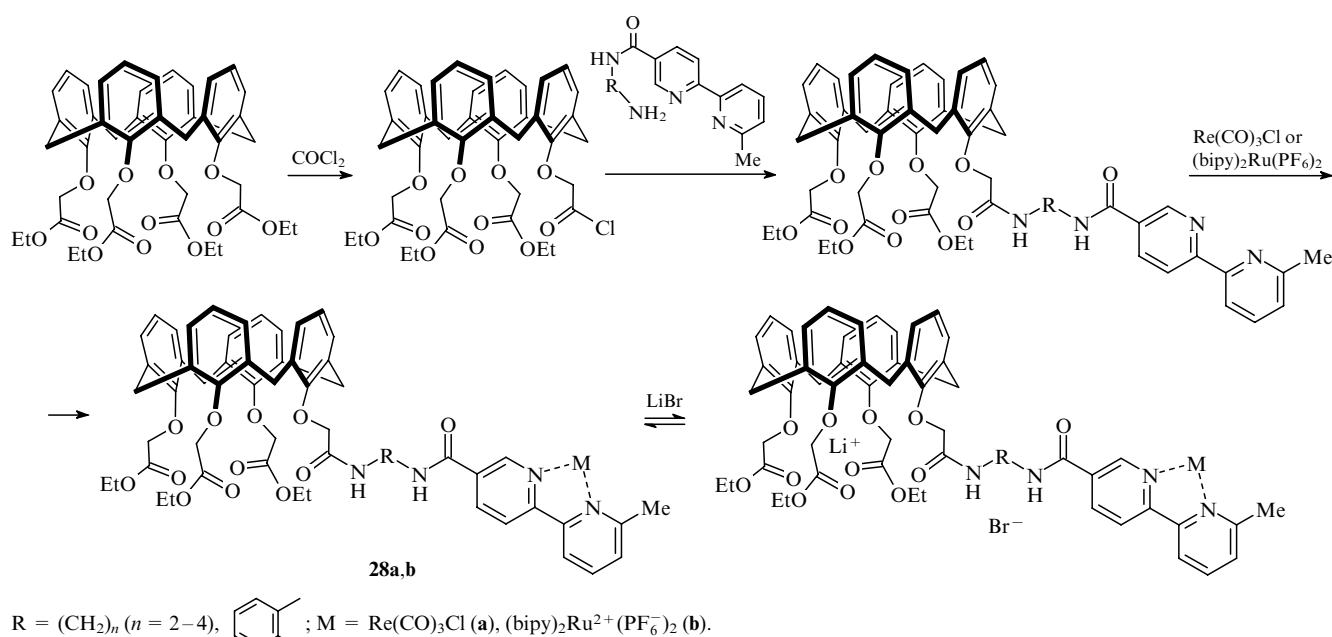




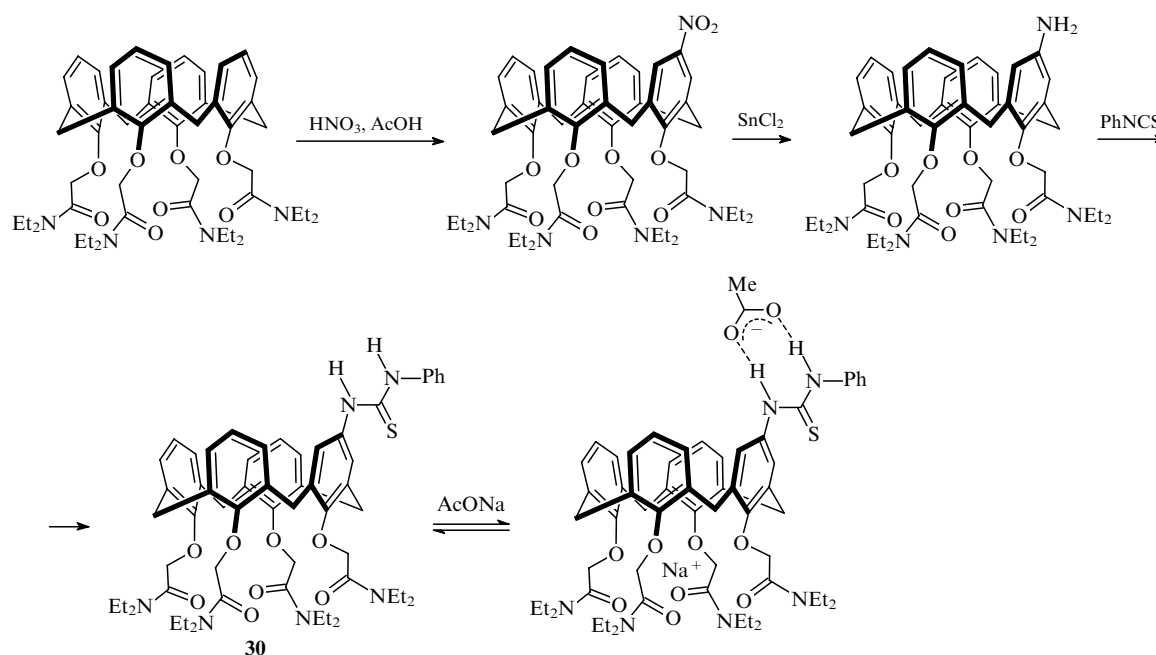
NMR titration has shown that calixarenes containing a crown ether substituent in the lower rim<sup>43,44</sup> and urea residues in the upper rim can be employed as heteroditopic receptors. The binding constant of the anion decreases in the order  $\text{H}_2\text{PO}_4^- \gg \text{Cl}^- > \text{Br}^- > \text{NO}_3^-$ . The complexation with  $\text{NaH}_2\text{PO}_4$  affords an ion pair.<sup>44</sup> Asymmetric thioureidocalixarenes **30** can be used for selective binding of sodium acetate ( $K_{\text{ass}} = 1200$ ) (Scheme 4).<sup>45</sup>

Linking two calixarenes by an ethylene bridge produces a molecular cavity suitable for the formation of complexes with cations. The modification of these calixarenes by urea fragments results in receptor **31**, which forms a complex with potassium

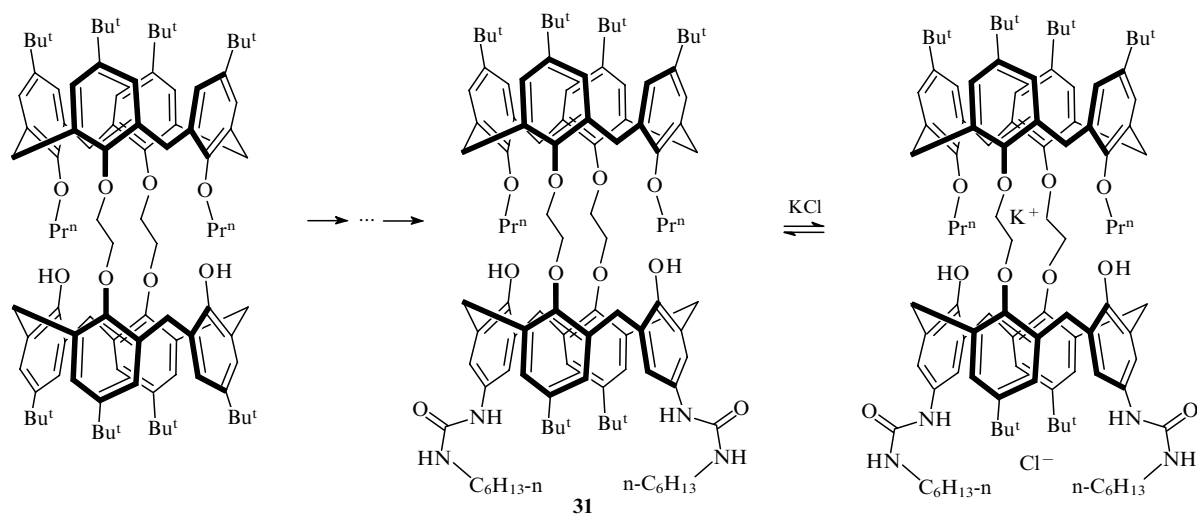
Scheme 3



Scheme 4

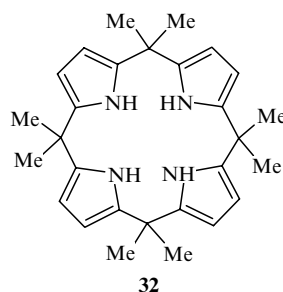


Scheme 5

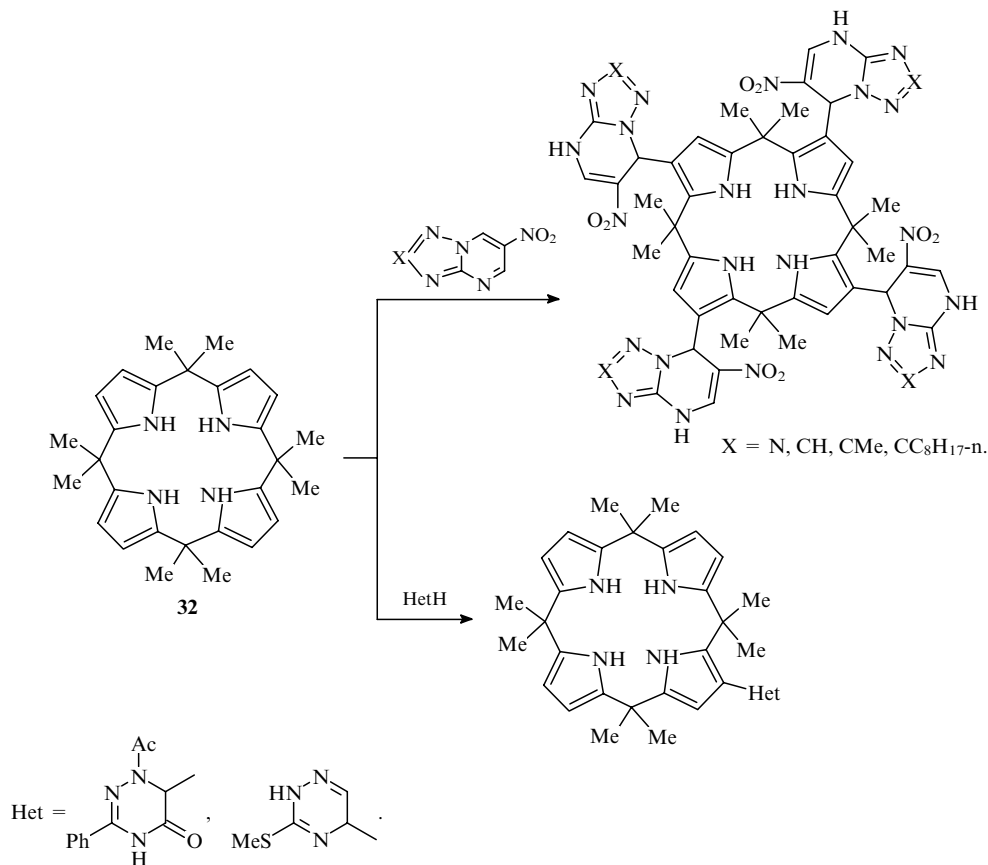


chloride ( $K_{\text{ass}} > 730$ ), as confirmed by NMR titration data (Scheme 5).<sup>46</sup>

The heteroanalogue of calixarene, calixpyrrole **32**, is a promising heteroditopic ligand. In combination with benzocrown ether, this compound can selectively bind fluoride anions and metal cations.<sup>47</sup> Development of direct methods for the modification of calixpyrrole **32** by azine fragments<sup>48</sup> would pave the way to ligands of a heteroditopic nature (Scheme 6).



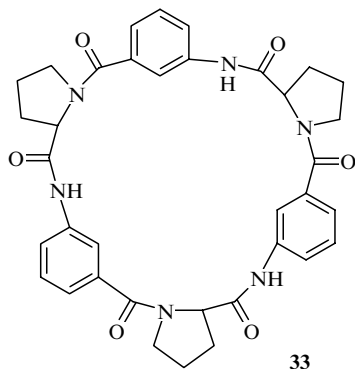
Scheme 6



### 3. Heteroditopic complexing agents based on other macrocycles

A method for the development of heteroditopic receptors based on cyclic peptides **33** has been proposed.<sup>49</sup>

These compounds can be used to bind ammonium iodide. In this case, the ligand adopts a conformation similar to the conical calixarene conformation and, similarly, it binds the cation through the interaction of the  $\pi$ -electrons of the carbonyl function, whereas the iodide anion is bound by hydrogen bonding with the NH groups of the peptide.



## IV. Conclusion

The review summarises the data on the synthesis of bifunctional ligands and their complexing properties. The publications devoted to the design of heteroditopic receptors for the recognition of ion pairs on the basis of known cation and anion acceptors are analysed. All the described syntheses have a strategy in common which implies the design of a host molecule containing complexing sites of different nature. The resulting systems can be used not only for simultaneous binding of cations and anions but also for the selective complexation of bipolar organic molecules (for example, amino acids).

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# Methods of synthesis and properties of hexanitrohexaazaisowurtzitane

S V Sysolyatin, A A Lobanova, Yu T Chernikova, G V Sakovich

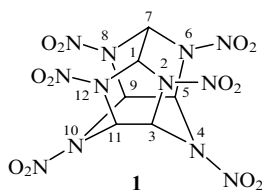
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**Abstract.** Methods of synthesis and properties of 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0<sup>3,11</sup>.0<sup>5,9</sup>]dodecane (also referred to as CL-20 or HNIW), a highly energetic polycyclic nitramine, are surveyed. The bibliography includes 49 references.

## I. Introduction

The progress in the defence technologies is naturally related to the development of novel more efficient components of mixed solid propellants, explosive compositions and gunpowders. A possible route to accomplish this task consists of the preparation of highly energetic compounds that provide the explosion power superior to any existing substance. According to the theoretical predictions on the physicochemical and explosion characteristics, polycyclic nitramines, in particular, hexanitrohexaazaisowurtzitane, 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0<sup>3,11</sup>.0<sup>5,9</sup>]dodecane (**1**), HNIW, CL-20, a unique representative of this class of compounds, hold much promise in this respect.



An HNIW molecule possesses a compact structure, so that both the density<sup>†</sup> and energetic characteristics of **1** are exceptionally high (Table 1).<sup>1–3</sup>

**S V Sysolyatin, G V Sakovich** Institute of Problems of Chemical and Energetic Technologies, Siberian Branch of the Russian Academy of Sciences, Socialisticheskaya ul 1, 659322 Biysk, Altai Territory, Russian Federation. Fax (7-3854) 31 13 09, tel. (7-3854) 31 07 84 (S V Sysolyatin), (7-3854) 30 59 98 (G V Sakovich)  
**A A Lobanova, Yu T Chernikova** Federal State Unitary Enterprise 'Federal Scientific and Production Centre 'Altai', Socialisticheskaya ul 1, 659322 Biysk, Altai Territory, Russian Federation. Fax (7-3854) 31 13 09, tel. (7-3854) 31 25 54 (A A Lobanova), (7-3854) 34 24 06, e-mail: ipcetadm@yourline.ru (Yu T Chernikova)

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**Table 1.** Physicochemical and energetic characteristics of hexanitro-wurtzitane.

| Parameter                                                          | Value                                                         | Ref. |
|--------------------------------------------------------------------|---------------------------------------------------------------|------|
| Molecular formula                                                  | C <sub>6</sub> H <sub>6</sub> N <sub>12</sub> O <sub>12</sub> |      |
| Molecular mass                                                     | 438.186                                                       |      |
| Decomposition temperature /°C                                      | 250–260                                                       | 1, 2 |
| Density ( $\rho$ ) /g cm <sup>–3</sup>                             | 2.044                                                         | 2    |
| Enthalpy of formation ( $\Delta H_f^\circ$ ) /kJ mol <sup>–1</sup> | 377.411                                                       | 3    |
| Oxygen balance (CO <sub>2</sub> and H <sub>2</sub> O) (%)          | 20                                                            |      |
| Calculated detonation rate /km s <sup>–1</sup>                     | 9.38                                                          | 1    |

Hexanitrohexaazaisowurtzitane was synthesised for the first time in 1987 at the Naval Air Warfare Center (USA).<sup>4</sup> Since then, intense investigations into optimisation of the methods for its synthesis as well as technologies of its production and preparation of explosives and propellants for diverse applications based on it are being conducted.

A pilot plant for the production of HNIW with a performance of 200 kg of the target product per load was designed in 1990 by the Thiokol corporation (USA).<sup>4</sup>

In the present review, the published data on the methods for the synthesis of polycyclic nitramine **1** and studies of its physicochemical properties are considered systematically. In all the documented methods for the synthesis of compound **1**, the overall process can be divided into two steps: first, construction of the hexanitrohexaazaisowurtzitane cage and, second, substitution of the nitro groups for functional groups at the nitrogen atoms.

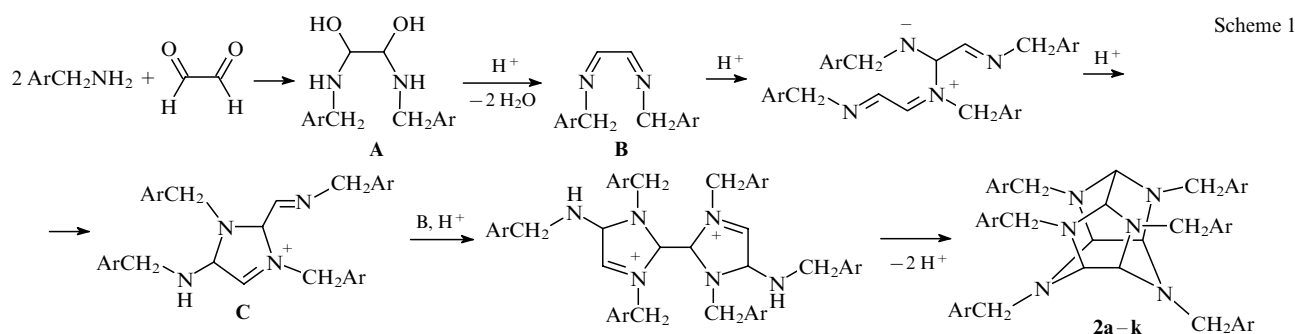
## II. Construction of the hexanitrohexaazaisowurtzitane cage

The only available method for the construction of the hexanitrohexaazaisowurtzitane cage is based on the condensation of glyoxal<sup>‡</sup> with benzylamine or its derivatives.<sup>5,6</sup> A mechanism suggested for this reaction is shown in Scheme 1.

Two intermediates, *viz.*, diol **A** and diimine **B**, have been isolated and identified.<sup>5</sup> The reaction was carried out in aqueous

<sup>†</sup> The detonation pressure of an energetic compound is proportional to its density.

<sup>‡</sup> 2,3-Dihydroxy-1,4-dioxane can be used instead of glyoxal.



Ar = Ph (**a**), C<sub>6</sub>H<sub>4</sub>Me-*p* (**b**), C<sub>6</sub>H<sub>4</sub>Me-*o* (**c**), C<sub>6</sub>H<sub>4</sub>OMe-*p* (**d**), C<sub>6</sub>H<sub>4</sub>OMe-*o* (**e**), C<sub>6</sub>H<sub>3</sub>(OMe)<sub>2</sub>-3,4 (**f**), C<sub>6</sub>H<sub>4</sub>Pr<sup>i</sup>-*p* (**g**), C<sub>6</sub>H<sub>4</sub>Cl-*p* (**h**), C<sub>6</sub>H<sub>4</sub>Cl-*o* (**i**), C<sub>6</sub>H<sub>4</sub>F-*o* (**j**), C<sub>6</sub>H<sub>4</sub>Br-*o* (**k**).

acetonitrile,<sup>5</sup> methanol,<sup>6,7</sup> ethanol<sup>7,8</sup> or isopropyl alcohol<sup>7</sup> in the presence of an acidic catalyst at 0–25 °C. Various organic and inorganic acids, such as formic,<sup>7</sup> acetic,<sup>2</sup> salicylic, *p*-toluenesulfonic,<sup>9</sup> nitric<sup>1</sup> and perchloric acids, were used as catalysts.<sup>10</sup> Table 2 summarises the yields and properties of the products obtained.

**Table 2.** Yields and properties of the condensation products of glyoxal with benzylamine derivatives.

| Com-pound | Ar                                                       | Molecular formula                                              | Melting point /°C | Yield (%) | Ref. |
|-----------|----------------------------------------------------------|----------------------------------------------------------------|-------------------|-----------|------|
| <b>2a</b> | Ph                                                       | C <sub>48</sub> H <sub>48</sub> N <sub>6</sub>                 | 153–157           | 80        | 5    |
|           |                                                          |                                                                | 153               | 67        | 6    |
| <b>2b</b> | C <sub>6</sub> H <sub>4</sub> Me- <i>p</i>               | C <sub>54</sub> H <sub>60</sub> N <sub>6</sub>                 | 172–174           | 68        | 5    |
|           |                                                          |                                                                | 174               | 66        | 6    |
| <b>2c</b> | C <sub>6</sub> H <sub>4</sub> Me- <i>o</i>               | C <sub>54</sub> H <sub>60</sub> N <sub>6</sub>                 | 203               | 45        | 6    |
| <b>2d</b> | C <sub>6</sub> H <sub>4</sub> OMe- <i>p</i>              | C <sub>54</sub> H <sub>60</sub> N <sub>6</sub> O <sub>6</sub>  | 148–150           | 60        | 5    |
| <b>2e</b> | C <sub>6</sub> H <sub>4</sub> OMe- <i>o</i>              | C <sub>54</sub> H <sub>60</sub> N <sub>6</sub> O <sub>6</sub>  | 148–150           | 60        | 5    |
|           |                                                          |                                                                | 136               | 28        | 6    |
| <b>2f</b> | C <sub>6</sub> H <sub>3</sub> (OMe) <sub>2</sub> -3,4    | C <sub>60</sub> H <sub>72</sub> N <sub>6</sub> O <sub>12</sub> | 160–161           | 50        | 5    |
| <b>2g</b> | C <sub>6</sub> H <sub>3</sub> Pr <sup>i</sup> - <i>p</i> | C <sub>66</sub> H <sub>84</sub> N <sub>6</sub>                 | 144–145           | 24        | 5    |
| <b>2h</b> | C <sub>6</sub> H <sub>4</sub> Cl- <i>p</i>               | C <sub>48</sub> H <sub>42</sub> Cl <sub>6</sub> N <sub>6</sub> | 212–214           | 46        | 5    |
|           |                                                          |                                                                | 191               | 20        | 6    |
| <b>2i</b> | C <sub>6</sub> H <sub>4</sub> Cl- <i>o</i>               | C <sub>48</sub> H <sub>42</sub> Cl <sub>6</sub> N <sub>6</sub> | 208–211           | 68        | 5    |
|           |                                                          |                                                                | 182               | 15        | 6    |
| <b>2j</b> | C <sub>6</sub> H <sub>4</sub> F- <i>o</i>                | C <sub>48</sub> H <sub>42</sub> F <sub>6</sub> N <sub>6</sub>  | 126               | 33        | 6    |
| <b>2k</b> | C <sub>6</sub> H <sub>4</sub> Br- <i>o</i>               | C <sub>48</sub> H <sub>42</sub> Br <sub>6</sub> N <sub>6</sub> | 210               | 22        | 6    |

As can be judged from Table 2, the highest yield was obtained in the case of the condensation of glyoxal and unsubstituted benzylamine. The reaction product, 2,4,6,8,10,12-hexabenzyl-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0<sup>3,11</sup>.0<sup>5,9</sup>]dodecane (**2a**), represents a white non-hygroscopic crystalline substance, which decomposes in acetic acid.<sup>5–7</sup> UV spectroscopic studies have shown that the decomposition of the hexabenzyl derivative **2a** in aqueous acetonitrile is catalysed by acids and probably involves protonation followed by decomposition of the isowurtzitane cage.<sup>6</sup>

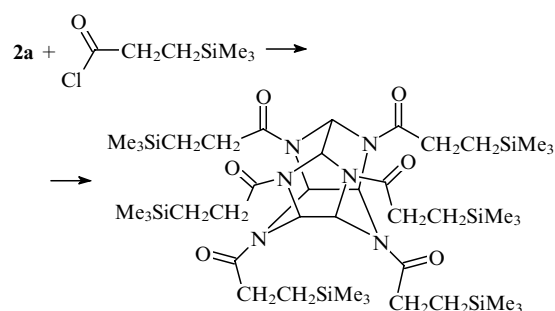
The molecular structures of the condensation products **2b** (see Ref. 6), **2d** (see Ref. 5) and **2h** (see Ref. 7) have been confirmed by the data from IR and NMR spectroscopy and X-ray crystallography.

No compounds with the isowurtzitane cage could be synthesised upon condensation of glyoxal with *o*-aminobenzylamine, acetamide and *p*-carboxybenzylamine.<sup>7,11</sup>

### III. Preparation of hexaazaisowurtzitane derivatives to be used in the synthesis of hexanitrohexaazawurtzitane

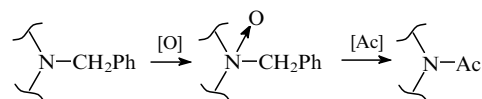
No hexanitrohexaazaisowurtzitane was formed upon direct nitrolysis of the hexabenzyl derivative **2a** due to both competitive nitration of the benzene rings and instability of the intermediates. Therefore, the benzyl groups at the nitrogen atoms in **2a** should be first replaced by groups that are susceptible to nitrolysis, *e.g.*, AlkC(O), CHO, NO, *etc.*

Preparation of acylated hexaazaisowurtzitane is an especially promising direction for the synthesis of HNIW, since typically the acyl groups at the nitrogen atoms can easily be replaced by nitro groups. Direct acidolysis of **2a** with trimethylsilylpropionyl chloride is documented.<sup>12</sup>



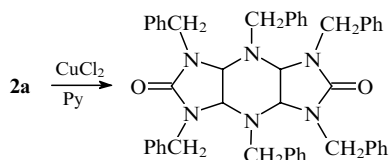
Treatment of the hexabenzyl derivative **2a** with such acylation agents as acetic, chloroacetic and trifluoroacetic anhydrides results only in its extensive decomposition and resinification.<sup>11</sup>

Another approach to the synthesis of the hexaazaisowurtzitane *N*-acetyl derivative consists of the oxidation of **2a** to the respective *N*-oxide followed by the Polonovsky rearrangement.

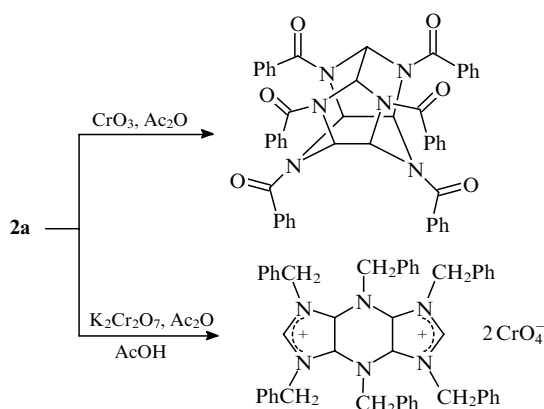


The selection of a proper oxidant is a non-trivial problem, since oxidation of the hexabenzyl derivative **2a** often results in the decomposition of the polycyclic cage. For instance, it has been established experimentally that the C(1)–C(7) bond is cleaved upon oxidation of **2a** with copper(II) chloride in the presence of pyridine to yield 1,3,4,5,7,8-hexabenzyl-2,6-dioxo-*cis-cisoid-cis*-hexahydro-1*H*,5*H'*-diimidazo[4,5-*b*:4',5'-*e*]pyrazine.<sup>13</sup>

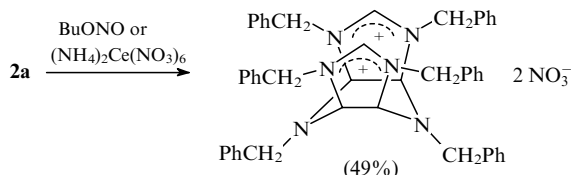




It is known that Cr(VI) species is the oxidant of choice for the benzylic C–H bonds. Therefore, Oiu *et al.*<sup>14</sup> tested various Cr(VI) compounds in the oxidation of the hexabenzyl derivative **2a**. In particular, the oxidation of **2a** with CrO<sub>3</sub> in acetone afforded the target product, *viz.*, hexabenzoylhexasaisowurtzitane,<sup>14</sup> whereas the oxidation with the system K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>–Ac<sub>2</sub>O–AcOH resulted in the cleavage of the C(1)–C(7) bond to yield diimidazolinopyrazinium chromate.

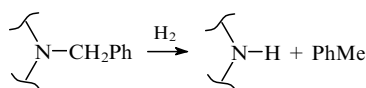


An analogous product was obtained in the oxidation of **2a** with butyl nitrite or ammonium cerium nitrate.<sup>15</sup>



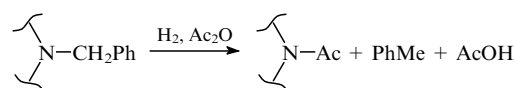
The use of hydrogen peroxide or peroxy acids as oxidants does not result in the target product, defragmentation of the polycyclic cage occurs instead. *N,N'*-Dibenzylurea has been isolated as a product of the oxidative decomposition of the hexabenzyl derivative **2a**.<sup>11, 16</sup>

In principle, the benzyl groups at the nitrogen atoms can be removed by catalytic hydrogenolysis.

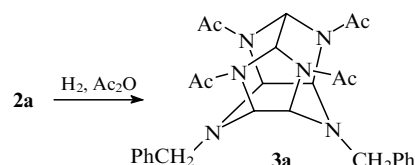


However, the reduction of **2a** with molecular hydrogen at an elevated pressure resulted in the decomposition of the polycyclic cage. The irreversible decomposition proceeds competitively in several directions to yield a mixture of products with both cyclic and linear structures.<sup>17</sup>

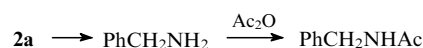
If the reduction is carried out in the presence of an acylation agent, it becomes possible to protect the secondary amino groups generated and thus to reduce the extent of decomposition of the polycyclic cage. As a result, the reductive debenzylation of **2a** can be successfully accomplished to afford the respective acyl derivative. If acetic anhydride is used as the acylation agent, the reaction proceeds stepwise and yields a mixture of various polyacetylpolymethyl derivatives.<sup>17–19</sup>



2,6,8,12-Tetraacetyl-4,10-dibenzyl-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0.3.11.0.5.9]dodecane (**3a**) is the main reaction product, which apparently suggests higher stability of the benzyl groups at the nitrogen atoms of the piperazine ring against debenzylation as compared to other benzyl groups that can be rather easily substituted.



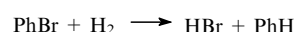
A chromatographic analysis of the reaction mixture revealed at least four by-products, in particular, *N*-benzylacetamide. This implies that the hydrogenation is accompanied by partial decomposition of the polycyclic cage.<sup>18</sup>



*N*-Benzylacetamide is a catalyst poison and stops the hydrogenation reaction almost completely, which consequently results in a decrease in the yield of the dibenzyl derivative **3a**.<sup>18</sup>

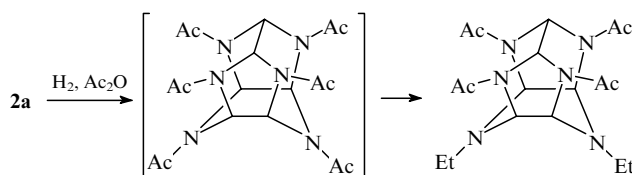
The yield of **3a** also depends on the amount and activity of the hydrogenation catalyst utilised, concentration of acetic anhydride and the nature of the solvent. Typically, hydrogenation is performed in the presence of palladium catalysts supplemented with catalytic amounts of hydrohalide acids.<sup>1, 5, 19</sup>

The selectivity of the reaction can be substantially enhanced by choosing a proper solvent. For instance, the yield of **3a** was 50%–65% (with respect to the hexabenzyl derivative **2a**) in acetic anhydride<sup>19</sup> and increased to 75% in a mixture of ethylbenzene with *N*-acetoxysuccinimide and acetic anhydride (20 h, *p*H<sub>2</sub> = 9.8 kPa)<sup>18</sup> and further to 80% in DMF, *N*-methylpyrrolidone or 1,2-dimethoxyethane in the presence of a bromine source (*e.g.*, molecular bromine, bromobenzene or acetyl bromide) and acetic acid (20–50 °C, 6–12 h).<sup>20</sup> The role of the bromine source is to supply hydrobromic acid, which is necessary to activate the acetylating agent.<sup>20</sup>



According to the kinetic studies of the hydrogenation process, the activation energy is 48 kJ mol<sup>–1</sup> at a stirring velocity of 2.43 × 10<sup>6</sup> min<sup>–1</sup> and a temperature of 30 °C. The rate constant for the first-order reaction is 1.33 × 10<sup>–2</sup> min<sup>–1</sup> (see Ref. 21).

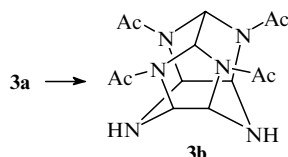
2,6,8,12-Tetraacetyl-4,10-diethyl-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0.3.11.0.5.9]dodecane was isolated as the main hydrogenation product of **2a** on a palladium catalyst at a hydrogen pressure of 2942–3923 kPa in acetic anhydride containing 10%–20% of acetic acid.<sup>17</sup>



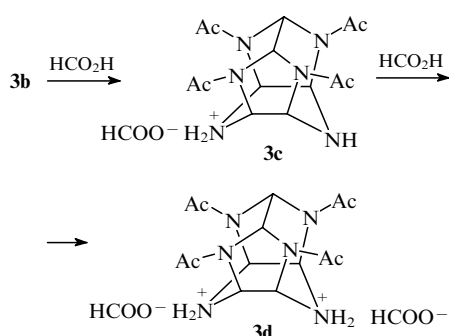
Presumably, the reaction proceeds *via* a hexaazaisowurtzitane hexaacetyl derivative, but this mechanism has not been confirmed. A single reaction intermediate has been isolated by HPLC, most probably, 2,6,8,12-tetraacetyl-4-benzyl-10-ethyl-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0.3.11.0.5.9]dodecane.

Based on the experimental facts outlined above, one can conclude that debenzilation of **2a** should be carried out in two steps of which the first involves the formation of the dibenzyl derivative **3a** and its isolation from the reaction mixture and the second, removal of the remaining benzyl groups at the nitrogen atoms of the piperazine ring.

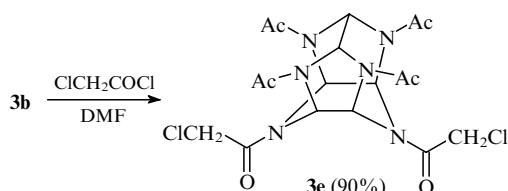
The reduction of the dibenzyl derivative **3a** in acetic acid at a hydrogen pressure of 4.53 kPa in the presence of  $\text{Pd}(\text{OAc})_2$  for 15 h affords 2,6,8,12-tetraacetyl-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0<sup>3,11</sup>.0<sup>5,9</sup>]dodecane (**3b**) in a 73% yield.<sup>18</sup>



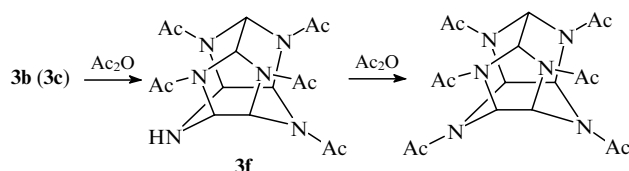
Hydroformates **3c** and **3d** are obtained in solutions of **3b** in formic acid.<sup>22</sup>



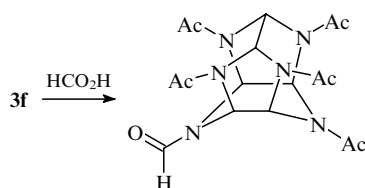
The reaction of the dihydro derivative **3b** with chloroacetyl chloride in DMF yields the respective bis(chloroacetate) **3e**.<sup>23</sup>



Compound **3b** and its mono(hydroformate) **3c** are converted into 2,4,6,8,12-pentaacetyl-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0<sup>3,11</sup>.0<sup>5,9</sup>]dodecane (**3f**) in the presence of an acylation agent.<sup>24</sup> The synthesis of the hexaacetyl derivative has also been reported.<sup>22</sup> The reaction is performed in the presence of pyridine at 60 °C.

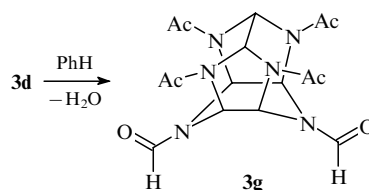


Formylation of the pentaacetyl derivative **3f** yields 2,6,8,10,12-pentaacetyl-4-formyl-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0<sup>3,11</sup>.0<sup>5,9</sup>]dodecane.<sup>24</sup>

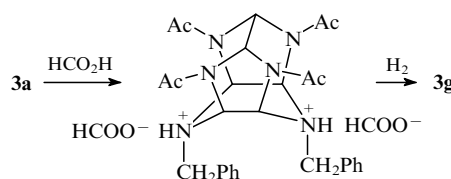


2,6,8,12-Tetraacetyl-4,10-diformyl-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0<sup>3,11</sup>.0<sup>5,9</sup>]dodecane (**3g**) was synthesised by the reac-

tion of the bis(hydroformate) **3d** with acetic anhydride in the presence of pyridine or with acetyl chloride.<sup>22</sup> This dehydration reaction also occurs when the salt **3d** is boiled in benzene with azeotropic distillation of water.<sup>15</sup>

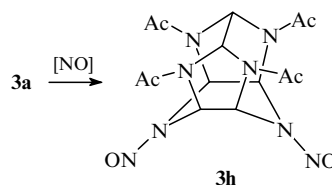


The diformyl derivative **3g** is also formed upon hydrogenation of the dibenzyl derivative **3a** in concentrated formic acid.<sup>18,22</sup> It was suggested that formic acid plays a prominent role in the process by converting the benzylamine fragment into benzylammonium formate, which undergoes the reduction more easily.



This suggestion on the involvement of protonation is supported by the isolation of the formates **3c** and **3d** from the reaction mixture and by the fact that the activity of the hydrogenation catalyst used for the removal of the two remaining benzyl groups is not critical. Therefore, the catalyst used in the first hydrogenation step (*i.e.*, in the conversion of **2a** into **3a**) can also be used for the preparation of the diformyl derivative **3g** without regeneration.<sup>20,22</sup> For the synthesis of **3g**, the use of formic acid with a concentration not lower than 88% is preferable. In dilute solutions, the dihydro derivative **3b** or its formates **3c,d** can be isolated.<sup>20</sup> The formation of the diformyl derivative **3g** proceeds at a lower rate than that of the dibenzyl derivative **3b** due to lower reactivity of the benzyl groups at the nitrogen atoms of the piperazine ring as compared to the benzyl groups in other positions. The yield of the diformyl derivative **3g** is as high as 86%.<sup>20</sup>

Nitrosation is an established method for the substitution of benzyl groups at nitrogen atoms of secondary amines. Wardle *et al.*<sup>4</sup> adapted this method to the nitrosation of the tertiary amine **3a** containing two benzyl groups and obtained 2,6,8,12-tetraacetyl-4,10-dinitroso-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0<sup>3,11</sup>.0<sup>5,9</sup>]dodecane (**3h**).

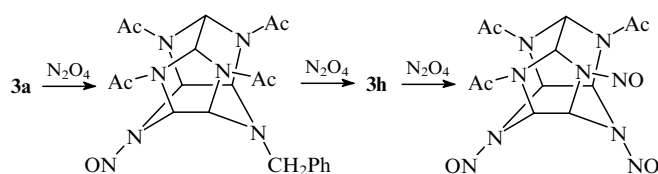


Nitrosonium tetrafluoroborate was used as the nitrosation agent. The reaction was carried out in aqueous sulfolane. The overall process included two steps: first, oxidation of the benzyl groups (to form benzaldehyde) and subsequent nitrosation of the amino groups.<sup>4</sup> The yield of the dinitroso derivative **3h** was 55%. In acetonitrile as the solvent, the yield was lower (10%).<sup>25</sup>

Nitrosation of the dibenzyl derivative **3a** with excess of  $\text{N}_2\text{O}_4$  at 15–16 °C for 20 h afforded **3h** in 92% yield.<sup>25</sup>

In acetic acid, the reaction is more safe than in pure  $\text{N}_2\text{O}_4$ , but is slower.<sup>26</sup> TLC analysis of the reaction products confirmed the presence of an intermediate, 2,6,8,12-tetraacetyl-10-benzyl-4-nitroso-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0<sup>3,11</sup>.0<sup>5,9</sup>]dodecane. Contamination of the dinitroso derivative **3h** with this intermediate can be avoided by increasing the reaction time and  $\text{N}_2\text{O}_4$

concentration, but 10%–12% of another admixture, *viz.*, 6,8,12-triacetyl-2,4,10-trinitroso-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0<sup>3,11</sup>.0<sup>5,9</sup>]dodecane, is formed. The presence of this admixture substantially lowers the melting point of the product **3h** but does not prevent the next step, *i.e.*, nitrolysis.<sup>26</sup>

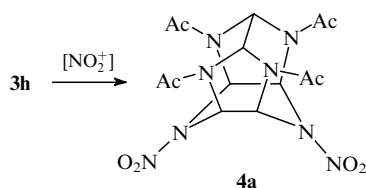


Nitrosation of the dihydro derivative **3b** with sodium nitrite in acetic acid affords the dinitroso derivative **3h** in a yield as high as 95%–100%.<sup>27</sup>

The tetraacetylhexaazaisowurtzitane derivatives described above are used as the starting materials in the synthesis of HNIW.

#### IV. Nitrolysis of tetraacetylhexaazaisowurtzitane derivatives

The final step in the synthesis of HNIW is the nitrolysis of tetraacetylhexaazaisowurtzitane derivatives. In general, this is a complex multi-step process, which yields an array of intermediate hexaazaisowurtzitane nitro derivatives, for instance, 2,6,8,12-tetraacetyl-4,10-dinitro-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0<sup>3,11</sup>.0<sup>5,9</sup>]dodecane (**4a**), which is produced upon partial nitrolysis of **3h**.

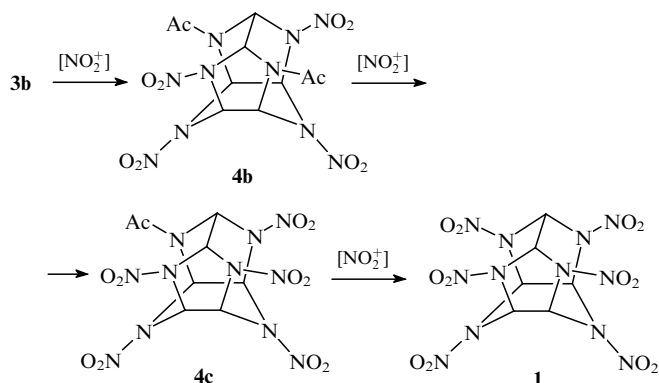


Compound **4a** was synthesised by treating the nitrosation products of the dibenzyl derivative **3a** with nitronium tetrafluoroborate in acetonitrile at 45 °C. The yield of the product **4a** was 59%.<sup>28</sup> The reaction of the dinitroso derivative **3h** with nitric acid at room temperature afforded **4a** in 95% yield.<sup>29</sup>

The target hexanitro derivative can be obtained by nitrolysis of various tetraacetyl derivatives, *viz.*, compound **3b**, its mono- (**3c**) and bis(hydroformate) (**3d**), bis(chloroacetyl) (**3e**), diformyl (**3g**), dinitroso (**3h**) and dinitro (**4a**) derivatives.

Nitrolysis of **4a** with nitronium tetrafluoroborate in sulfolane afforded **1** in 90% yield. The yield decreased to 30% if the reaction was carried out in a mixture of sulfuric and nitric acids.<sup>18</sup>

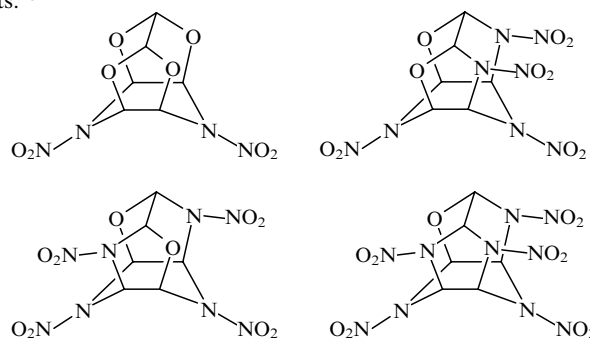
Several authors reported consecutive nitrosation and nitrolysis of the dibenzyl derivative **3a** without isolation of the intermediate dinitroso derivative **3h**. Thus the nitrosation of compound **3a** with nitronium tetrafluoroborate in sulfolane followed by nitrolysis of the dinitroso derivative **3h** obtained with nitronium tetrafluoroborate afforded compound **1** in 93%–97% yield.<sup>4,8</sup> In another synthesis,<sup>25</sup> compound **3a** was nitrosated with N<sub>2</sub>O<sub>4</sub> and then nitrated with a mixture of sulfuric and nitric acids (20:80); the yield of HNIW was 97%. A major disadvantage of such one-pot syntheses is the higher explosion hazard due to the presence of benzaldehyde in the reaction mixture after nitrosation, which is nitrated to yield trinitrobenzoic acid.<sup>2</sup> Isolation of the nitrosation product **3h** from the reaction mixture significantly increases safety of the nitrolysis step. The isolated product **3h** is further nitrated with a mixture of sulfuric and nitric acids to give HNIW in 93% yield.<sup>26</sup> As has been established, the conversion of the dinitroso derivative **3h** into HNIW proceeds slowly even in 99% nitric acid and is accompanied by the formation of two by-products, *viz.*, 2,8-diacetyl-4,6,10,12-tetranitro- (**4b**) and 2-acetyl-4,6,8,10,12-pentanitro-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0<sup>3,11</sup>.0<sup>5,9</sup>]dodecane (**4c**). Both intermediates have been isolated chromatographically and their structures have been confirmed by NMR and IR spectroscopy and elemental analysis.<sup>26,27</sup>



The addition of sulfuric acid (10%–15%) to the reaction mixture accelerates the reaction substantially. However, the higher rate of the nitrolysis does not guarantee the absence of admixtures in the final product, since sulfuric acid decreases solubility of the intermediates. This results in the co-crystallisation of the intermediates **4b** and **4c** with the target product **1**. If the modulus<sup>8</sup> is larger than 15, after 2 h the yield of HNIW at 70–75 °C is 99% (TLC).<sup>26</sup>

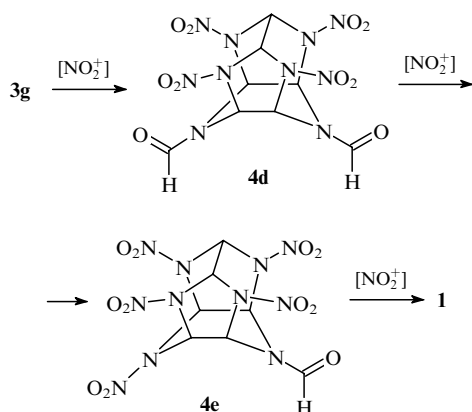
Yet another method for the nitrolysis of the diformyl derivative **3g** has been developed,<sup>28</sup> which makes it possible to prepare **1** in a virtually quantitative yield using 99% nitric acid (with the modulus of 4) in 4 h. Mixtures of sulfuric and nitric acids<sup>29</sup> or nitric acid and ammonium nitrate<sup>30–32</sup> can also be used as nitration agents. During the nitrolysis of **3g**, the temperature of the reaction mixture is gradually raised to 75–80 °C (*i.e.*, the temperature of the reaction onset). The upper temperature limit is determined by the boiling point of the reaction mixture.

The mechanism of the nitrolysis of the diformyl derivative **3g** has not been studied in detail so far. Presumably, concomitantly with consumption of nitric acid present in the nitration mixture water is accumulated, which can induce partial hydrolysis of the hexaazaisowurtzitane cage at an elevated temperature to yield oxatetracyclo[5.5.0.0<sup>3,11</sup>.0<sup>5,9</sup>]dodecane derivatives as by-products.<sup>28</sup>



Furthermore, products of incomplete nitrolysis of the diformyl derivative **3g**, *viz.*, diformyltetranitrohexaazawurtzitane (**4d**) and monoformylpentanitrohexaazawurtzitane (**4e**) derivatives are formed due to insufficiently drastic reaction conditions.<sup>29</sup> Both these products were isolated by preparative chromatography and their structures were confirmed by IR and NMR spectroscopy. The isolation of the intermediates **4d** and **4e** suggests that formyl groups in **3g** are substituted more slowly than the acetyl groups.

§ Hereinafter, the amount of the acid (in g) per 1 g of the substrate is meant.



The incomplete nitrolysis product, *viz.*, compound **4e**, is the major by-product in the synthesis of HNIW from the diformyl derivative **3g**.<sup>28, 29, 32–36</sup> This admixture cannot be efficiently removed by recrystallisation. The complete nitrolysis can only be achieved by prolonged (7–14 h) reaction at high temperature (115–120 °C) (Fig. 1).<sup>31, 32</sup> Such modes were realised if mixtures of sulfuric and nitric acids or nitric acid and ammonium nitrate with a modulus smaller than 10 were used as nitration agents. The role of ammonium nitrate consists of stabilisation of the nitration mixture and an increase in its boiling point, which makes it possible to achieve yields of the target product **1** as high as 98%–99% at a contamination level of 1.5%–0.5% (see Fig. 1).<sup>30, 32</sup>

Nitration of the dihydro derivative **3b** is faster than that of the diformyl derivative **3g**, but the yield of **1** is smaller in this case (90%).<sup>33</sup> Nitrolysis of **3b** is of interest since HNIW synthesised by this route is free of formyl admixtures, although other by-products can still be present (no intermediates have been isolated so far), which can affect the sensitivity of compound **1** to mechanical actions.<sup>33</sup> The nitrolysis of compound **3b** is a multi-step process. Probably, at the beginning of the reaction, the free amino groups of the substrate **3b** undergo protonation in the acidic solution. Then, the nitrolysis of the AcN fragments occurs, which gives rise to an increase in the concentration of acetic acid in the reaction mixture. Acetic acid reacts with nitric acid to yield acetyl nitrate. Presumably,<sup>33</sup> it is acetyl nitrate, which is the reagent of choice for the nitration of secondary amines, that is involved in the nitration of the  $\text{NH}_2^+$  fragments.

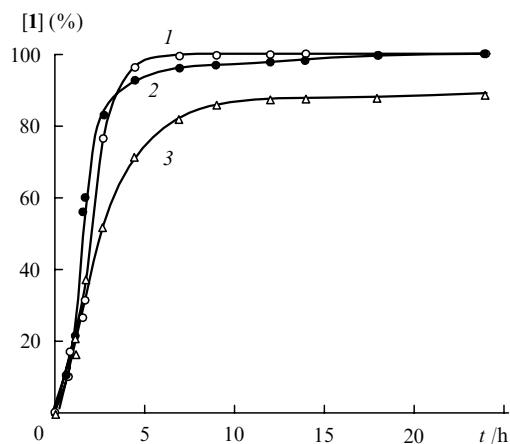


**Figure 1.** The fraction of hexanitrohexaazaisowurtzitane **1** in the nitrolysis products of the diformyl derivative **3g** as a function of the nitrolysis time and the type of nitration agent.

Nitration agents: a mixture of sulfuric and nitric acids (15:85) at a modulus of 5 (**1**); nitric acid–ammonium nitrate (25%) at a modulus of 6 (**2**); 98% nitric acid at a modulus of 5 (**3**).

This simplified scheme is complicated by the nature of the substrate subject to nitration. It is known that the basicity of the nitrogen atoms in polycyclic cage compounds are low. Therefore, unlike the nitration of standard amines that occurs rather smoothly, the nitration in this case is accompanied by partial decomposition of the cage. No oxides are evolved in this process and upon splitting of the acetyl groups in the nitrolysis of compound **3b** in contrast to the nitrolysis of the diformyl derivative **3g**, which is accompanied by the intense gas evolution, probably, owing to the decomposition of the formyl fragments. Thus, one can conclude that the decomposition products of **3b**, which can contain water and stable acidic fragments of the cage, do not undergo oxidation under the nitrolysis conditions.<sup>29</sup> Compound **3b** can be nitrated with an anhydrous mixture of nitric and sulfuric acids (85:15) at a modulus of 9 and 83 °C to afford HNIW in 91.8% yield.<sup>33</sup>

The product **1** obtained upon nitration of the chloroacetyl derivative **3e** is contaminated with 4-chloroacetyl-2,6,8,10,12-pentanitro-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0<sup>3,11</sup>.0<sup>5,9</sup>]dodecane.<sup>23</sup>

Thus, the methods based on the use of hexabenzylhexaazaisowurtzitane **2a** as a key compound and various tetraacetyl derivatives **3a–h** as intermediates have found the widest application among all methods for the synthesis of hexanitrohexaazaisowurtzitane reported in the literature.<sup>27, 29, 31, 32, 35</sup>

## V. Polymorphism of hexanitrohexaazawurtzitane and preparation of its $\epsilon$ -polymorph

Under normal conditions, HNIW has four stable polymorph modifications, *viz.*,  $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\epsilon$ .<sup>4, 37, 38</sup> which differ from each other in the spatial orientation of the nitro groups relative to the five- and six-membered rings of the cage, the type of the crystal packing and the number of molecules per unit cell (Table 3).<sup>37</sup>

The  $\beta$  polymorph isolated by recrystallisation of crude HNIW from benzene was the first crystalline modification discovered.<sup>4</sup> This modification is the least stable as regards polymorphic transformations: it readily converts into the  $\gamma$  polymorph at 185 °C.<sup>37</sup> The latter can be obtained by the nitrolysis of the diformyl derivative **3g** with nitric acid at a modulus no more than 4.5.<sup>28</sup> Heating of  $\gamma$  HNIW to 230 °C changes the crystal structure. According to data from IR spectroscopy, this is most likely due to a structural modification of the  $\gamma$  HNIW<sup>4</sup> rather than a phase transition into another polymorph form (*e.g.*,  $\delta$  polymorph, as was suggested earlier<sup>37</sup>). The conformations of the HNIW molecules in the  $\beta$  and  $\gamma$  polymorphs are identical, but their packing types are different, which results in different symmetries of their crystal structures [orthorhombic and monoclinic, respectively (see Table 3)].<sup>37</sup>

The  $\alpha$  polymorph is formed upon precipitation of HNIW with chloroform from its solutions in sulfolane.<sup>4</sup> Crystalline hemihydrate was obtained upon recrystallisation of this polymorph from 75% nitric acid. The crystal structure of the  $\alpha$  polymorph is stabilised by inclusion of water molecules in cavities at the inversion centres of the crystal lattice. The inclusion of a water molecule in each cavity gives rise to the hemihydrate whereas the quarterhydrate is formed if only 50% of all cavities are occupied (see Table 3).<sup>37</sup>

The  $\epsilon$  polymorph is characterised by the maximum density and thermal stability among all known crystalline modifications of HNIW. In addition to the modifications listed in Table 3, one more modification, *viz.*, the labile  $\delta$  form, is known. This form, which is stable only at elevated pressures, was detected during the equilibrium transformation of the  $\gamma$  phase. The crystal structure of the  $\delta$  polymorph and the conformation of the HNIW molecules therein have not been determined so far.<sup>37, 39</sup>

Theoretically, 24 conformers of the HNIW molecule with different orientations of six nitro groups relative to the molecular cage are possible. The number of most probable conformations is reduced to nine if steric hindrance is taken into consideration.

**Table 3.** Properties of the HNIW polymorphs.

| Property                                                              | Polymorph                  |                                    |                                     |                         |
|-----------------------------------------------------------------------|----------------------------|------------------------------------|-------------------------------------|-------------------------|
|                                                                       | $\alpha$                   | $\beta$                            | $\gamma$                            | $\epsilon$              |
| Orientation of the NO <sub>2</sub> groups at the atoms N(4) and N(10) | <i>exo,exo</i>             | <i>exo,exo</i>                     | <i>exo,exo</i>                      | <i>exo,endo</i>         |
| Number of molecules per unit cell                                     | 8                          | 4                                  | 4                                   | 4                       |
| Space group                                                           | <i>Pbca</i>                | <i>Pb2<sub>1</sub>a</i>            | <i>P2<sub>1</sub>/n</i>             | <i>P2<sub>1</sub>/n</i> |
| Symmetry                                                              | orthorhombic               | orthorhombic                       | monoclinic                          | monoclinic              |
| Crystal habitus                                                       | prisms                     | needles                            | plates                              | prisms                  |
| Decomposition temperature /°C                                         | 260                        | 260                                | 260                                 | 260                     |
| Polymorphic transition temperature (and type) /°C                     | —                          | 185 ( $\beta \rightarrow \gamma$ ) | 230 ( $\gamma \rightarrow \delta$ ) | —                       |
| Density /g cm <sup>-3</sup>                                           | 1.961 (2.001) <sup>a</sup> | 1.985                              | 1.916                               | 2.04                    |

<sup>a</sup> The value is given for the hemihydrate of the  $\alpha$  polymorph.

Presumably, the density of the most symmetrical structure is higher than that of the  $\epsilon$  polymorph. However, the high symmetry does not ensure necessarily the stability of the conformer: according to calculations, the  $\epsilon$  polymorph is more stable.<sup>37</sup>

Two groups of methods, *viz.*, precipitation and evaporation crystallisation, are used for the preparation of HNIW as the  $\epsilon$  polymorph.

The technology of precipitation methods implies that a crystallisation seed is first placed into a solution of HNIW in a suitable solvent and then a precipitant is gradually added to the solution.<sup>38,40</sup> The precipitate formed is filtered off and dried. The reverse sequence of steps, *i.e.*, addition of a HNIW solution to a precipitant with stirring, is also documented.<sup>41</sup>

Prior to crystallisation, crude HNIW is dissolved in ethyl acetate, and the solution is washed with water or 10% aqueous sodium carbonate (to remove acids) to neutral pH of the aqueous layer, then traces of water are removed by azeotropic distillation with the solvent or using a desiccant, such as anhydrous magnesium sulfate or sodium sulfate.<sup>42</sup>

The solvents for crystallisation where the solubility of HNIW is more than 20% include ethyl acetate or acetone,<sup>†</sup> whereas in precipitants the solubility of HNIW does not exceed 1% (aliphatic and aromatic hydrocarbons: heptane, hexane, benzene, toluene, xylenes, mineral oil or chloroform).<sup>38,42,43</sup> Hexanitrohexaazaisowurtzitane forms crystalline solvates with sulfolane and DMF.<sup>2,44</sup>

An original procedure of the preparation of solutions for the precipitation crystallisation of  $\epsilon$  HNIW was proposed by Bescond *et al.*<sup>25</sup> Pre-purified and dried HNIW is repeatedly heated and cooled in a mixture containing 27.5% of poly(glycidyl azide), 35% of trimethylolethane trinitrate, 35% of butane-1,2,4-triol trinitrate, 1.25% of 2-nitrodiphenylamine and 1.25% of *N*-methyl-*p*-nitroaniline. This procedure yields the  $\epsilon$  polymorph with a density of  $\sim 2.04$  g cm<sup>-3</sup>.

The technology of the evaporation crystallisation is based on the gradual distillation of the solvent from a mixture of HNIW – solvent – precipitant, which favours an increase in the concentration of HNIW and precipitation of the  $\epsilon$  polymorph. The solvent used has to be more volatile than the precipitant. Acetone, ethyl acetate, isopropyl acetate, methyl acetate, tetrahydrofuran, acetonitrile and ethyl methyl ketone are typically used as solvents, whereas toluene, dichloroethane or xylene are used as precipitants. Precipitation of the  $\epsilon$  polymorph with a certain particle size and granulometric composition can be achieved by adjusting temperature, stirring velocity and distillation rate.<sup>25</sup>

The thermal stabilities of different polymorphs of HNIW and possibilities of the phase transitions have been studied in detail by IR and optical spectroscopy, thermography and manometry.<sup>37,43,45–48</sup> It has been established that the thermal stability of

the polymorphs increases in the series  $\beta < \alpha < \alpha \cdot \text{H}_2\text{O} < \gamma < \epsilon$ .<sup>37</sup> The process of the thermal decomposition of HNIW in a solid phase follows first-order autocatalytical kinetics. The thermolysis of HNIW and its inflammation are accompanied by the formation of a solid residue.<sup>45</sup> Nitrogen constitutes a half of the gaseous products generated upon thermolysis.

According to tests, the explosion power of compositions based on HNIW is 14% higher than that of analogous octogen-based compositions.<sup>3</sup> Furthermore, the propelling performance (according to the faceplate acceleration tests) of hexanitrohexaazaisowurtzitane is superior to that of octogen. The energy density of HNIW is 8% higher than that of octogen.<sup>3</sup> This indicates that HNIW is currently the most powerful explosive and it will undoubtedly find wide applications in the armaments industry. More details on the sensitivity and thermal stability of HNIW as well as of compositions using its base can be found in a recent review by Nair *et al.*<sup>49</sup>

## VI. Conclusion

The analysis of published data indicates that there are several convenient methods for the synthesis of hexanitrohexaazaisowurtzitane. In all cases, hexabenzylhexaazaisowurtzitane **2a** is used as the starting material. The divergence of the synthetic routes begins from the step for the preparation of derivatives suitable for nitrolysis and the conditions of the nitrolysis. The best studied method for the synthesis of hexanitrohexaazaisowurtzitane implemented at the industrial scale is the two-step reductive debenzoylation of hexabenzylhexaazaisowurtzitane **2a** to yield the dihydro (**3b**) or diformyl (**3g**) derivatives, which are subsequently nitrated with nitric acid-based systems.

The establishment and development of industrial technologies for the production of HNIW will favour wider utilisation of this highly promising product.

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# Supramolecular porphyrin complexes

G M Mamardashvili, N Zh Mamardashvili, O I Koifman

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**Abstract.** The published data on the complexation properties and abilities of porphyrins to recognise charged particles and neutral molecules are systematised. The bibliography includes 91 references.

## I. Introduction

The formation of supramolecular complexes is the groundwork of many biological processes and phenomena. Such processes as enzymatic catalysis, inhibition, immune response, reproduction of genetic information, bioregulation, drug effects, ion transport, *etc.* all include structural recognition in complexation. In molecular recognition, certain molecules ('host' or receptor molecules) select and bind other molecules ('guest' or substrate molecules) through intermolecular forces, resulting in the formation of systems with highly ordered structures. The existence of several binding sites is a prerequisite for attaining a high level of structural organisation of organic complexes, since the energy of a single intermolecular interaction is far too low in comparison with the energies of the covalent bonds.

Like crown ethers and calixarenes, porphyrin molecules are extremely interesting subjects as regards the design of 'host–guest'-type supramolecules. The rigid backbones of porphyrins make them ideal structural elements of 'host' molecules, the substituents in which are arranged in a definite order enabling specific interactions with 'guest' molecules. The presence, in the porphyrin molecule, of an extended conjugated  $\pi$ -system allows successful application of a variety of spectroscopic and analytical methods in the investigations of intermolecular interactions.

Publications on supramolecular porphyrin complexes containing no less than two binding sites appeared in the literature only 10–15 years ago. The aim of the present review is to generalise and analyse the published data on supramolecular porphyrin complexes and to track modern trends in the development of the supramolecular chemistry of porphyrins and its main achievements.

The ability of most porphyrin receptors to perform molecular recognition of various species is based on the possible axial coordination of ligands to the reaction centres of porphyrin metallocomplexes.<sup>1–4</sup> The overwhelming majority of metalloporphyrin receptors are represented by zinc–porphyrin complexes.

## II. Axial coordination of monodentate ligands to Zn-containing porphyrins

Axial coordination of ligands is inherent in many complexes with planar coordination centres ( $ML_4$ ), but is especially well-defined and peculiar for metalloporphyrins.<sup>1–5</sup> The structures, compositions and stabilities of axial metalloporphyrin–ligand complexes depend on the nature of the metal. The Zn(II) ion, which is prone to  $sp^3$ - or  $sp^2d^2$ -hybridisation, has to acquire an  $sp^2d$ -configuration in complexes with planar porphyrin molecules. This results in electron-deficient  $4p_z$ - and  $4d_{z^2}$ -orbitals, which enter into donor–acceptor interactions with electron-donor ligands.

Upon coordination of a ligand to a metalloporphyrin, the central metal atom exits the plane of the porphyrin macrocycle towards the axial ligand, which is accompanied by a bathochromic shift of the Soret and  $Q$ -bands in the electronic absorption spectra. The reason for such spectral changes is the weakening of the electronic  $\sigma$ -effects, which characterise the strengths of the M–N bonds and the positive charge on the metal cation.<sup>5</sup> A distinct correlation exists between the magnitude of the bathochromic shift of the adsorption bands and the basicity of the axial ligand.<sup>5,6</sup>

It is known that zinc–porphyrin complexes bind nitrogen bases easily, but coordinate oxygen- and sulfur-containing molecular ligands to a lesser degree. Nevertheless, the coordination of oxygen-containing molecules to zinc ions can also serve as a non-selective 'anchor' site in multisite recognition.<sup>7,8</sup> Monomeric Zn-containing porphyrins usually bind only one axial ligand to form pentacoordinate complexes.<sup>6</sup> In the case of weaker bases (*e.g.*, DMSO, DMF), zinc–porphyrin complexes bind two axial ligands, however, their bond strengths are different.<sup>9–12</sup>

Upon coordination of oxygen-, sulfur- or nitrogen-containing ligands to monomeric zinc–porphyrin complexes, the binding constants (also referred to as the association, extracoordination or stability constant,  $K_a$ ) strongly depend on the basicity of the ligand. In the general case, the greater the basicity of the ligand the stronger its coordination to the metalloporphyrin. The value of the binding constant for the zinc–tetraphenylporphyrine complex (I) in toluene increases by five orders of magnitude in the series: methanol < pyrrole < DMSO < pyridine < imidazole < piperidine.<sup>9</sup> Such a correlation is violated, if the lone electron pair of the ligand involved in the coordination is delocalised over the

G M Mamardashvili, N Zh Mamardashvili, O I Koifman Institute of Solution Chemistry, Russian Academy of Sciences, ul. Akademicheskaya 1, 153045 Ivanovo, Russian Federation. Fax: (7-0932) 33 63 27, tel. (7-0932) 33 69 90, e-mail: gmm@isc-ras.ru (G M Mamardashvili), ngm@isc-ras.ru (N Zh Mamardashvili), tel. (7-0932) 32 92 41, e-mail: oik@isuct.ru (O I Koifman)

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adjacent substituents. The effects of the solvent, structure and position of the substituents in the porphyrin molecule on the axial coordination are less pronounced than the effect of the nature of the axial ligand (Table 1).<sup>13</sup>

**Table 1.** Binding constants of alkyl- and aryl-substituted monomeric Zn-containing porphyrins with monodentate ligands at 298 K.

| Porphyrin | Ligand                        | Solvent                         | $K_a$<br>/litre mol <sup>-1</sup> | Ref. |
|-----------|-------------------------------|---------------------------------|-----------------------------------|------|
| <b>1</b>  | piperidine                    | toluene                         | 809000                            | 5, 9 |
|           | methylimidazole               | <i>o</i> -xylene                | 110000                            | 14   |
|           | imidazole                     | toluene                         | 24000                             | 5, 9 |
|           | imidazole                     | <i>o</i> -xylene                | 15000                             | 14   |
|           | quinoline                     | toluene                         | 16900                             | 5, 9 |
|           | pyridine                      | toluene                         | 5800                              | 5, 9 |
|           | pyridine                      | toluene                         | 4790                              | 15   |
|           | pyridine                      | benzene                         | 3750                              | 16   |
|           | pyridine                      | <i>o</i> -xylene                | 1800                              | 14   |
|           | pyridine                      | CHCl <sub>3</sub>               | 2525                              | 17   |
|           | pyridine                      | CHCl <sub>3</sub>               | 617                               | 18   |
|           | pyridine                      | CHCl <sub>3</sub>               | 900                               | 19   |
|           | 4-methylpyridine              | CHCl <sub>3</sub>               | 1600                              | 19   |
|           | pyrazole                      | CHCl <sub>3</sub>               | 1500                              | 19   |
|           | DMF                           | <i>o</i> -xylene                | 560                               | 14   |
|           | pyrrole                       | toluene                         | 200                               | 5, 9 |
|           | methanol                      | toluene                         | 4.6                               | 5, 9 |
| <b>2</b>  | pyrazole                      | CH <sub>2</sub> Cl <sub>2</sub> | 2600 <sup>a</sup>                 | 20   |
| <b>3</b>  | imidazole                     | benzene                         | 51920                             | 5, 9 |
| <b>4</b>  | pyridine                      | CH <sub>2</sub> Cl <sub>2</sub> | 2890 <sup>b</sup>                 | 21   |
| <b>5</b>  | pyrazole                      | CH <sub>2</sub> Cl <sub>2</sub> | 800                               | 20   |
| <b>6</b>  | pyridine                      | benzene                         | 10300                             | 17   |
|           | pyridine                      | toluene–MeOH (2:1)              | 1380                              | 22   |
| <b>7</b>  | pyridine                      | toluene                         | 5000                              | 23   |
|           | 4-methylpyridine              | toluene                         | 11000                             | 23   |
|           | 4- <i>tert</i> -butylpyridine | toluene                         | 14000                             | 23   |
| <b>8</b>  | pyridine                      | CH <sub>2</sub> Cl <sub>2</sub> | 2800 <sup>c</sup>                 | 24   |
| <b>9</b>  | pyridine                      | CH <sub>2</sub> Cl <sub>2</sub> | 5200                              | 24   |
| <b>10</b> | imidazole                     | benzene                         | 59740                             | 1    |
|           | pyridine                      | benzene                         | 4694                              | 25   |
|           | pyridine                      | CHCl <sub>3</sub>               | 1136                              | 25   |
| <b>11</b> | imidazole                     | benzene                         | 33140                             | 1    |
|           | pyridine                      | benzene                         | 5586                              | 25   |
|           | pyridine                      | CHCl <sub>3</sub>               | 2590                              | 25   |
| <b>12</b> | imidazole                     | benzene                         | 35450                             | 1    |
|           | pyridine                      | benzene                         | 5795                              | 25   |
|           | pyridine                      | CHCl <sub>3</sub>               | 3267                              | 25   |

<sup>a</sup> The data for 295 K are given. <sup>b</sup> The measurement temperature is not indicated. <sup>c</sup> The data for 303 K are given.

Axial coordination to metalloporphyrins is usually carried out in inert solvents (*e.g.*, benzene, toluene, dichloromethane). V'yugin *et al.*<sup>26,27</sup> studied the axial coordination of solvents to a vast variety of metalloporphyrins by calorimetry. The enthalpies of coordination of the aforementioned inert solvents to Zn-containing porphyrins were found to be close to zero. The values of the binding constants for the Zn–porphyrin–ligand complexes changed no more than fourfold on going from one inert solvent to another (see Table 1). The highest  $K_a$  values were observed in aromatic solvents, *viz.*, benzene and toluene.

The dependence of the binding constants on the structures of the substituents in porphyrins **1–12** was even less pronounced, since the electronic effects of the aryl and alkyl groups on the state of the central zinc ion were insignificant.

At the same time, the  $K_a$  values for the monodentate nitrogen bases changed by several orders of magnitude in the series of metalloporphyrins **13–29**, which differ in the degree of distortion of the tetrapyrrole macrocycle (Table 2). The major factors determining the axial coordination to these porphyrins are shielding of the reaction centre of the tetrapyrrole macrocycle (from one or both sides); changes in the electron densities on the nitrogen atoms of the porphyrin and in the charge on the Zn(II) cation due to distortion of the macrocycle structure; matching of the size of the cavity formed by the distorted porphyrin macrocycle to the size of the axial ligand and also complementary  $\pi$ – $\pi$ , CH– $\pi$ , *etc.*, interactions between the metalloporphyrin ('host') and ligand ('guest') molecules.

The coordination of axial ligands to 'picket-fence', 'strapped' and dimeric porphyrins has a number of specific features. The term 'picket-fence' is usually applied to porphyrins containing bulky peripheral substituents. In the majority of cases, these are tetraphenylporphine derivatives with *ortho*-substituents in each benzene ring. Depending on the orientation of the substituents relative to the plane of the tetrapyrrole macrocycle ( $\alpha$  on one side and  $\beta$  on the other side), there are four atropoisomers, *viz.*,  $\alpha,\alpha,\alpha,\alpha$ - ( $\alpha^4$ ),  $\alpha,\beta,\alpha,\alpha$ -,  $\alpha,\alpha,\beta,\beta$ - (*cis*- $\alpha^2$ ) and  $\alpha,\beta,\alpha,\beta$ - (*trans*- $\alpha^2$ ).

The axial coordination of pyridine, piperidine and quinoline to 'picket-fence' metalloporphyrins **13** and **14** in toluene and other non-coordinating solvents has been studied.<sup>28</sup> The results obtained suggest that the affinities of *trans*- $\alpha^2$ -atropoisomers for pyridine and quinoline are higher than those of  $\alpha^4$ -atropoisomers.

Both sides of the metalloporphyrin reaction centre of the *trans*- $\alpha^2$ -atropoisomer **14** are equally accessible for coordination. In this case, the enhanced affinities for pyridine and quinoline are due to weak CH– $\pi$  interactions between the bulky alkyl groups of the *ortho*-substituents and the  $\pi$ -electron systems of the ligand. In the case of the  $\alpha^4$ -atropoisomer **13**, both sides of the reaction centre of the metalloporphyrin are non-equivalent. The reaction centre is virtually completely shielded by four *ortho*-substituents, and the ligands are coordinated to the zinc cation only from the 'open' side of the porphyrin macrocycle and do not enter into any

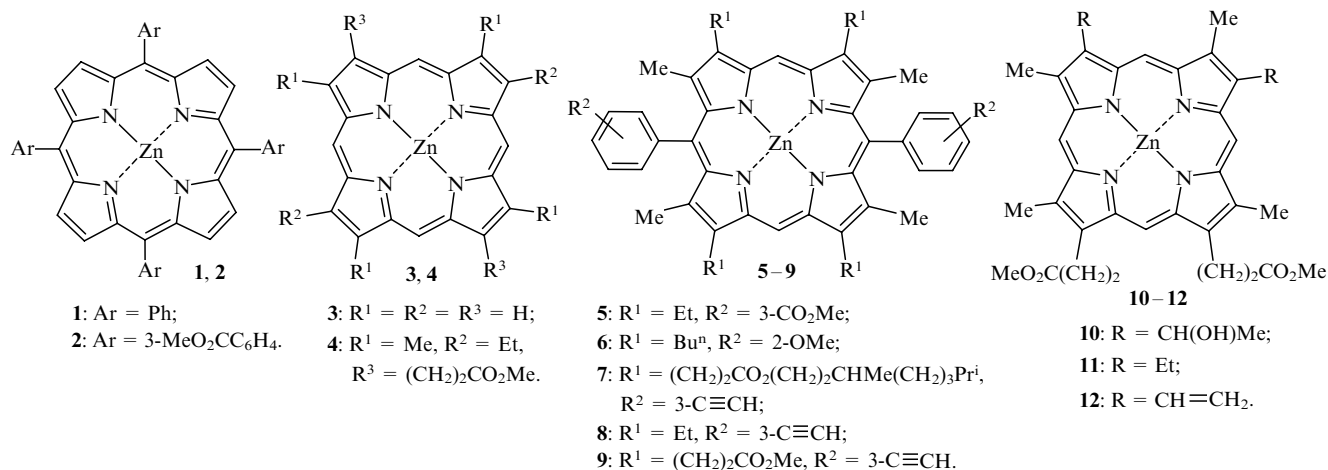


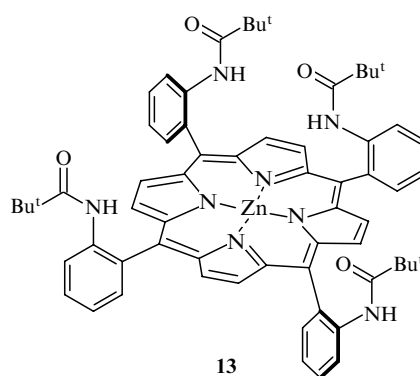


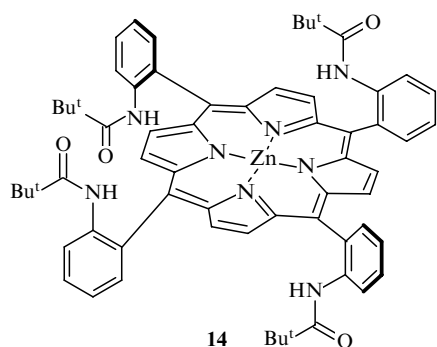
**Table 2.** Binding constants of sterically hindered monomeric and dimeric Zn-containing porphyrins with monodentate ligands at 298 K.

| Porphyrin | Ligand                        | Solvent                         | $K_a$ /litre mol <sup>-1</sup> | Reference porphyrin | $K_a/K_{comp}$ | Ref. |
|-----------|-------------------------------|---------------------------------|--------------------------------|---------------------|----------------|------|
| <b>13</b> | pyridine                      | toluene                         | $2.33 \times 10^4$             | <b>1</b>            | 3.8            | 28   |
|           | isoquinoline                  | toluene                         | $4.6 \times 10^5$              | —                   | —              | 28   |
| <b>14</b> | pyridine                      | toluene                         | $2.97 \times 10^4$             | <b>1</b>            | 4.9            | 28   |
|           | isoquinoline                  | toluene                         | $9.6 \times 10^5$              | —                   | —              | 28   |
| <b>15</b> | pyrazole                      | CH <sub>2</sub> Cl <sub>2</sub> | $2.3 \times 10^3$              | <b>2</b>            | 0.9            | 20   |
| <b>16</b> | pyridine                      | benzene                         | $3.1 \times 10^3$              | <b>6</b>            | 0.3            | 17   |
| <b>17</b> | 2-methylimidazole             | <i>o</i> -xylene                | $4.6 \times 10^2$              | <b>1</b>            | 0.004          | 14   |
|           | imidazole                     | <i>o</i> -xylene                | $9.3 \times 10^2$              | <b>1</b>            | 0.062          | 14   |
|           | pyridine                      | <i>o</i> -xylene                | $2.4 \times 10^2$              | <b>1</b>            | 0.133          | 14   |
|           | DMF                           | <i>o</i> -xylene                | 42                             | <b>1</b>            | 0.075          | 14   |
| <b>18</b> | pyrazole                      | CH <sub>2</sub> Cl <sub>2</sub> | $1.8 \times 10^2$              | <b>5</b>            | 0.225          | 20   |
| <b>19</b> | pyrazole                      | CH <sub>2</sub> Cl <sub>2</sub> | $5.9 \times 10^2$              | <b>5</b>            | 0.738          | 20   |
| <b>20</b> | pyridine                      | CH <sub>2</sub> Cl <sub>2</sub> | $1.3 \times 10^3$              | <b>4</b>            | 0.45           | 29   |
| <b>21</b> | pyridine                      | CH <sub>2</sub> Cl <sub>2</sub> | $3.6 \times 10^2$              | <b>4</b>            | 0.12           | 29   |
| <b>22</b> | pyridine                      | CH <sub>2</sub> Cl <sub>2</sub> | $1.99 \times 10^3$             | —                   | —              | 30   |
|           | imidazole                     | CH <sub>2</sub> Cl <sub>2</sub> | $1.259 \times 10^6$            | —                   | —              | 30   |
|           | 2-methylimidazole             | CH <sub>2</sub> Cl <sub>2</sub> | $1.95 \times 10^8$             | —                   | —              | 30   |
|           | 2-phenylimidazole             | CH <sub>2</sub> Cl <sub>2</sub> | $2.55 \times 10^6$             | —                   | —              | 30   |
|           | pyridine                      | CHCl <sub>3</sub>               | $1.8 \times 10^4$              | <b>1</b>            | 20             | 19   |
| <b>23</b> | 2-methylpyridine              | CHCl <sub>3</sub>               | $8.0 \times 10^4$              | <b>1</b>            | 50             | 19   |
|           | pyrazole                      | CHCl <sub>3</sub>               | $2.9 \times 10^5$              | <b>1</b>            | 193            | 19   |
| <b>24</b> | pyridine                      | CHCl <sub>3</sub>               | $6.8 \times 10^3$              | <b>1</b>            | 7.6            | 19   |
|           | 2-methylpyridine              | CHCl <sub>3</sub>               | $2.0 \times 10^4$              | <b>1</b>            | 12.5           | 19   |
|           | pyrazole                      | CHCl <sub>3</sub>               | $7.9 \times 10^4$              | <b>1</b>            | 52.7           | 19   |
| <b>25</b> | pyridine                      | CHCl <sub>3</sub>               | $1.47 \times 10^5$             | <b>1</b>            | 163            | 19   |
|           | 2-methylpyridine              | CHCl <sub>3</sub>               | $2.33 \times 10^5$             | <b>1</b>            | 146            | 19   |
|           | pyrazole                      | CHCl <sub>3</sub>               | $1.077 \times 10^6$            | <b>1</b>            | 718            | 19   |
| <b>26</b> | pyridine                      | CHCl <sub>3</sub>               | $1.5 \times 10^4$              | <b>1</b>            | 16.7           | 19   |
|           | 2-methylpyridine              | CHCl <sub>3</sub>               | $4.6 \times 10^3$              | <b>1</b>            | 2.9            | 19   |
|           | pyrazole                      | CHCl <sub>3</sub>               | $1.4 \times 10^5$              | <b>1</b>            | 93             | 19   |
| <b>27</b> | pyridine                      | CHCl <sub>3</sub>               | $1.433 \times 10^4$            | <b>1</b>            | 15.9           | 31   |
| <b>28</b> | pyridine                      | CHCl <sub>3</sub>               | $9.185 \times 10^4$            | <b>1</b>            | 102.0          | 31   |
| <b>29</b> | pyrazole                      | CH <sub>2</sub> Cl <sub>2</sub> | $1.3 \times 10^3$              | <b>2</b>            | 0.5            | 20   |
| <b>30</b> | pyridine                      | CH <sub>2</sub> Cl <sub>2</sub> | $1.02 \times 10^2$             | <b>4</b>            | 0.04           | 21   |
| <b>31</b> | pyridine                      | CH <sub>2</sub> Cl <sub>2</sub> | $1.05 \times 10^2$             | <b>4</b>            | 0.04           | 21   |
| <b>32</b> | pyridine                      | CH <sub>2</sub> Cl <sub>2</sub> | $4.1 \times 10^3$              | <b>4</b>            | 1.4            | 29   |
| <b>33</b> | pyridine                      | CH <sub>2</sub> Cl <sub>2</sub> | $9.6 \times 10^2$              | <b>4</b>            | 0.3            | 29   |
| <b>34</b> | pyridine                      | toluene                         | $1.6 \times 10^4$              | <b>7</b>            | 3.2            | 23   |
|           | 4-methylpyridine              | toluene                         | $6.2 \times 10^4$              | <b>7</b>            | 5.6            | 23   |
|           | 4- <i>tert</i> -butylpyridine | toluene                         | $7.3 \times 10^5$              | <b>7</b>            | 52.1           | 23   |
| <b>35</b> | pyridine                      | CH <sub>2</sub> Cl <sub>2</sub> | $4.5 \times 10^3$              | <b>8</b>            | 1.6            | 24   |
| <b>36</b> | pyrazole                      | CH <sub>2</sub> Cl <sub>2</sub> | $3.8 \times 10^2$              | —                   | —              | 1    |
| <b>37</b> | pyrazole                      | CH <sub>2</sub> Cl <sub>2</sub> | $6.6 \times 10^2$              | <b>5</b>            | 0.83           | 20   |
| <b>38</b> | pyrazole                      | CH <sub>2</sub> Cl <sub>2</sub> | $6.9 \times 10^2$              | <b>5</b>            | 0.86           | 20   |
| <b>39</b> | pyridine                      | toluene – MeOH (2 : 1)          | $2.7 \times 10^3$              | <b>6</b>            | 2.0            | 22   |
| <b>40</b> | pyridine                      | toluene – MeOH (2 : 1)          | $3.2 \times 10^3$              | <b>6</b>            | 2.3            | 22   |
| <b>41</b> | pyridine                      | benzene                         | $1.4 \times 10^3$              | —                   | —              | 17   |
|           | pyridine                      | benzene                         | $1.5 \times 10^4$              | <b>6</b>            | 1.5            | 17   |
| <b>42</b> | pyridine                      | CH <sub>2</sub> Cl <sub>2</sub> | $1.38 \times 10^3$             | —                   | —              | 32   |

additional interactions with the *ortho*-substituents in the benzene rings.

‘Strapped’ porphyrins are compounds with different types of bridges that link peripheral positions of the macrocycle.<sup>33</sup> Synthesis of such porphyrins was aimed at the construction of complexes that mimic natural enzymatic systems. The binding constants of ‘strapped’ porphyrins with the ligands are determined primarily by the shielding of the porphyrin cores and matching of the size of their intramolecular cavity to the size of the coordinated ligand. If the reaction centre is not shielded by bulky substituents, as is the case for porphyrin **15**, the  $K_a$  value is virtually the same as that of the non-distorted porphyrin (see Table 2).<sup>20</sup>





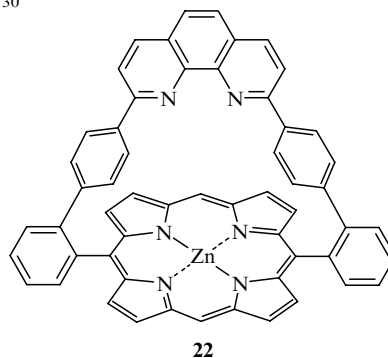
In the case of a unilateral shielding of the reaction centre by a bulky substituent, the binding constant depends first of all on the matching of the size of the intramolecular cavity of the metalloporphyrin to the size of the coordinated ligand. In the case of mismatch, the coordination of the ligand takes place exclusively to the 'open' side of the macrocycle. In this case, the binding constants of 'strapped' metalloporphyrins with different ligands are smaller than those of porphyrins devoid of steric shielding of the reaction centres, *e.g.*, compounds **16–21** (see Table 2).<sup>14, 17, 29, 34</sup>

Metalloporphyrins **16, 17, 20** and **21** contain aromatic fragments in their bridges that are involved in  $\pi$ – $\pi$  interactions with the porphyrin macrocycles.<sup>29</sup> This results in a decrease of charge on the Zn(II) cation of the reaction centre, which we consider as a

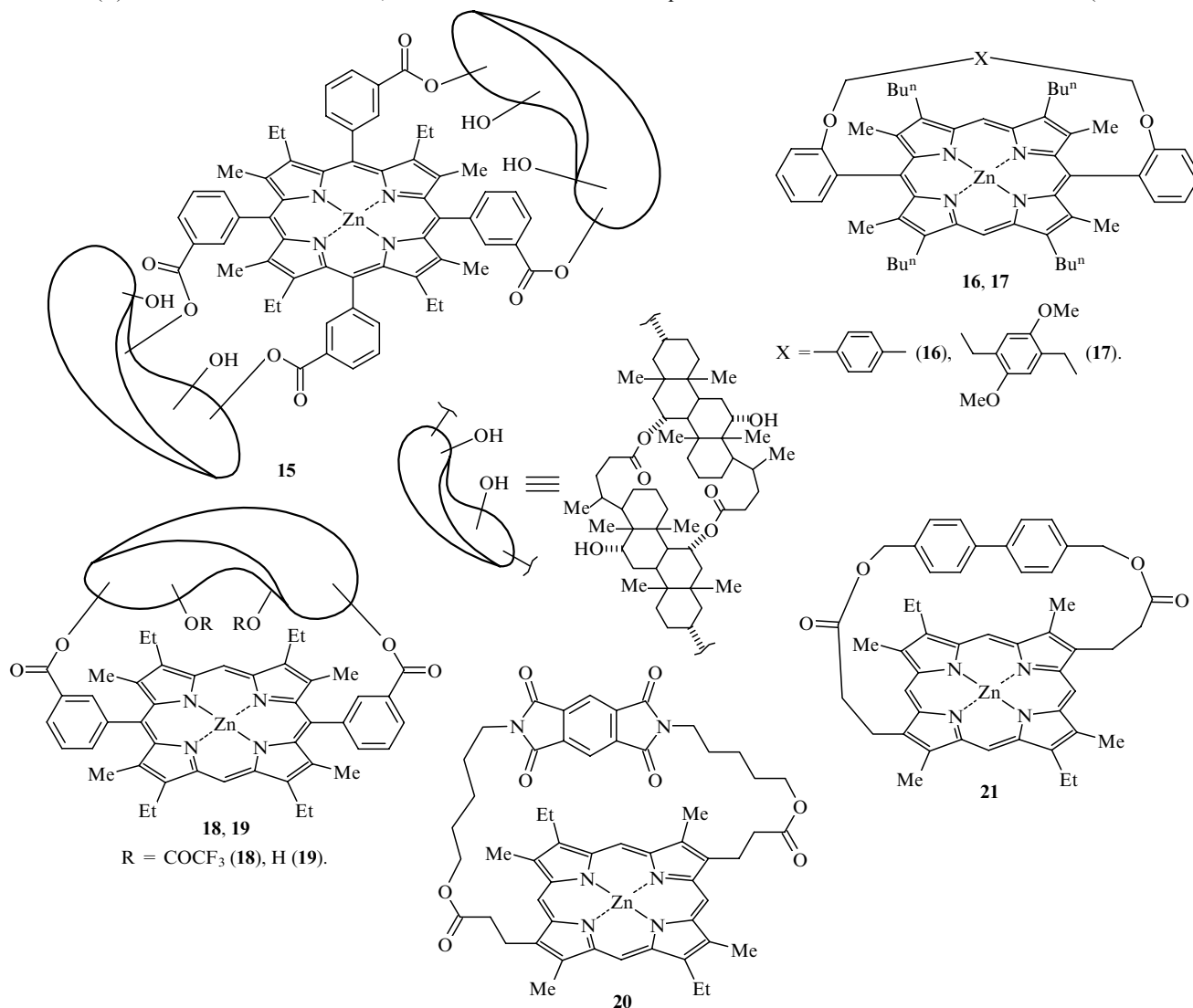
major reason for the decrease in the  $K_a$  values of complexes **16, 17, 20** and **21** in comparison with metalloporphyrins devoid of shielding substituents.

The value of  $K_a$  increases substantially if the size of the ligand matches the diameter of the intramolecular cavity of the sterically shielded porphyrin, which enables its incorporation into the cavity.

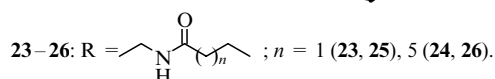
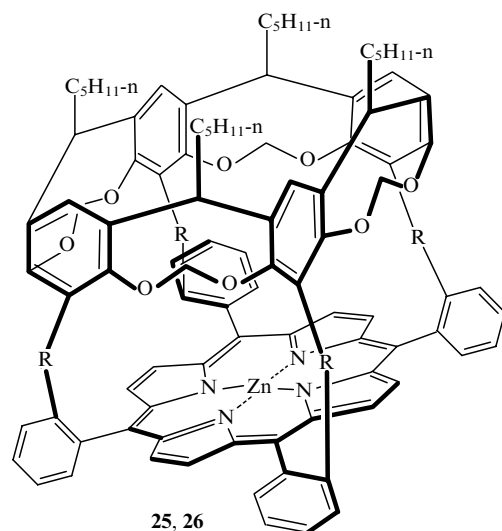
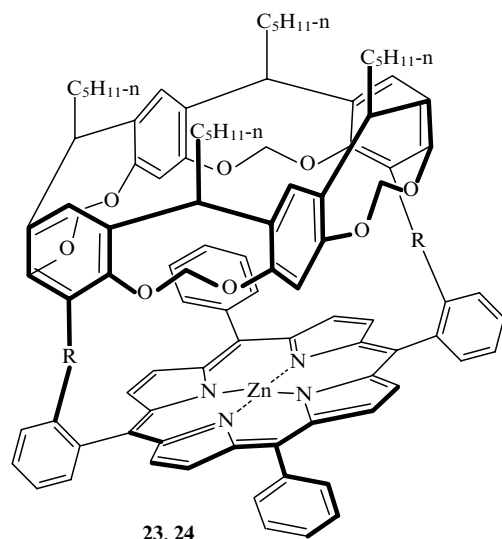
Interesting results were obtained in studies on the coordination of various imidazole derivatives to the porphyrin receptor **22**.<sup>30</sup>



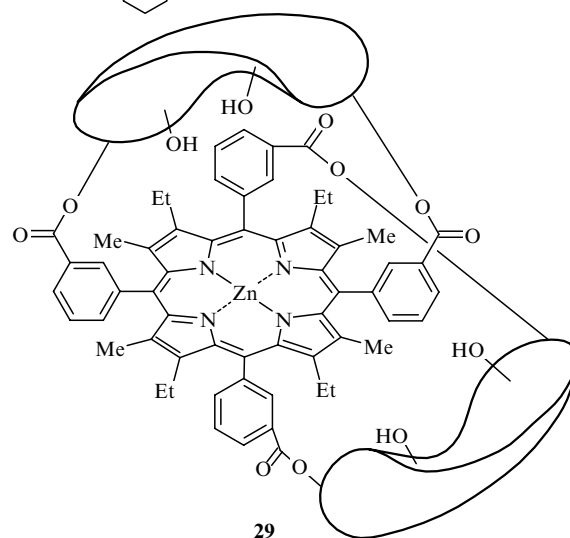
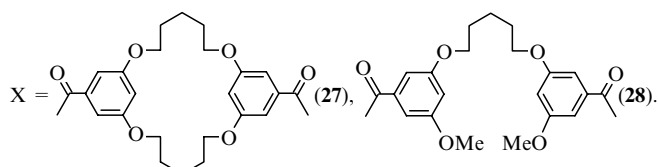
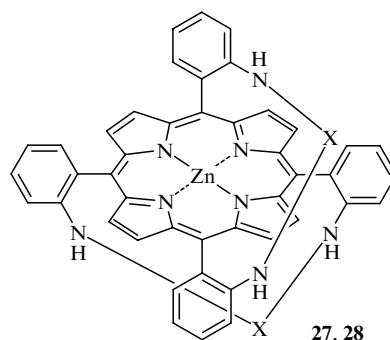
In this case, not only does the diameter of the intramolecular cavity of the porphyrin match the ligand size. Also, additional binding sites between the receptor and the ligand appear due to the nitrogen atoms of the 'strap'. The binding constants of such complexes are of the order of  $10^6$ – $10^8$  litre mol<sup>–1</sup> (see Table 2).



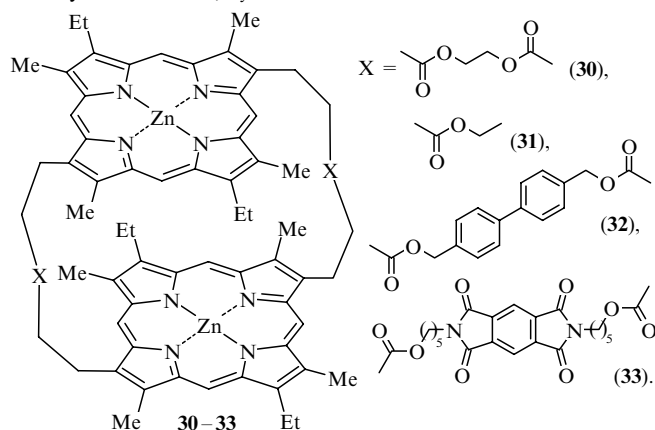
High values of binding constants are characteristic of porphyrins **23–26** containing a calix[4]arene molecule as the ‘strap’ fragment.<sup>19</sup> The receptor **25** with the smallest distance between the porphyrin and calixarene fragments and four bridges that stabilise the molecular structure and confer a strictly specific shape on the hydrophobic cavity forms the most stable complexes. The binding patterns of large and small ‘guest’ molecules differ significantly from one another. Larger molecules (*e.g.*, nicotine and 4-phenylpyridine) bind on the outer side of the receptor; their  $K_a$  values are equal to, or a little smaller than, the corresponding value for tetraphenylporphyrine **1**. Binding of smaller molecules (*e.g.*, pyridine,  $\alpha$ - and  $\gamma$ -picolines) occurs in the inner cavity and depends critically on the electron density on the donor nitrogen atom.<sup>19</sup>



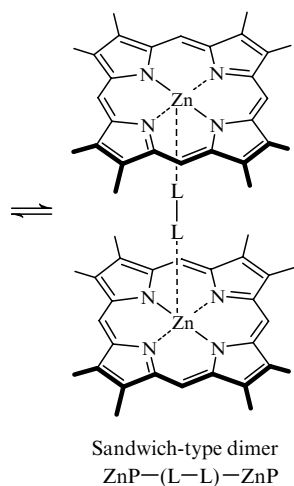
The phenyl fragments in the ‘basket-handle’ porphyrins **27–29** are linked by bridges on both sides of the porphyrin macrocycle. The complexation properties of the derivative **29** do not disappear completely despite shielding of the coordination centre of the metalloporphyrin and the geometrical mismatch of the size of the intramolecular cavity of the receptor to that of the ligand, they are only twice as weak as those of the sterically non-shielded porphyrin **2**. This suggests the incomplete shielding of the coordination centre of the porphyrin by the cyclophane ligands. If the size of the intramolecular cavity of the ‘host’ matches the size of the ‘guest’, as in the case of porphyrins **27** and **28**, their  $K_a$  values exceed that of compound **1**.<sup>8, 31</sup>



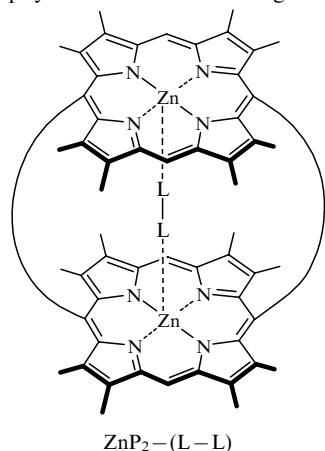
Each monomeric porphyrin fragment in the cyclophane dimers **30–42** is shielded on one side by another porphyrin fragment, as a result of which the  $K_a$  values of the dimers **30**, **31**, **33**, **36** and **42** are smaller than those of their monomeric analogues. Contrariwise, the coordination of monodentate ligands to the dimers **32**, **34**, **35** and **39–41**, which results in the formation of 1:1 complexes, is characterised by higher binding constants in comparison with the monomeric porphyrins. For example, in the coordination of pyridine the  $K_a$  value increases 1.5–3-fold. Some authors suggest<sup>17, 34</sup> that in addition to the formation of a donor–acceptor  $\sigma$ -bond  $Zn-N$ , pyridine interacts with the metal by a  $\pi$ -type mechanism with a transfer of the electron density from the  $d_{xz}$ -,  $d_{yz}$ -orbitals







In the coordination of a bifunctional ligand to a dimeric cyclophane porphyrin, formation of complexes on both the inner [ $K_{a(in)}$ ] and outer [ $K_{a(out)}$ ] sides of the dimeric molecule is possible. The most stable complexes are formed where the bifunctional ligand is coordinated inside the dimer cavity. In the general case, the binding energy of such a complex is not equivalent to the double energy of formation of the monomeric complex due to a number of factors such as the chelating effect, interactions between different reaction centres of the bidentate ligand, conformational changes and new interactions that appear in the system. These contributions to the total binding energy of the dimeric porphyrin–bidentate ligand complex depend on the nature and the conformations of the bridges in the dimeric porphyrin and can be rather significant.



Sanders *et al.*<sup>21,29</sup> have developed formulae for calculating the concentration ratios of dimeric and trimeric complexes of a dimeric porphyrin with DABCO as a function of biporphyrin concentration,  $\alpha$ ,  $K_{a(in)}$  and  $K_{a(out)}$

$$\frac{[\text{ZnP}_2 - \text{DABCO} - \text{ZnP}_2]}{[\text{ZnP}_2 - 1 - \text{DABCO}]} = \frac{\alpha K_{a(out)}^2 [\text{ZnP}_2]}{4K_{a(in)}}, \quad (2)$$

and for calculating energies of different effects associated with the coordination of bidentate ligands to a dimer and forming a part of the general equation:

$$\begin{aligned} \Delta G_{a(in)} = & 2\Delta G_{a(m)} + \Delta G_{a(z)} + \\ & + \Delta G_{a(chel)} + \Delta G_{a(conf)} + \Delta G_{a(new)}, \end{aligned} \quad (3)$$

where  $\Delta G_{a(in)}$  is the energy of formation of a complex of the bidentate ligand with the inner cavity of the dimer;  $\Delta G_{a(m)}$  is the energy of formation of a complex of the same ligand and the monomeric porphyrin;  $\Delta G_{a(z)}$  is the energy of the interaction between the reaction centres of the bidentate ligand;  $\Delta G_{a(chel)}$  is the energy of the chelating effect;  $\Delta G_{a(conf)}$  is the energy of conformational changes and  $\Delta G_{a(new)}$  is the energy of new interactions in the system.

Depending on the nature of the bridges, the binding constant of a dimeric porphyrin to a bidentate ligand according to a bidentate scheme is 3–5000 times higher than the  $K_a$  for a monomeric analogue (Table 3).

The coordination of bidentate ligands to linear dimeric porphyrins depends on their flexibilities.

Thus the porphyrin fragments in the dimer **43** with a rigid aromatic bridge are at a large distance from one another; their interactions with DABCO in  $\text{CH}_2\text{Cl}_2$  yield 1:2 complexes with  $K_a \approx 10^5 \text{ litre mol}^{-1}$  where each metalloporphyrin fragment of the dimer binds one molecule of the bidentate ligand.<sup>36</sup> The interaction of the dimer **44** with a more flexible bridge with DABCO yields a 1:1 ‘internal’ complex ( $K_a \approx 10^7 \text{ litre mol}^{-1}$ ) where two metalloporphyrin fragments of the dimer bind one molecule of the bidentate ligand. The dimer **45** forms similar ‘internal’ complexes with DABCO ( $K_a = 6 \times 10^6 \text{ litre mol}^{-1}$ ).<sup>24</sup>

Dimeric porphyrins containing calixarene and crown-ether fragments possessing multifunctional recognising abilities present special interest. The calixarene and crown-ether fragments of these molecules form stable complexes with metal cations; porphyrin fragments coordinate nitrogen bases, whereas the bridges between the calixarene and porphyrin fragments can bind anions.

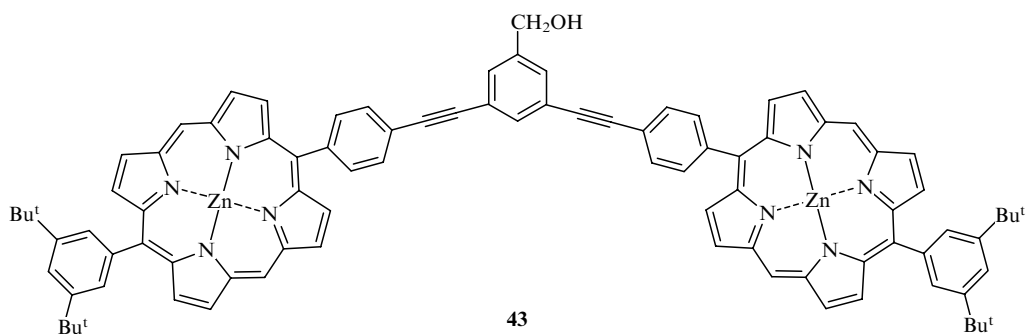
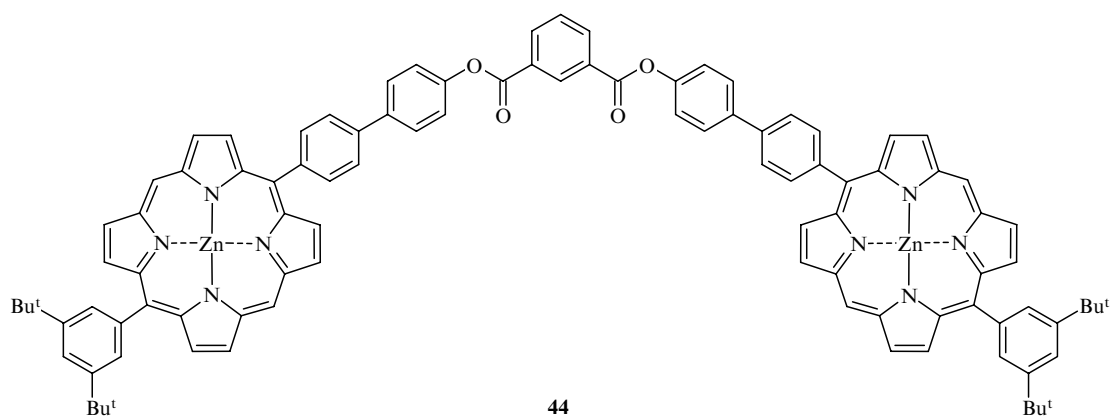
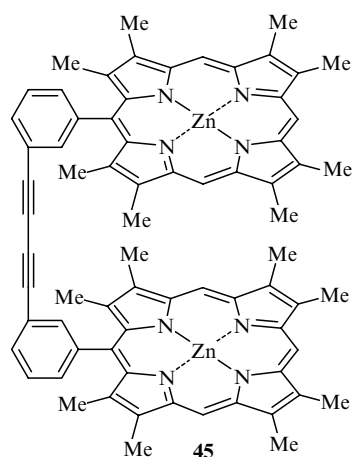


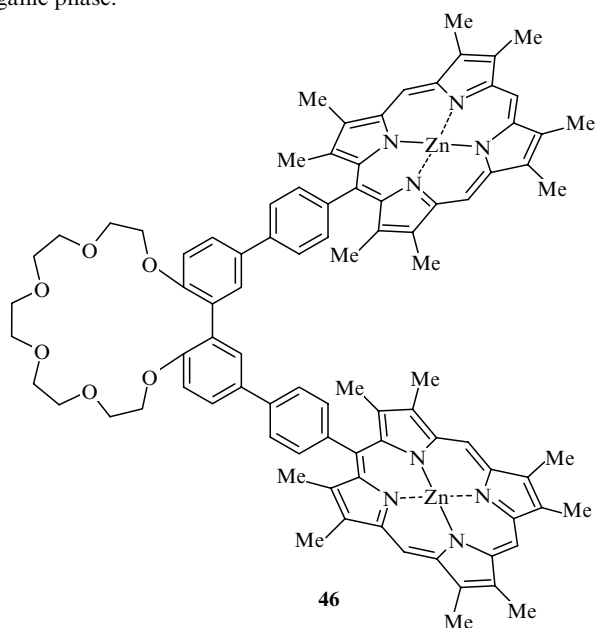
**Table 3.** Binding constants of 1 : 1 complexes of Zn-containing porphyrins with bidentate ligands.

| Porphyrin                                                                       | Ligand            | Solvent                         | $K_a$ /litre mol <sup>-1</sup> | Reference porphyrin | $K_a/K_{comp.}$ | Ref.   |
|---------------------------------------------------------------------------------|-------------------|---------------------------------|--------------------------------|---------------------|-----------------|--------|
| Complexes of monomeric porphyrins without steric shielding                      |                   |                                 |                                |                     |                 |        |
| <b>1</b>                                                                        | ethylenediamine   | CHCl <sub>3</sub>               | $1.827 \times 10^4$            | —                   | —               | 17     |
| <b>4</b>                                                                        | DABCO             | CH <sub>2</sub> Cl <sub>2</sub> | $2.4 \times 10^5$              | —                   | —               | 21     |
| <b>5</b>                                                                        | DABCO             | CH <sub>2</sub> Cl <sub>2</sub> | $1.6 \times 10^4$              | —                   | —               | 20     |
|                                                                                 | bipy              | CH <sub>2</sub> Cl <sub>2</sub> | $5.4 \times 10^3$              | —                   | —               | 20     |
| <b>6</b>                                                                        | DABCO             | toluene–MeOH (2 : 1)            | $5.4 \times 10^3$              | —                   | —               | 22     |
|                                                                                 | pyrazine          | toluene–MeOH (2 : 1)            | $5.0 \times 10^2$              | —                   | —               | 22     |
| <b>7</b>                                                                        | ethylenediamine   | CHCl <sub>3</sub>               | $1.897 \times 10^4$            | —                   | —               | 34     |
| <b>8</b>                                                                        | bipy              | CH <sub>2</sub> Cl <sub>2</sub> | $4.7 \times 10^3$              | —                   | —               | 24     |
|                                                                                 | Py <sub>3</sub> P | CH <sub>2</sub> Cl <sub>2</sub> | $3.9 \times 10^3$              | —                   | —               | 24     |
| <b>9</b>                                                                        | bipy              | CH <sub>2</sub> Cl <sub>2</sub> | $8.4 \times 10^3$              | —                   | —               | 24     |
|                                                                                 | Py <sub>3</sub> P | CH <sub>2</sub> Cl <sub>2</sub> | $7.6 \times 10^3$              | —                   | —               | 24     |
| Complexes of sterically shielded monomeric porphyrins                           |                   |                                 |                                |                     |                 |        |
| <b>18</b>                                                                       | bipy              | CH <sub>2</sub> Cl <sub>2</sub> | $9.7 \times 10^2$              | <b>5</b>            | 0.2             | 20     |
| <b>19</b>                                                                       | bipy              | CH <sub>2</sub> Cl <sub>2</sub> | $2.6 \times 10^3$              | <b>5</b>            | 0.5             | 20     |
| <b>20</b>                                                                       | DABCO             | CH <sub>2</sub> Cl <sub>2</sub> | $4.9 \times 10^4$              | <b>4</b>            | 0.2             | 29     |
| <b>21</b>                                                                       | DABCO             | CH <sub>2</sub> Cl <sub>2</sub> | $2.3 \times 10^4$              | <b>4</b>            | 0.1             | 29     |
| Complexes of dimeric porphyrins (binding constants of the ‘internal’ complexes) |                   |                                 |                                |                     |                 |        |
| <b>30</b>                                                                       | DABCO             | CH <sub>2</sub> Cl <sub>2</sub> | $7.4 \times 10^7$              | <b>4</b>            | 308             | 21     |
| <b>31</b>                                                                       | DABCO             | CH <sub>2</sub> Cl <sub>2</sub> | $1 \times 10^7$                | <b>4</b>            | 41.6            | 21     |
| <b>32</b>                                                                       | DABCO             | CH <sub>2</sub> Cl <sub>2</sub> | $1.3 \times 10^6$              | <b>4</b>            | 5.4             | 29     |
|                                                                                 | bipy              | CH <sub>2</sub> Cl <sub>2</sub> | $3.8 \times 10^3$              | —                   | —               | 29     |
|                                                                                 | pyrazine          | CH <sub>2</sub> Cl <sub>2</sub> | $6 \times 10^2$                | —                   | —               | 29     |
| <b>33</b>                                                                       | DABCO             | CH <sub>2</sub> Cl <sub>2</sub> | $2.4 \times 10^5$              | <b>4</b>            | 1               | 29     |
|                                                                                 | bipy              | CH <sub>2</sub> Cl <sub>2</sub> | $1.8 \times 10^3$              | —                   | —               | 29     |
|                                                                                 | pyrazine          | CH <sub>2</sub> Cl <sub>2</sub> | $6.9 \times 10^2$              | —                   | —               | 29     |
| <b>37</b>                                                                       | DABCO             | CH <sub>2</sub> Cl <sub>2</sub> | $2.0 \times 10^5$              | <b>5</b>            | 12.5            | 20     |
|                                                                                 | bipy              | CH <sub>2</sub> Cl <sub>2</sub> | $1.7 \times 10^4$              | <b>5</b>            | 3.1             | 20     |
| <b>38</b>                                                                       | DABCO             | CH <sub>2</sub> Cl <sub>2</sub> | $8.0 \times 10^7$              | <b>5</b>            | 5000            | 20     |
|                                                                                 | bipy              | CH <sub>2</sub> Cl <sub>2</sub> | $2.5 \times 10^6$              | <b>5</b>            | 463             | 20     |
| <b>39</b>                                                                       | DABCO             | toluene–MeOH (2 : 1)            | $2.86 \times 10^4$             | <b>6</b>            | 5.3             | 22     |
|                                                                                 | pyrazine          | toluene–MeOH (2 : 1)            | $4.5 \times 10^3$              | <b>6</b>            | 9.0             | 22     |
| <b>40</b>                                                                       | DABCO             | toluene–MeOH (2 : 1)            | $3.2 \times 10^4$              | <b>6</b>            | 5.9             | 22     |
|                                                                                 | pyrazine          | toluene–MeOH (2 : 1)            | $5.4 \times 10^3$              | <b>6</b>            | 10.8            | 22     |
| <b>41</b>                                                                       | ethylenediamine   | CHCl <sub>3</sub>               | $4.2 \times 10^3$              | <b>7</b>            | 0.22            | 17     |
| <b>42</b>                                                                       | bipy              | CH <sub>2</sub> Cl <sub>2</sub> | $3 \times 10^7$                | —                   | —               | 32, 35 |
|                                                                                 | ethylenediamine   | CH <sub>2</sub> Cl <sub>2</sub> | $6.129 \times 10^5$            | —                   | —               | 32, 35 |





Interesting results were obtained for the dimer **46** with a crown-ether bridge binding  $\text{Ba}^{2+}$  ions (see Ref. 37). On the one hand, this dimer manifested high affinity for diamines in the presence of barium perchlorate. On the other hand, the presence of diamines in the reaction system and their coordination to the porphyrin fragments of the dimer **46** increased the extraction coefficients of the barium salts from the aqueous phase to the organic phase.

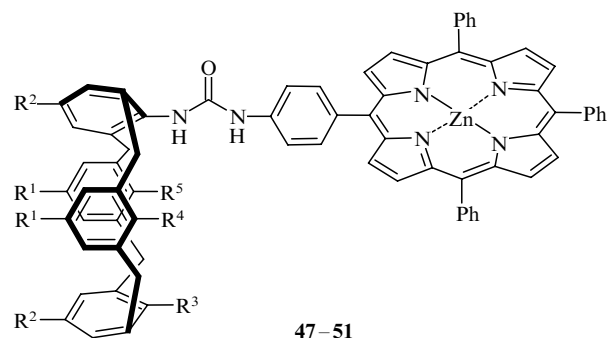


The ability of supramolecular metallocomplexes containing crown-substituted porphyrins to recognise metal cations is considered in detail in a review by Tsivadze.<sup>38</sup>

The ability of calixarenes to recognise metal cations has been studied extensively over the past two decades.<sup>39–41</sup> The addition of porphyrin chromophores to calixarene molecules has made it possible to apply conventional spectrophotometric methods of porphyrin chemistry to ion binding studies. Some papers<sup>42, 43</sup> describe the use of calixarene–porphyrin receptors for the recognition of anions based on the formation of hydrogen bonds with the NH groups of bridges.

An analysis of the binding constants ( $K_a$ ) of  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$  and  $\text{NO}_3^-$  with calixarene–porphyrins **47–51** (Table 4) has shown that compound **50**, which contains an additional complex-forming cavity formed by four ethyl acetate groups in the lower rim of the calixarene base, manifested the highest recognising capacity.<sup>43</sup>

Smaller anions ( $\text{Cl}^-$  and  $\text{Br}^-$ ) are characterised by higher  $K_a$  values than larger anions  $\text{I}^-$  and  $\text{NO}_3^-$ , which points to the existence of specific steric requirements for the complexation process.



$\text{R}^1 = \text{R}^2 = \text{OPr}^n$ ;  $\text{R}^3 = \text{R}^4 = \text{R}^5 = \text{H}$  (**47**),  $\text{R}^3 = \text{R}^5 = \text{H}$ ,  $\text{R}^4 = \text{Y}$  (**48**),  $\text{R}^3 = \text{Y}$ ,  $\text{R}^4 = \text{R}^5 = \text{H}$  (**49**);  $\text{R}^1 = \text{R}^2 = \text{OCH}_2\text{CO}_2\text{Et}$ ,  $\text{R}^3 = \text{Y}$ ,  $\text{R}^4 = \text{R}^5 = \text{H}$  (**50**);  $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{R}^4 = \text{R}^5 = \text{OPr}^n$ ,  $\text{R}^3 = \text{Y}$  (**51**),

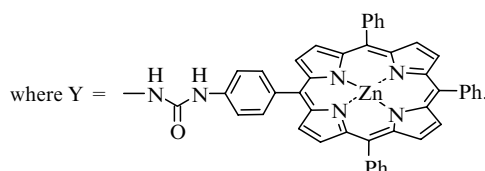
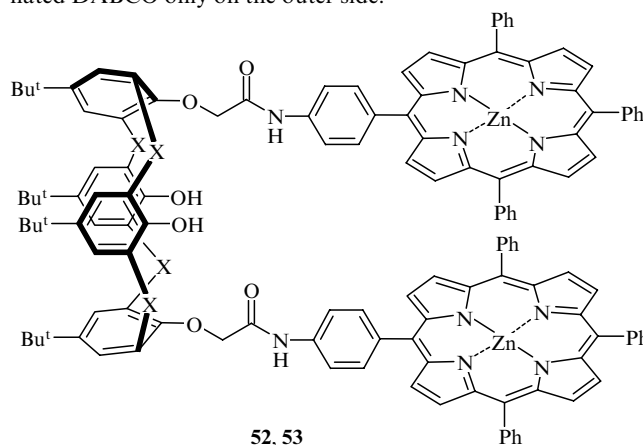


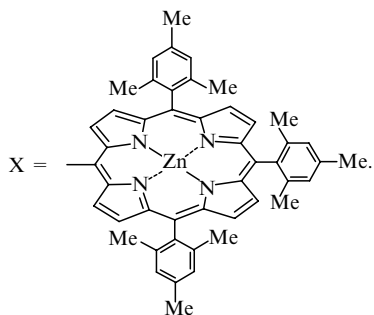
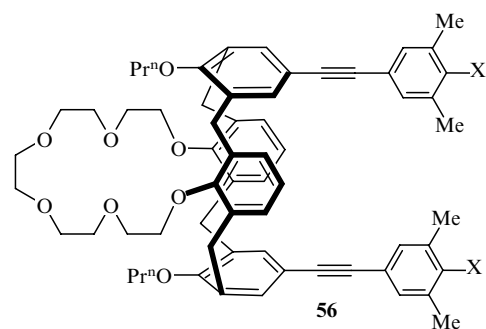
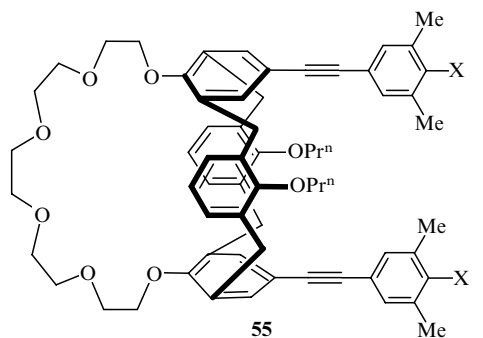
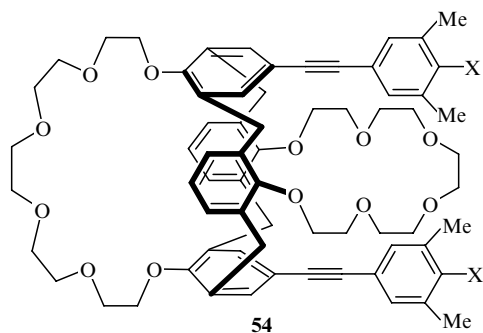
**Table 4.** Binding constants of anions to calixarene–porphyrins **47–51** in  $\text{CH}_2\text{Cl}_2$  at 24 °C obtained by spectrophotometric titration.<sup>43</sup>

| Compound  | $K_a$ /litre mol <sup>−1</sup> of anions |                   |                   |                   |
|-----------|------------------------------------------|-------------------|-------------------|-------------------|
|           | $\text{Cl}^-$                            | $\text{Br}^-$     | $\text{I}^-$      | $\text{NO}_3^-$   |
| <b>47</b> | $6.3 \times 10^3$                        | $1.2 \times 10^3$ | $2.4 \times 10^2$ | $8.2 \times 10^2$ |
| <b>48</b> | $5.8 \times 10^5$                        | $7.8 \times 10^4$ | $8.0 \times 10^3$ | $3.0 \times 10^4$ |
| <b>49</b> | $6.9 \times 10^5$                        | $6.9 \times 10^4$ | $2.4 \times 10^3$ | $1.3 \times 10^4$ |
| <b>50</b> | $1.4 \times 10^6$                        | $2.2 \times 10^5$ | $2.9 \times 10^4$ | —                 |
| <b>51</b> | $6.6 \times 10^5$                        | $6.5 \times 10^4$ | $4.8 \times 10^3$ | $4.5 \times 10^3$ |

The ability of the calixarene–porphyrin conjugates **52–56** to recognise bidentate ligands including DABCO has been studied.<sup>44, 45</sup> Compounds **53**, **55** and **56** formed 1 : 1 complexes where DABCO was coordinated to both porphyrin fragments ( $K_a \sim 10^7$  litre mol<sup>−1</sup>), whereas the derivatives **52** and **54** coordinated DABCO only on the outer side.

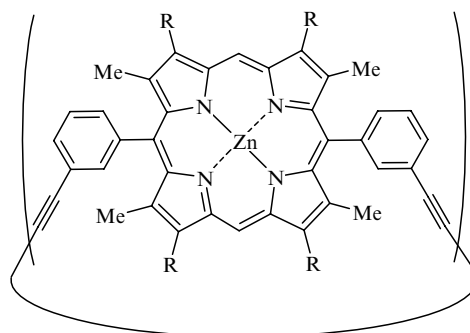


$\text{X} = \text{CH}_2$  (**52**),  $\text{S}$  (**53**).

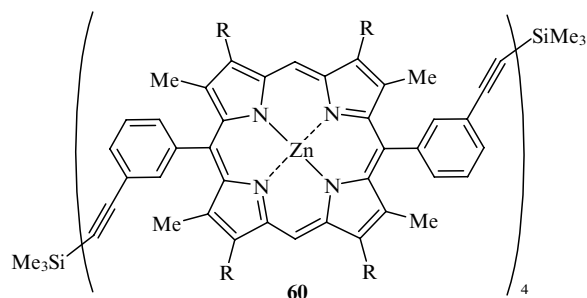


A detailed study of the binding of oligopyridyl ligands to di-, tri- and tetrameric porphyrins has been carried out.<sup>24, 46–50</sup> A good geometrical matching of the size of the porphyrin cavity to the ligand was observed for the dimeric porphyrin **35** with bipy ( $K_a = 6 \times 10^6$  litre mol<sup>-1</sup>), for the trimeric porphyrins **57** and **58** with Py<sub>3</sub>P ( $K_a = 9 \times 10^9$  and  $4 \times 10^{10}$  litre mol<sup>-1</sup>, respectively) and for the cyclic porphyrin **59** and the linear tetrameric porphyrin **60** with H<sub>2</sub>PPy<sub>4</sub> ( $K_a = 2 \times 10^{10}$  and  $7 \times 10^9$  litre mol<sup>-1</sup>, respectively).<sup>24</sup>

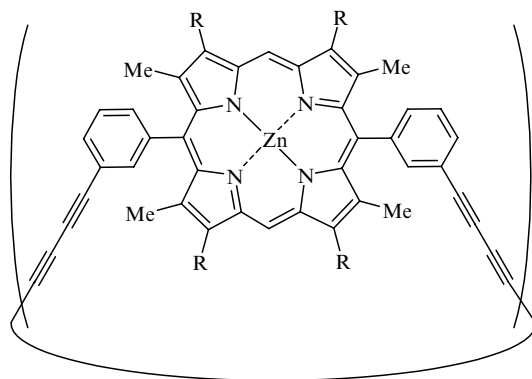
The distance between the porphyrin fragments in the dimer **36** is ~1.5 nm, which makes it a ‘host’ for the matching ‘guest’, viz., bis(4-pyridyl)acetylene (Py<sub>2</sub>C<sub>2</sub>) ( $K_a = 7 \times 10^6$  litre mol<sup>-1</sup>). The diameter of the spacious intramolecular cavity of the trimer **61** matches the size of the ligand Py<sub>3</sub>C<sub>12</sub>H<sub>3</sub> ( $K_a = 2 \times 10^8$  litre mol<sup>-1</sup>).<sup>47</sup>



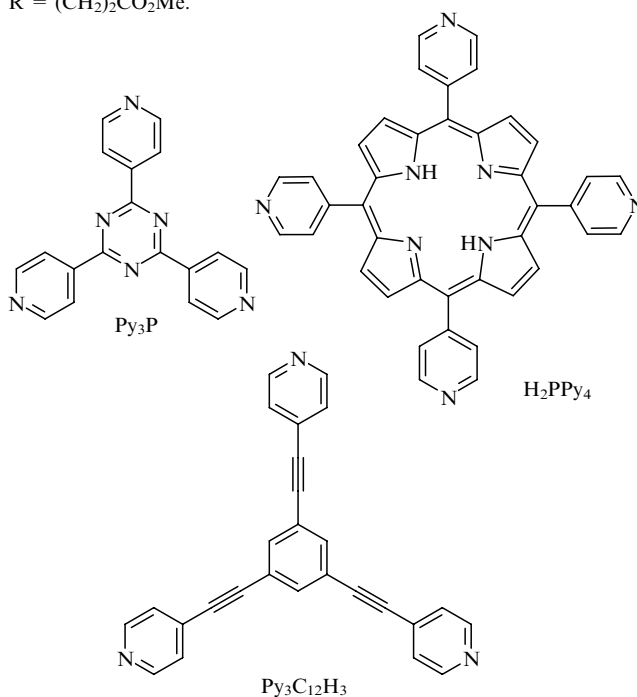
R = Et,  $n = 3$  (**57**); R = (CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>Me:  $n = 3$  (**58**), 4 (**59**).



R = (CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>Me.

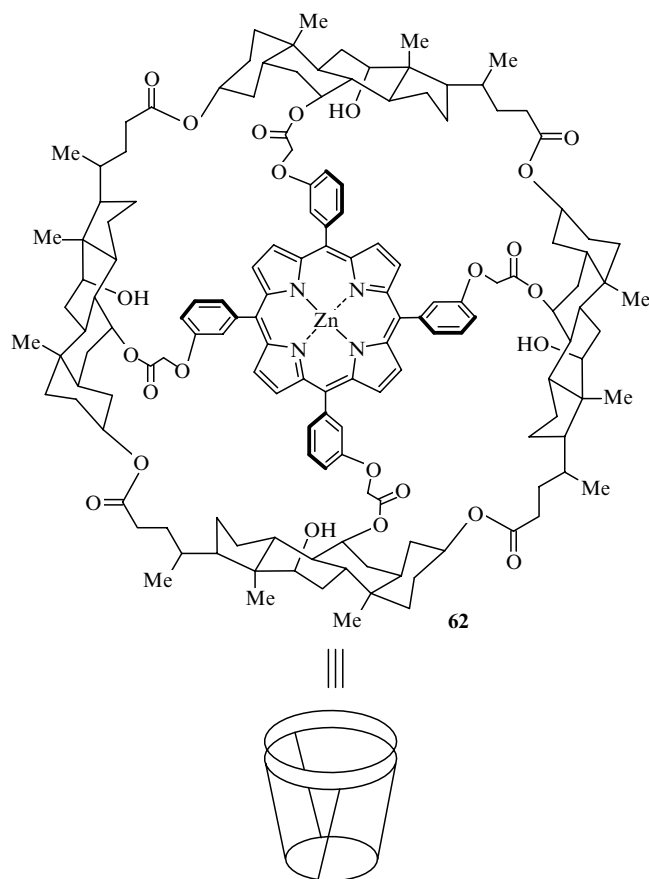


R = (CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>Me.





Some porphyrin-based derivatives of cholic acid, *e.g.*, the conjugate **62**, form the so-called 'calix', which can be used for the recognition of enantiomers of different bases, of morphine in particular.<sup>51, 52</sup> The interaction between the nitrogen atom of the ligand and the zinc atom of the 'calix' is the main driving force for this process. Moreover, the ligand can form hydrogen bonds with the 'calix'. For example, morphine forms two strong hydrogen bonds with the 'calix'; the  $K_a$  values for the morphine (+)- and (–)-enantiomers differ 43-fold.



The synthesis and complex-forming properties of porphyrin dendrimers built of nine covalently linked monomeric porphyrins have been documented.<sup>36, 53</sup> The complex-forming properties of the dendrimers, like those of the dimers **43** and **44**, depend on the flexibilities of the bridges between the porphyrin fragments. Dendrimers coordinate DABCO either to two parallel porphyrin fragments<sup>36</sup> or through one-point binding of each metalloporphyrin fragment of the nanomer to one molecule of the bidentate ligand.<sup>53</sup>

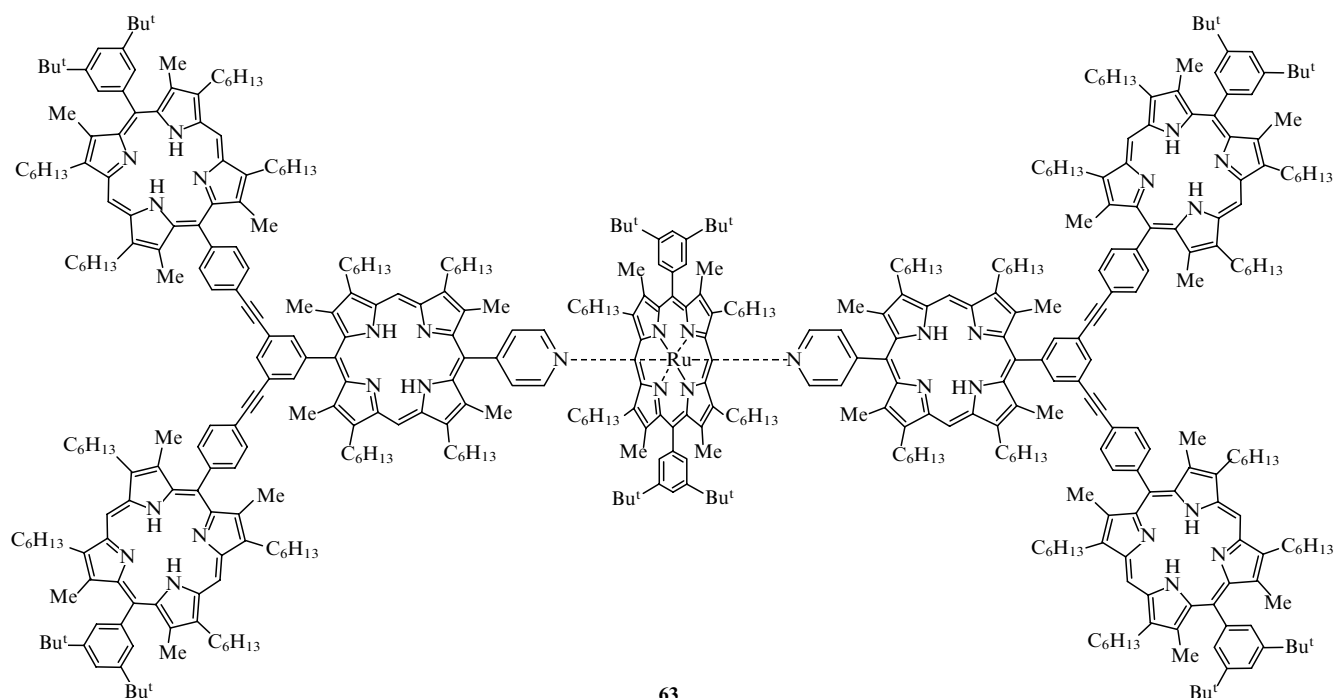
Among porphyrin–metal complexes, Ni- and Ru-containing porphyrins are especially popular as receptors. The strength of binding of nitrogen bases to the central metal atom decreases in the following order: Ru  $\gg$  Zn  $\gg$  Ni.<sup>54–57</sup> Supramolecular compounds containing 5, 7 or 9 porphyrins, *e.g.*, complex **63**, were prepared based on Ru–porphyrin complexes.<sup>55</sup>

#### IV. Recognition of amino acids, purine bases, sugars and quinones by porphyrins

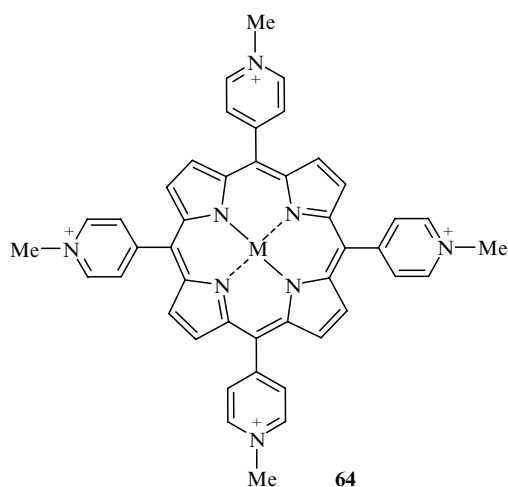
In addition to axial coordination of ligands to metalloporphyrins, other interactions, such as the formation of hydrogen bonds, van der Waals and dispersion interactions in molecular complexes, are also important. It is these interactions that are crucial for the molecular recognition of amino acids, sugars, quinones, purine bases, *etc.*, by the porphyrins.

The recognition of amino acids in aqueous media has been studied using tetrakis(*N*-methylpyridyl)porphine **64** and its zinc and cobalt complexes as examples.<sup>58, 59</sup> Axial coordination of the amino group of the amino acid to the central metal atom is the main driving force in the recognition of amino acids by metalloporphyrins. If the amino acid contains several electron-donating groups, the contribution of each of these groups to the binding to the coordination centre of the metalloporphyrin is determined by the pH of the medium. For methionine, the coordination involves the sulfur atom at low (3.8) and the amino group at high (9.8) pH values. The coordination of lysine involves predominantly the  $\alpha$ -NH<sub>2</sub> group at low and both the  $\alpha$ - and  $\epsilon$ -NH<sub>2</sub> groups at high (10.3) pH values.

In addition to the axial coordination, dispersion interactions between the carboxylate anions of the 'guest' and the pyridine cation of the 'host' play a prominent role in the recognition of amino acids by porphyrins. The strength of such interactions is pH-dependent and increases with pH.<sup>59</sup> In the case of amino acids



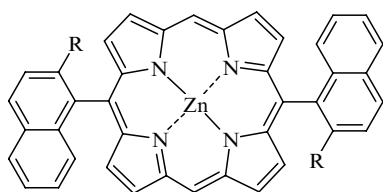
containing aromatic substituents, phenylalanine and tryptophan, the interaction with the porphyrin molecule occurs according to the  $\pi$ - $\pi$  mechanism, which stabilises the complex<sup>60</sup> and appreciably increases  $K_a$  (from 60 litre mol<sup>-1</sup> for glycine to 1200 litre mol<sup>-1</sup> for tryptophan).<sup>58</sup>



M = 2 H, Zn, Co.

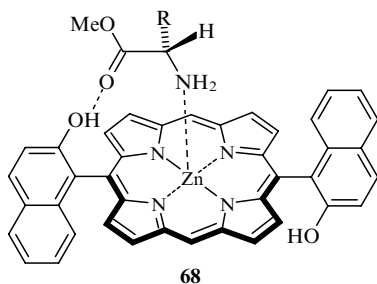
In organic solvents, the recognition of amino acids by porphyrin complexes is achieved through coordination to the metal cation and is accompanied by the formation of hydrogen bonds on the periphery of the macrocycle.<sup>61-66</sup>

The complex-forming properties of metalloporphyrins **65-67** with respect to some methyl esters of  $\alpha$ -amino acids have been studied.<sup>63</sup> Porphyrin **66** manifested the highest binding constants. The complex **68** is stabilised through coordination of the amino group to the central zinc atom and formation of a hydrogen bond with the peripheral OH group.



**65-67**

R = H (**65**), OH (**66**), OMe (**67**).



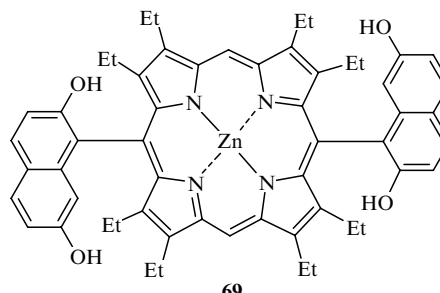
**68**

A comparison of the recognising abilities of metalloporphyrins **65-67** has made it possible to estimate the contributions of different energy components, viz., the axial coordination energy ( $\Delta G_{\text{coord}}^\circ$ ) and the energy of hydrogen bond formation ( $\Delta G_{\text{H-bond}}^\circ$ ), to the total energy of the complex formation ( $\Delta G_{\text{total}}^\circ$ ). If  $\Delta G_{\text{coord}}^\circ$  for complex **66** in CH<sub>2</sub>Cl<sub>2</sub> is 15 kJ mol<sup>-1</sup>,  $\Delta G_{\text{H-bond}}^\circ$  varies from -1 to -6 kJ mol<sup>-1</sup> depending on the amino acid. As regards aliphatic amino esters, those containing bulky side groups bind preferentially to the porphyrin: the absolute value of  $\Delta G_{\text{H-bond}}^\circ$  is the highest for L-leucine (-6.2 kJ mol<sup>-1</sup>) and the lowest for glycine (-0.8 kJ mol<sup>-1</sup>).<sup>61, 63</sup> Although the  $K_a$  values of aliphatic

and aromatic amino acids (phenylalanine and tryptophan) to metalloporphyrin **66** are commensurable, higher  $K_a$  values of the latter are due to additional  $\pi$ - $\pi$  interactions rather than to the formation of hydrogen bonds.

The relationship between the position of the hydroxy groups in the benzene rings and the ability of arylporphyrins to recognise L-leucine methyl ester has been studied.<sup>65</sup> A comparison of arylporphyrins with hydroxy groups in the *ortho*-, *meta*- and *para*-positions of the benzene rings has shown that only porphyrins containing hydroxy groups in the *ortho*-positions form hydrogen bonds with this amino acid ( $\Delta G^\circ$  = from -1 to -1.4 kJ mol<sup>-1</sup>).

The hydroxy groups in the porphyrin receptor **69** are arranged on both sides of the macrocycle plane.<sup>66</sup>

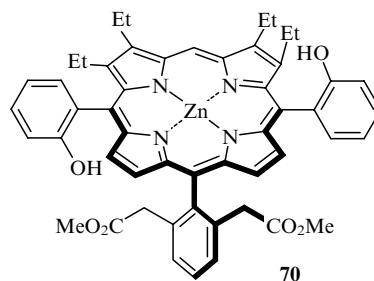


**69**

Dimethyl aspartate has the highest  $K_a$  value ( $6.9 \times 10^4$  litre mol<sup>-1</sup>) (two CO<sub>2</sub>Me groups form hydrogen bonds with the OH groups on the periphery of the macrocycle); the value of the binding constant for the leucine methyl ester is four times as low ( $1.8 \times 10^4$  litre mol<sup>-1</sup>).

'Host-guest'<sup>67</sup> interactions are widely used for the chiral recognition of optically active amino acids. In addition to two binding points, porphyrin receptors responsible for the chiral recognition of amino acids should create steric hindrance against interaction of certain groups of the receptor with the side substituents of the ligands. Such steric hindrance results from the limitation of rotational freedom upon 'bicentred' binding. The energy of chiral recognition,  $\Delta\Delta G_{\text{DL}}^\circ$ , is defined as the difference between the binding energies of the L- and D-enantiomers:  $\Delta\Delta G_{\text{DL}}^\circ = \Delta G_{\text{D}}^\circ - \Delta G_{\text{L}}^\circ$ . An exhaustive description of porphyrins capable of chiral recognition of amino acids is given in a review.<sup>3</sup> The chiral recognition energies of the porphyrin receptors **70-73** are listed in Table 5.

In the case of porphyrin **70**, steric hindrance is created by methyl acetate groups at positions 2 and 6 of the benzene ring. If at least one ester or hydroxy group is missing, the receptor loses the ability for chiral recognition.<sup>73, 74</sup>



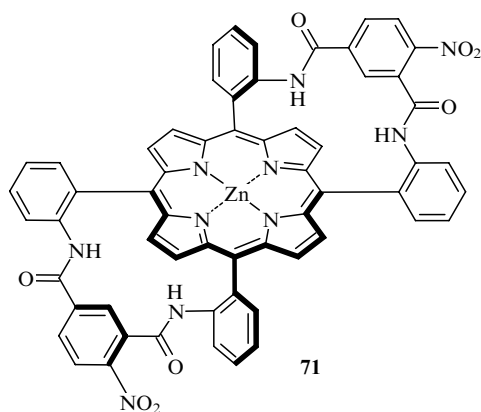
**70**

In the 'strapped' porphyrin **71**, steric hindrance is created by the nitrophenyl groups present in the bridges.<sup>69, 75</sup> Porphyrin **71** manifests intrinsic chirality due to its C<sub>2</sub> molecular symmetry and can therefore distinguish optically active amino acids. The leucine methyl ester enantiomers manifest the highest values of  $\Delta\Delta G_{\text{DL}}^\circ = -5.28$  kJ mol<sup>-1</sup> in CH<sub>2</sub>Cl<sub>2</sub>.

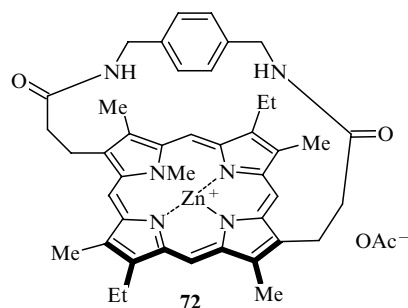
**Table 5.** Energies of chiral recognition of amino acids by porphyrin receptors.

| Porphyrin | Amino acid derivative                  | $\Delta\Delta G_{\text{DL}}^{\circ}/\text{kJ mol}^{-1}$ | Solvent                         | Method                                          | Ref. |
|-----------|----------------------------------------|---------------------------------------------------------|---------------------------------|-------------------------------------------------|------|
| <b>70</b> | isoleucine methyl ester                | −2.47                                                   | CHCl <sub>3</sub>               | electronic absorption spectroscopy <sup>a</sup> | 68   |
|           | leucine methyl ester                   | −2.20                                                   | CHCl <sub>3</sub>               | electronic absorption spectroscopy <sup>a</sup> | 68   |
|           | valine methyl ester                    | −2.21                                                   | CHCl <sub>3</sub>               | electronic absorption spectroscopy <sup>a</sup> | 68   |
|           | phenylalanine methyl ester             | −1.67                                                   | CHCl <sub>3</sub>               | electronic absorption spectroscopy <sup>a</sup> | 68   |
|           | alanine methyl ester                   | −0.27                                                   | CHCl <sub>3</sub>               | electronic absorption spectroscopy <sup>a</sup> | 68   |
| <b>71</b> | leucine methyl ester                   | −5.28                                                   | CH <sub>2</sub> Cl <sub>2</sub> | electronic absorption spectroscopy <sup>a</sup> | 69   |
|           | valine methyl ester                    | −4.89                                                   | CH <sub>2</sub> Cl <sub>2</sub> | electronic absorption spectroscopy <sup>a</sup> | 69   |
|           | phenylalanine methyl ester             | −4.75                                                   | CH <sub>2</sub> Cl <sub>2</sub> | electronic absorption spectroscopy <sup>a</sup> | 69   |
|           | alanine methyl ester                   | −3.43                                                   | CH <sub>2</sub> Cl <sub>2</sub> | electronic absorption spectroscopy <sup>a</sup> | 69   |
|           |                                        |                                                         |                                 |                                                 |      |
| <b>72</b> | <i>N</i> -(benzyloxycarbonyl)valine    | −7.74                                                   | CDCl <sub>3</sub>               | <sup>1</sup> H NMR                              | 70   |
|           | <i>N</i> -(benzyloxycarbonyl)norvaline | −5.64                                                   | CDCl <sub>3</sub>               | <sup>1</sup> H NMR                              | 70   |
|           | <i>N</i> -(benzyloxycarbonyl)leucine   | −4.23                                                   | CDCl <sub>3</sub>               | <sup>1</sup> H NMR                              | 70   |
|           | polyglutamic acid                      | −4.18                                                   | MeOH–H <sub>2</sub> O (3 : 1)   | electronic absorption spectroscopy <sup>a</sup> | 71   |
|           |                                        |                                                         |                                 |                                                 |      |
| <b>73</b> | histidine methyl ester                 | −6.4                                                    | CDCl <sub>3</sub>               | <sup>1</sup> H NMR                              | 72   |
|           | histidine benzyl ester                 | −5.4                                                    | deuteriotoluene                 | <sup>1</sup> H NMR                              | 72   |
|           | lysine benzyl ester                    | −2.5                                                    | deuteriotoluene                 | <sup>1</sup> H NMR                              | 72   |

<sup>a</sup> The data were obtained by spectrophotometric titration.



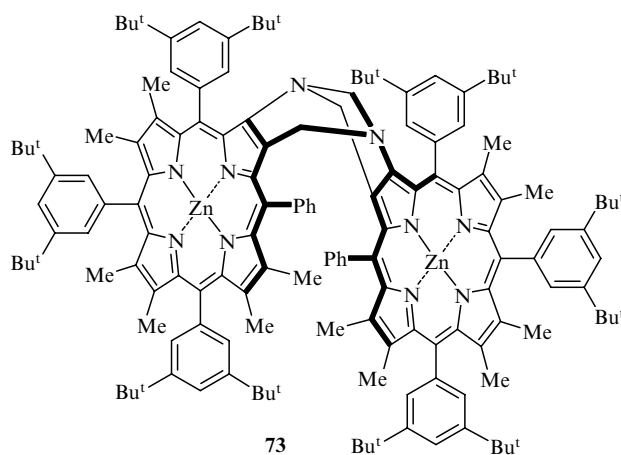
The paper by Konishi *et al.*<sup>70</sup> is devoted to the recognition of *N*-benzyloxycarbonyl-substituted amino acids by the *N*-methylporphyrin receptor **72**. The role of three binding elements responsible for chiral recognition is played by the coordination of the carboxylate anion to the Zn(II) cation, the hydrogen bond between the amide group of the porphyrin and the substituted amino group of the amino acid and the steric interactions between the side substituents of the amino acid molecule and the ‘strapping’ ligand of the porphyrin.



This receptor **72** also possesses high energy in the chiral recognition of polyglutamic acid<sup>71</sup> due to the interaction between the Zn(II) cation and the  $\gamma$ -carboxy group of the ligand.

The enantioselective recognition of histidine esters by the bisporphyrin receptor **73** possessing a chiral cavity with a rigid structure, occurs due to the binding of two central zinc atoms to two basic nitrogen atoms of the amino acid and the steric interactions between the cavity walls and the side group of the

amino acid. The difference between the free binding energies for the two diastereomeric complexes ( $\Delta\Delta G_{\text{DL}}^{\circ} = -6.4 \text{ kJ mol}^{-1}$ ) exceeds the corresponding values for the complexes of the porphyrin receptors **70** and **71** with neutral amino acid derivatives. At the same time, the formation of less stable complexes between lysine benzyl ester and the dimeric porphyrin **73** and lesser enantioselectivities of recognition are due to the greater flexibility of the side chain linking two nitrogen atoms in the ligand molecule.

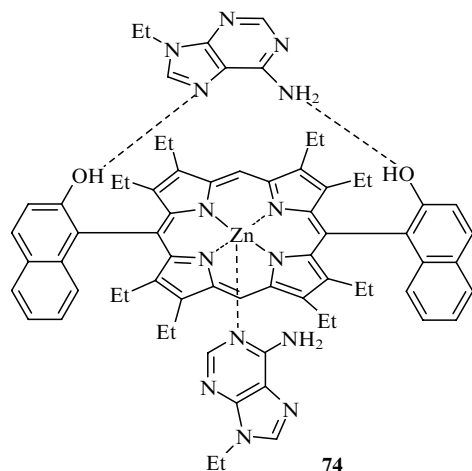


Chiral recognition of amino acid esters was the subject of an investigation<sup>76</sup> in which porphyrin **19** was used as a receptor. The  $\Delta\Delta G_{\text{DL}}^{\circ}$  values for serine and threonine derivatives in CD<sub>2</sub>Cl<sub>2</sub> were equal to 6.3 and 8.2 kJ mol<sup>−1</sup>, respectively.

The ability of porphyrin receptors to recognise purine bases was studied using porphyrin complexes with Rh(III) and Zn(II) as examples. Porphyrin complexes with Rh(III) possessed very high affinities for heterocyclic bases, especially for adenine. For example, Rh(III) *meso*-tetraphenylporphinate binds 9-ethyladenine in CH<sub>2</sub>Cl<sub>2</sub> with  $K_a \sim 10^6 \text{ litre mol}^{-1}$ , which suggests that the binding was irreversible.<sup>77</sup> 9-Ethyladenine is coordinated to the Rh(III) ion of the metalloporphyrin through the N(1)-atom as can be judged from X-ray spectroscopic data.<sup>62</sup> Unlike the case of Rh(III)-containing porphyrins, the coordination of heterocyclic bases to Zn(II)–porphyrin complexes is reversible. The  $K_a$  values for the Zn(II)–porphyrin–purine base complexes (1 : 1) lie in the range  $10^2$ – $10^4 \text{ litre mol}^{-1}$  (see Ref. 78).

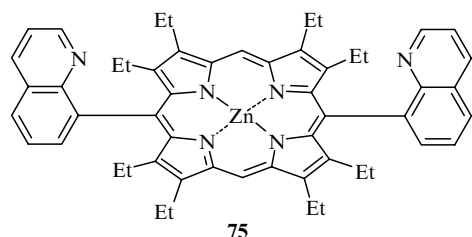
Porphyrins containing two hydroxy groups on one side of the macrocycle form complexes **74** with adenine. In these complexes,

one adenine molecule is coordinated to the central metal cation of the tetrapyrrolic fragment, while the second one binds to the hydroxy groups of the naphthalene substituents.



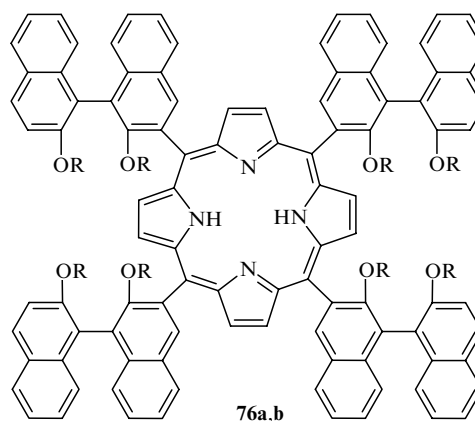
Such porphyrins are usually referred to as ‘bidentate’ complexes; their  $K_a$  values are several orders of magnitude higher.<sup>78</sup>

In complexes of Zn-containing porphyrins **19**, **69** and **75** with carbohydrates, the hydroxy groups of the sugars bind to the zinc cation of the coordination centre of the porphyrin and to heteroatoms of the peripheral substituents.<sup>79–84</sup> The  $K_a$  values of some carbohydrate–porphyrin complexes are presented in Table. 6.

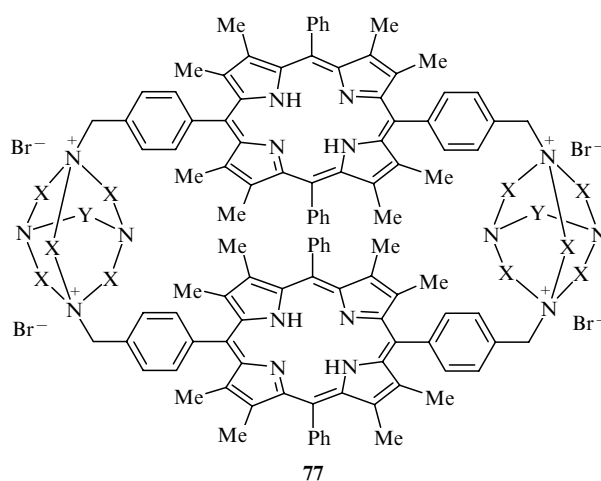


In addition to zinc complexes, the ability to recognise sugars is also inherent in some free porphyrin bases. Thus Král *et al.*,<sup>85–87</sup> demonstrated that porphyrin receptors containing 1,1-binaphthol

substituents **76** and cyclic cryptand–porphyrin conjugates **77** are especially efficient in aqueous media.



R = Me (a), H (b).



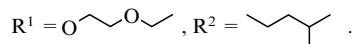
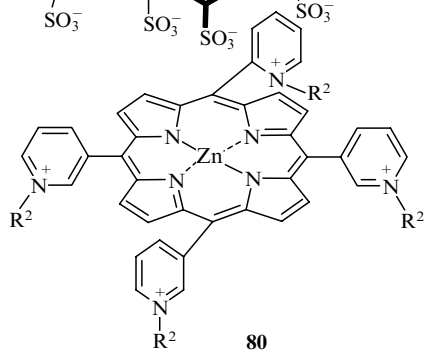
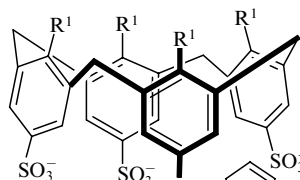
X = (CH<sub>2</sub>)<sub>6</sub>, Y = CO(CH<sub>2</sub>)<sub>4</sub>CO.

The keen interest of investigators in donor–pigment–acceptor ternary systems as valuable tools for the study of individual photosynthetic steps has culminated in the appearance of a large

**Table 6.** Binding constants of various sugars by porphyrin receptors.

| Porphyrin  | Sugar                | $K_a$ /litre mol <sup>−1</sup> | Solvent                         | $T$ /K | Ref. |
|------------|----------------------|--------------------------------|---------------------------------|--------|------|
| <b>19</b>  | octyl β-D-mannoside  | $4.8 \times 10^3$              | CH <sub>2</sub> Cl <sub>2</sub> | 297    | 79   |
|            | octyl α-D-mannoside  | $6.4 \times 10^3$              | CH <sub>2</sub> Cl <sub>2</sub> | 297    | 79   |
|            | octyl β-D-glucoside  | $1.4 \times 10^3$              | CH <sub>2</sub> Cl <sub>2</sub> | 297    | 79   |
|            | octyl α-D-glucoside  | $8.5 \times 10^2$              | CH <sub>2</sub> Cl <sub>2</sub> | 297    | 79   |
| <b>69</b>  | octyl β-D-mannoside  | $2.97 \times 10^3$             | CHCl <sub>3</sub>               | 288    | 81   |
|            | octyl α-D-mannoside  | $3.86 \times 10^3$             | CHCl <sub>3</sub>               | 288    | 81   |
|            | octyl β-D-glucoside  | $2.09 \times 10^3$             | CHCl <sub>3</sub>               | 288    | 81   |
|            | octyl α-D-glucoside  | $3.67 \times 10^3$             | CHCl <sub>3</sub>               | 288    | 81   |
| <b>75</b>  | octyl β-D-mannoside  | $6.17 \times 10^4$             | CHCl <sub>3</sub>               | 288    | 81   |
|            | octyl α-D-mannoside  | $1.55 \times 10^4$             | CHCl <sub>3</sub>               | 288    | 81   |
|            | octyl β-D-glucoside  | $4.14 \times 10^4$             | CHCl <sub>3</sub>               | 288    | 81   |
|            | octyl α-D-glucoside  | $7.57 \times 10^3$             | CHCl <sub>3</sub>               | 288    | 81   |
| <b>76a</b> | octyl β-D-glucoside  | $0.08 \times 10^2$             | DMSO                            | 297    | 85   |
|            | octyl α-D-glucoside  | $5.42 \times 10^2$             | DMSO                            | 297    | 85   |
| <b>76b</b> | octyl β-D-glucoside  | $1.96 \times 10^2$             | DMSO                            | 297    | 85   |
|            | octyl α-D-glucoside  | $6.41 \times 10^2$             | DMSO                            | 297    | 85   |
|            | D-glucose            | $1.16 \times 10^2$             | DMSO                            | 297    | 85   |
|            | α-D-lactose          | $2.76 \times 10^3$             | DMSO                            | 297    | 85   |
| <b>77</b>  | D-glucose            | $3.3 \times 10^3$              | H <sub>2</sub> O                | 297    | 86   |
|            | methyl α-D-glucoside | $7.8 \times 10^3$              | H <sub>2</sub> O                | 297    | 86   |
|            | octyl α-D-glucoside  | $7.2 \times 10^3$              | H <sub>2</sub> O                | 297    | 86   |

Chemical reaction scheme showing the synthesis of Zn complex 78. The starting material is a macrocyclic ligand with four methyl-substituted pyrrole rings, two phenyl rings, and a phthalate ester group. It reacts with  $\text{Zn}(\text{OAc})_2$  to form the Zn complex 78, where the zinc ion is coordinated by the four nitrogen atoms of the pyrrole rings in a square planar geometry.

Oc1ccc2c(c1)c3c4c5c2c6c7c8c9c5c10c11c12c13c14c15c16c17c18c19c20c21c22c23c24c25c26c27c28c29c30c31c32c33c34c35c36c37c38c39c40c41c42c43c44c45c46c47c48c49c50c51c52c53c54c55c56c57c58c59c60c61c62c63c64c65c66c67c68c69c70c71c72c73c74c75c76c77c78c79c80c81c82c83c84c85c86c87c88c89c90c91c92c93c94c95c96c97c98c99c100c101c102c103c104c105c106c107c108c109c110c111c112c113c114c115c116c117c118c119c120c121c122c123c124c125c126c127c128c129c130c131c132c133c134c135c136c137c138c139c140c141c142c143c144c145c146c147c148c149c150c151c152c153c154c155c156c157c158c159c160c161c162c163c164c165c166c167c168c169c170c171c172c173c174c175c176c177c178c179c180c181c182c183c184c185c186c187c188c189c190c191c192c193c194c195c196c197c198c199c200c201c202c203c204c205c206c207c208c209c210c211c212c213c214c215c216c217c218c219c220c221c222c223c224c225c226c227c228c229c230c231c232c233c234c235c236c237c238c239c240c241c242c243c244c245c246c247c248c249c250c251c252c253c254c255c256c257c258c259c260c261c262c263c264c265c266c267c268c269c270c271c272c273c274c275c276c277c278c279c280c281c282c283c284c285c286c287c288c289c290c291c292c293c294c295c296c297c298c299c300c301c302c303c304c305c306c307c308c309c310c311c312c313c314c315c316c317c318c319c320c321c322c323c324c325c326c327c328c329c330c331c332c333c334c335c336c337c338c339c340c341c342c343c344c345c346c347c348c349c350c351c352c353c354c355c356c357c358c359c360c361c362c363c364c365c366c367c368c369c370c371c372c373c374c375c376c377c378c379c380c381c382c383c384c385c386c387c388c389c390c391c392c393c394c395c396c397c398c399c400c401c402c403c404c405c406c407c408c409c410c411c412c413c414c415c416c417c418c419c420c421c422c423c424c425c426c427c428c429c430c431c432c433c434c435c436c437c438c439c440c441c442c443c444c445c446c447c448c449c450c451c452c453c454c455c456c457c458c459c460c461c462c463c464c465c466c467c468c469c470c471c472c473c474c475c476c477c478c479c480c481c482c483c484c485c486c487c488c489c490c491c492c493c494c495c496c497c498c499c500c501c502c503c504c505c506c507c508c509c510c511c512c513c514c515c516c517c518c519c520c521c522c523c524c525c526c527c528c529c530c531c532c533c534c535c536c537c538c539c540c541c542c543c544c545c546c547c548c549c550c551c552c553c554c555c556c557c558c559c560c561c562c563c564c565c566c567c568c569c570c571c572c573c574c575c576c577c578c579c580c581c582c583c584c585c586c587c588c589c590c591c592c593c594c595c596c597c598c599c600c601c602c603c604c605c606c607c608c609c610c611c612c613c614c615c616c617c618c619c620c621c622c623c624c625c626c627c628c629c630c631c632c633c634c635c636c637c638c639c640c641c642c643c644c645c646c647c648c649c650c651c652c653c654c655c656c657c658c659c660c661c662c663c664c665c666c667c668c669c670c671c672c673c674c675c676c677c678c679c680c681c682c683c684c685c686c687c688c689c690c691c692c693c694c695c696c697c698c699c700c701c702c703c704c705c706c707c708c709c710c711c712c713c714c715c716c717c718c719c720c721c722c723c724c725c726c727c728c729c730c731c732c733c734c735c736c737c738c739c740c741c742c743c744c745c746c747c748c749c750c751c752c753c754c755c756c757c758c759c760c761c762c763c764c765c766c767c768c769c770c771c772c773c774c775c776c777c778c779c780c781c782c783c784c785c786c787c788c789c790c791c792c793c794c795c796c797c798c799c800c801c802c803c804c805c806c807c808c809c810c811c812c813c814c815c816c817c818c819c820c821c822c823c824c825c826c827c828c829c830c831c832c833c834c835c836c837c838c839c840c841c842c843c844c845c846c847c848c849c850c851c852c853c854c855c856c857c858c859c860c861c862c863c864c865c866c867c868c869c870c871c872c873c874c875c876c877c878c879c880c881c882c883c884c885c886c887c888c889c890c891c892c893c894c895c896c897c898c899c900c901c902c903c904c905c906c907c908c909c910c911c912c913c914c915c916c917c918c919c920c921c922c923c924c925c926c927c928c929c930c931c932c933c934c935c936c937c938c939c940c941c942c943c944c945c946c947c948c949c950c951c952c953c954c955c956c957c958c959c960c961c962c963c964c965c966c967c968c969c970c971c972c973c974c975c976c977c978c979c980c981c982c983c984c985c986c987c988c989c990c991c992c993c994c995c996c997c998c999

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<sup>a</sup> — *Russ. J. Coord. Chem. (Engl. Transl.)*

<sup>b</sup> — *Russ. J. Phys. Chem. (Engl. Transl.)*

<sup>c</sup> — *Russ. J. Org. Chem. (Engl. Transl.)*

# Organic chemistry of elemental phosphorus

V A Milyukov, Yu H Budnikova, O G Sinyashin

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**Abstract.** The principal achievements and the modern trends in the development of the chemistry of elemental phosphorus are analysed, described systematically and generalised. The possibilities and advantages of the preparation of organophosphorus compounds directly from white phosphorus are demonstrated. Attention is focused on the activation and transformation of elemental phosphorus in the coordination sphere of transition metal complexes. The mechanisms of the reactions of white phosphorus with nucleophilic and electrophilic reagents are discussed. Electrochemical approaches to the synthesis of organic phosphorus derivatives based on white phosphorus are considered. The bibliography includes 251 references.

## I. Introduction

The extensive use of organic derivatives of phosphorus in various branches of industry imposes certain requirements on the methods of their preparation. Until recently, phosphorus chlorides and their derivatives (oxy- and thiochlorides) have served as the main starting reagents for the synthesis of compounds containing an organic substituent at a phosphorus atom. Industrial methods for the production of organophosphorus compounds (OPC) by direct chlorination of white phosphorus and by substitution of organic ligands for the chlorine atoms suffer from a number of serious drawbacks. The first one is evolution of large amounts of hazardous and corrosive wastes (hydrogen chloride, alkyl halides, *etc.*), which damage the process equipment and are harmful for the environment. Modern requirements for environmental safety of industrial plants dictate the need to develop OPC production processes free from the chlorination stage. This has attracted attention to the chemistry of elemental phosphorus.

The search for highly efficient methods for the synthesis of OPC from elemental phosphorus, long carried out in scientific centres of the world, has resulted in the discovery of a large

number of new reactions. The chemical behaviour of phosphorus with respect to reagents of different nature was investigated.

Elemental phosphorus has two allotropes, white and red phosphorus. The white phosphorus molecule is a P<sub>4</sub> tetrahedron with a P–P bond length of 2.21 Å. The ring strain and the presence of vacant p orbitals and a lone pair at each P atom account for its high reactivity. Red phosphorus has a planar layered polymeric structure; therefore, it is chemically more inert than white phosphorus.

In many cases, reactions involving white and red phosphorus are of the same type, although they differ in their rates and conditions of conduction. For this reason, we consider them in the same review. It should be noted, however, that irregularities in the polymeric structure of red phosphorus hamper investigation of the mechanisms of its reactions and identification of intermediates, whereas the molecular structure of white phosphorus unambiguously indicates that its reactions would require cleavage of the P<sub>4</sub> tetrahedron. This permits one to predict the structures of intermediates and to control the process.

In the last 15 years, phosphorus chemistry has undergone a qualitative change. The line of research dealing with methods for activating white phosphorus in the coordination sphere of transition metal complexes has been developed most appreciably. Meanwhile, the existing reviews dealing with the chemistry of elemental phosphorus<sup>1–12</sup> consider only particular aspects and give no general view of the new trends in this field of chemistry. We have attempted to generalise and analyse the information on the chemistry of elemental phosphorus published in recent years from modern standpoint.

This review considers the reactions of elemental phosphorus that take place under relatively mild conditions. In these reactions, intermediates can be detected and, in some cases, even isolated, which provides information on the reaction mechanisms. Attention is concentrated on the chemical behaviour of white phosphorus towards organic transition metal complexes. This is one of the most convenient and promising approaches to investigating the transformation routes of the P<sub>4</sub> molecule. Determination of the structures of the intermediates underlies the development of new catalytic processes for the preparation of organophosphorus compounds directly from white phosphorus. This study considers the reactions of white phosphorus with organic and organometallic compounds from a unified standpoint, which clearly demonstrates the relationship between various fields of chemistry. A special section is devoted to reactions of white phosphorus with organic substrates under electrochemical activation, which is a promising method for the preparation of organophosphorus compounds from elemental phosphorus under mild conditions.

V A Milyukov, Yu G Budnikova, O G Sinyashin A E Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Centre of the Russian Academy of Sciences, ul. Akad. Arbuzova 8, 420088 Kazan, Russian Federation. Fax (7-8432) 75 22 53, tel. (7-8432) 73 23 92, e-mail: milyukov@iopc.knc.ru (V A Milyukov), yulia@iopc.knc.ru (Yu G Budnikova), tel. (7-8432) 73 93 64, e-mail: oleg@iopc.knc.ru (O G Sinyashin)

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## II. Activation and transformations of a white phosphorus molecule in a metal coordination sphere

Despite certain progress in the study of the mechanisms of OPC formation from white phosphorus, these reactions have not been fully investigated as yet. The search for and the development of new methods for the preparation of phosphorus-containing derivatives are based on the elucidation of the rules of cleavage of the  $P_4$  molecule and the factors governing the formation of new compounds (including the structures and transformation pathways of the intermediates). This task is complicated by the high reactivity of white phosphorus and the instability of intermediates formed. In addition, the transformations of  $P_4$  into the target products require fairly drastic conditions.

For the correct interpretation of data on the structures and chemical properties of phosphorus intermediates, one can use the isolobal analogy principle,<sup>13</sup> which is the key link<sup>14</sup> and a sort of 'bridge between organic and inorganic chemistry and, hence, supports the continuity of chemistry as a whole'.<sup>15</sup> According to this principle, 'two fragments are isolobal if the number, symmetry properties, approximate energy and shape of the frontier orbitals, and the number of electrons in them are similar — not identical but similar'.<sup>13</sup> Thus, the phosphorus atom is isolobal to the CH fragment, which allows one to draw analogies between the usual organic compounds and the phosphorus fragments formed upon transformation of a white phosphorus molecule.

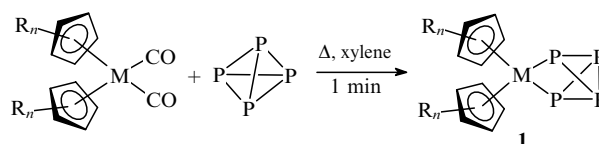
Study of the behaviour of the white phosphorus molecule in the coordination sphere of transition metal complexes is a promising approach that allows one to clarify the complex processes of opening of the initial  $P_4$  molecule and OPC formation. The transition metal atom acts as a sort of stabiliser for all phosphorus intermediates, ranging from the simple phosphide anion to complex phosphorus oligomers  $P_n$  containing up to 14 phosphorus atoms. The reactions of these complexes with other transition metal derivatives and with organic compounds may underlie the design of production processes of organic and organoelement phosphorus compounds directly from elemental phosphorus.<sup>7,8</sup>

Researchers who try to classify the reactions of white phosphorus with transition metal complexes are faced with the problem of identification of the diverse products formed in this seemingly simple reaction. Here we try to avoid the classifications used previously. Cleavage of the  $P_4$  tetrahedron is considered from the standpoint of a relationship between the structures of the initial complex (the electronic structure of the metal, the presence of vacant and latent coordination sites, and the ligand nature and stereochemistry) and the phosphorus intermediates stabilised in the metal coordination sphere. In our opinion, by using this approach, one can consider more comprehensively the activation of white phosphorus in the metal coordination sphere and identify the factors that determine the structure of the phosphorus fragment in the metal complex formed.

### 1. Derivatives of Group IVB metals (Ti, Zr, Hf)

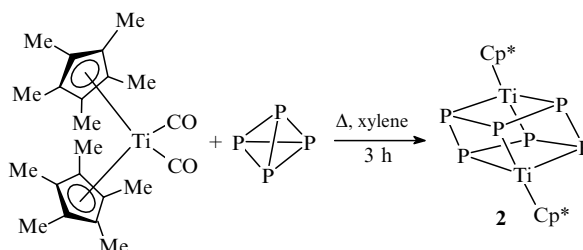
The chemical behaviour of white phosphorus towards Group IVB metal derivatives has been little studied. A probable reason for this is the low stability of the complexes formed, which can be attributed, from the standpoint of the hard and soft acid–base (HSAB) theory,<sup>16</sup> to the low affinity of the phosphorus atom (soft base) for Group IVB metal atoms (soft acids).

The reaction of white phosphorus with zirconium or hafnium bis(cyclopentadienyl)dicarbonyl complexes occurs *via* elimination of two carbonyl ligands, giving rise to bicyclo[1.1.0]tetraphosphabutane **1** stabilised in the metal coordination sphere.<sup>17</sup> The yields of complexes **1** are nearly quantitative.



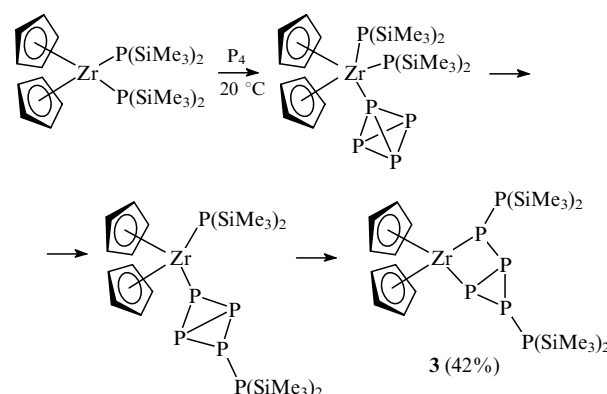
$M = \text{Zr, Hf}; R = \text{Bu}^t, 1,3\text{-Bu}_2^t.$

In the case of the bis(pentamethylcyclopentadienyl) titanium derivative, the reaction requires more drastic conditions.<sup>18</sup> Elimination of not only the CO groups but also one pentamethylcyclopentadienyl ring takes place. This gives a triple-decker compound of titanium **2** containing a  $\mu, \eta^3, \eta^3$ -distorted hexaphosphacyclohexane in the chair conformation (yield 19%). Note that the change in the structure of the phosphorus ligand is directly related to the change in the titanium coordination number.



$\text{Cp}^*$  is pentamethylcyclopentadienyl.

The structure of the phosphorus fragment also depends on the coordination environment of the metal. The replacement of the carbonyl groups in the zirconium dicyclopentadienyl complex by phosphide groups switches the route of reactions with white phosphorus, which now give under mild conditions, instead of complexes **1**, metal complexes **3** with basically different phosphorus ligands.<sup>19</sup> The reaction pathway considered by the authors includes the activation of white phosphorus *via* complexation to a coordinatively unsaturated zirconium atom and the subsequent double intramolecular rearrangement.



An X-ray diffraction study has shown that the P–P bond length in the cyclo- $P_3$ -fragment of complex **3**, equal to 2.213 Å, differs little from the bond length in the  $P_4$  molecule.

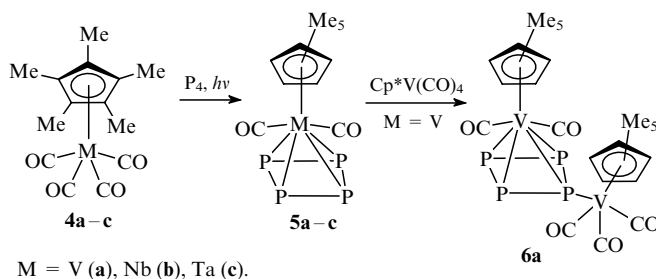
Thus, it can be seen from the above examples that in the reactions of white phosphorus with transition metal complexes, the nature of the ligands has a substantial influence on the structure of the phosphorus fragment formed.

### 2. Derivatives of Group VB metals (V, Nb, Ta)

The outcome of the reactions of white phosphorus with (cyclopentadienyl)carbonyl derivatives of vanadium group metals is a vivid example demonstrating the dependence of the structure of the polyphosphorus fragments stabilised in the metal coordination sphere on the process conditions.<sup>20–22</sup> For example, photochemical substitution of the carbonyl groups in compounds **4a–c**

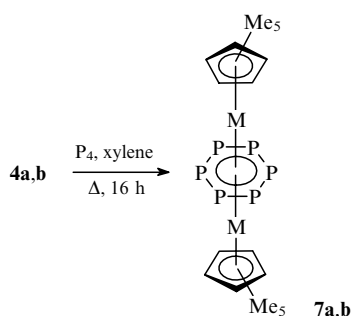


by a white phosphorus molecule yielded a product mixture which was separated by column chromatography to give organometallic tetraphosphacyclobutane derivatives **5a–c**. In the case of vanadium, the reaction did not stop at this stage but proceeded to give binuclear complex **6a**. It is of interest that the reaction of  $P_4$  with tantalum 1,3-di-*tert*-butylcyclopentadienyl complex followed a more complicated route, resulting in a polynuclear complex  $[(Cp''Ta)_3(\mu_3-P_4)(\mu_3-P_2)]$  ( $Cp''$ , 1,3-di-*tert*-butylcyclopentadienyl).<sup>22</sup>



According to X-ray diffraction, the phosphorus atom in niobium complex **5b** is slightly disordered; this should be considered as the initial stage of decomposition of the  $P_4$ -ring into  $P_3$ - and  $P_1$ -fragments.

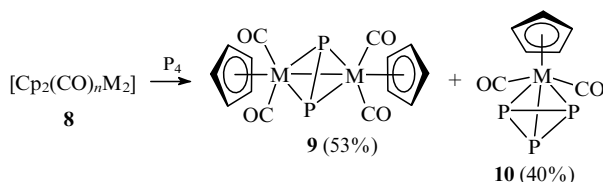
The same reactions carried out under thermolysis conditions (refluxing in xylene, 16 h) result in a different structure of the phosphorus ligands formed. The triple-decker compounds **7a,b** containing cyclo- $P_6$ , isolobal to benzene, as the central fragment were formed as the major products in the reaction of complexes **4a,b** with white phosphorus.<sup>15, 17, 20, 23</sup>



The  $^{51}V$  NMR spectrum of vanadium derivative **7a** exhibits a septet with the spin–spin coupling constant  $^1J(^{51}V^{31}P) = 56$  Hz, which confirms the structure of the complex.

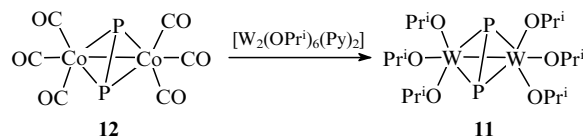
### 3. Derivatives of Group VIB metals (Cr, Mo, W)

The reactions of cyclopentadienylcarbonyl complexes formed by chromium group metals with white phosphorus are most studied. A number of research groups have detected various phosphorus intermediates stabilised in the metal coordination sphere. For example, the reaction of organometallic compounds **8** with white phosphorus yields a mixture of transition metal complexes **9** and **10**, containing  $\mu, \eta^2$ -diphosphorus and  $\mu^3$ -triposphacyclopentane ligands, respectively.<sup>23–25</sup>

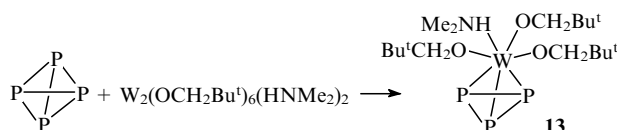


According to the isolobal analogy theory, both compounds represent a  $P_4$  molecule in which one or two phosphorus atoms

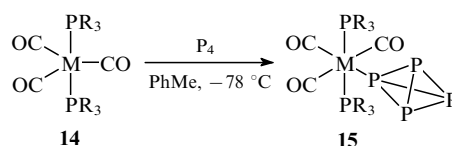
have been replaced by a 15-electron organometallic fragment  $[P \leftrightarrow M(CO)_3]$ . The tungsten alkoxide complex **11**, containing a  $\mu, \eta^2$ -coordinated diphosphine as an additional ligand, was prepared using diphosphine transfer from cobalt derivative **12**. The reaction takes place under mild conditions to give the target product in a high yield.<sup>26</sup>



However, the direct introduction of white phosphorus into the reaction with tungsten alkoxide results in metal complex **13**, containing a  $\eta^3$ -triposphacyclopentane fragment.<sup>27, 28</sup>



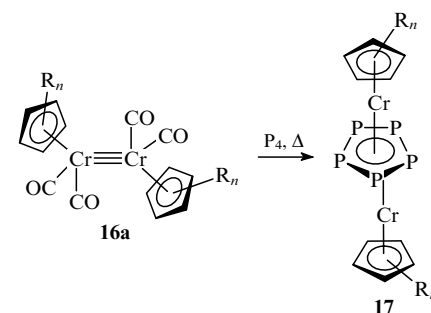
The change in the electronic state of tungsten on passing from cationic to neutral complexes and the appearance of bulky ligands both influence the structure of the phosphorus fragment formed. At low temperatures, coordinatively unsaturated tungsten and molybdenum complexes **14** form derivatives **15** containing an intact molecule of white phosphorus.<sup>29</sup>



$M = W$ ;  $R = cyclo-C_6H_{11}$  (Cy),  $Pr^i$ ;  $M = Mo$ ;  $R = Cy$ .

The structure of complexes **15** has only been proved<sup>29</sup> by  $^{31}P$  NMR spectroscopy as these compounds are stable only in toluene at a temperature below  $-40^\circ C$ .

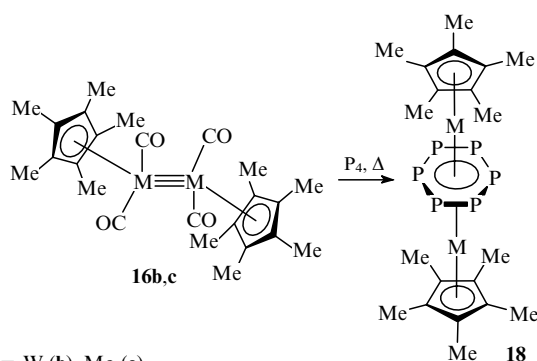
Thermolysis of white phosphorus in the presence of bis(cyclopentadienyl)dicarbonyldichromium **16a** affords a 27-electron triple-decker paramagnetic ( $\mu = 2.07 \mu_B$ ) chromium complex **17**, containing a  $\mu, \eta^5$ -pentaphosphacyclopentadienyl ligand.<sup>30</sup>



$R_n = Me_5, Bu^t$ .

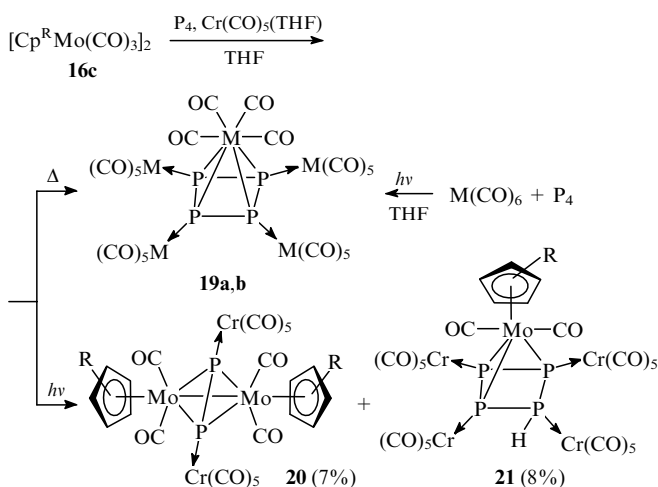
A cyclic voltammetry study of the electrochemical properties of compounds **17** has shown that they can be either reversibly reduced ( $E_{red} = -0.97$  V) or reversibly oxidised ( $E_{ox} = 0.07$  V). For preparative purposes, ferrocenium derivatives  $[Cp_2Fe]^+$  have been proposed as the oxidants.<sup>31</sup>

Thermolysis of white phosphorus in the presence of similar molybdenum and tungsten derivatives **16b,c** is also accompanied by the elimination of all carbonyl groups, and gives 28-electron triple-decker complexes **18**, containing hexaphosphabenzene as a ligand.<sup>23, 32–34</sup>

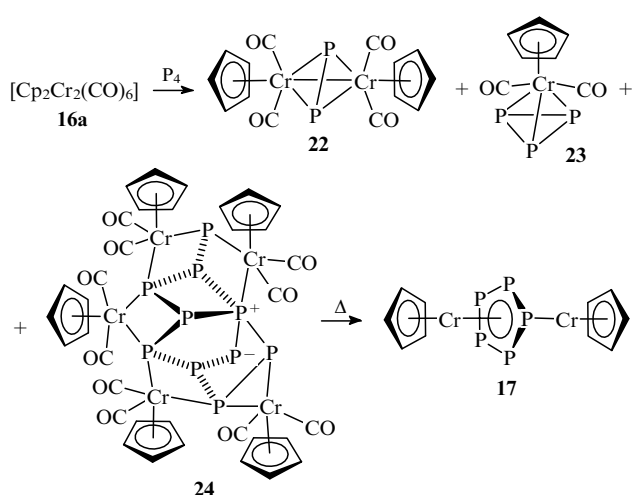


According to quantum-chemical data obtained for the model compound  $[\text{CpMoP}_6\text{MoCp}]$ ,<sup>35</sup> the optimal number of valence electrons for this complex is 28. For this reason, complexes **18** are distinguished by high thermal stability and resistance against oxidation by air oxygen.

Scheer *et al.*<sup>36</sup> have proposed a method for investigation of the mechanism of  $P_4$  cleavage. The method consists of conducting the reactions with organometallic compounds in the presence of labile metal complexes [as a rule,  $\text{Cr}(\text{CO})_5(\text{THF})$ ]. This method was successfully used to study the reactions of white phosphorus with the molybdenum dimer  $[\text{Cp}^R\text{Mo}(\text{CO})_3]_2$  (**16c**) (hereinafter  $\text{Cp}^R$  designates a cyclopentadienyl fragment containing an R substituent).<sup>36</sup> Heating a mixture of reactants in THF affords polynuclear complex **19a**, containing a distorted tetraphosphacyclobutane fragment. It is noteworthy that this complex and similar tungsten derivative **19b** were prepared previously by the photolysis of a mixture of white phosphorus and metal hexacarbonyl (of chromium or tungsten, respectively).<sup>37, 38</sup>



The photochemical reaction of dimer **16c** with white phosphorus in the presence of  $\text{Cr}(\text{CO})_5(\text{THF})$  (UV irradiation) yielded compound **20**, containing a  $P_2$  fragment, and unusual complex **21**. The formation of the P–H bond in the latter compound was interpreted<sup>36</sup> as being due to hydrolysis of the Mo–P bond by traces of water. The modelling of the last-mentioned reaction for a white phosphorus molecule and chromium compound **16a** (R = H) in the absence of other chromium derivatives resulted in the formation of two tetrahedral chromium complexes, **22** (with the composition  $[\{\text{CpCr}(\text{CO})_2\}_2(\mu, \eta^{2:2}\text{-P}_2)]$  similar to molybdenum derivative **20**) and **23**  $[\{\text{CpCr}(\text{CO})_2(\eta^3\text{-P}_3)]$  with the cyclo- $P_3$  fragment as the ligand), and polynuclear phosphorus-containing complex **24**.<sup>24, 39</sup>

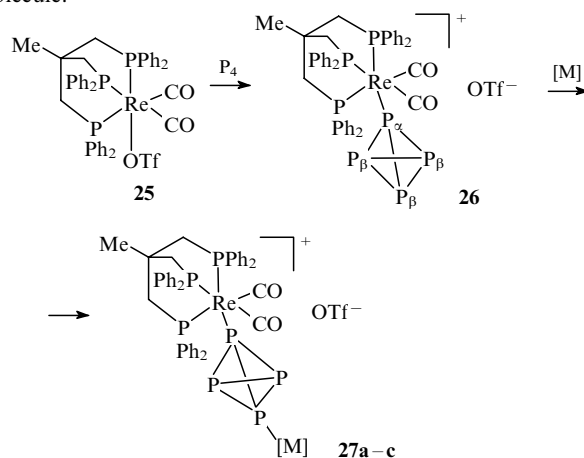


Thermolysis of this mixture furnished a triple-decker chromium complex **17** (R = H), containing a pentaphosphacyclopentadienyl ligand.<sup>30</sup> This reaction clearly demonstrates the ability of the phosphorus atom to form complex oligomers. Also noteworthy are the difficulties that arise in the studies of multi-component reaction mixtures formed in the reactions of white phosphorus with transition metal derivatives.

#### 4. Derivatives of group VIIB metals (Mn, Re)

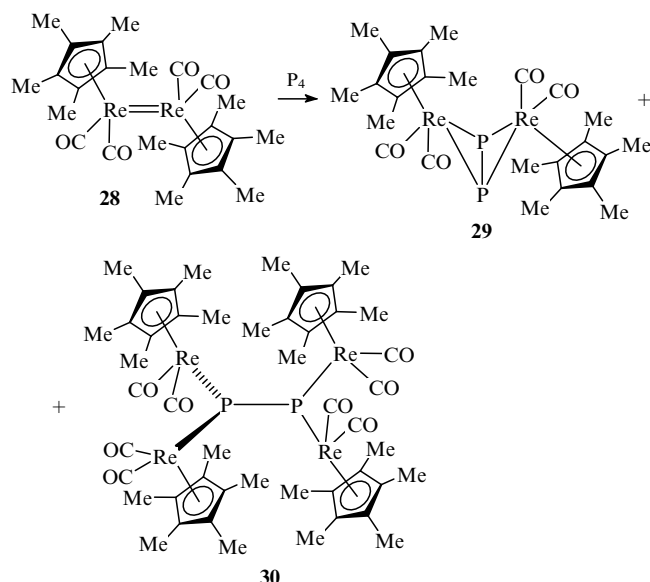
The chemical transformations of white phosphorus under the action of manganese group metal derivatives have been little studied. Only two examples have been described in the literature.<sup>40, 41</sup> The rhenium carbonyl complex **25** with a bulky 1,1,1-tris(diphenylphosphinomethyl)ethane (triphos) ligand reacts with white phosphorus under mild conditions to give charged rhenium compound **26**, containing an intact  $P_4$  molecule as a ligand. The properties of the molecule are typical of trivalent phosphorus derivatives.<sup>40</sup> The  $P_4$  ligand in complex **26** is coordinated by rhenium and ruthenium derivatives under mild conditions, giving rise to homo- and heterobinuclear complexes **27a–c**,<sup>41</sup> which also contain a  $P_4$  ligand.

The formation of binuclear complexes **27** was demonstrated by  $^{31}\text{P}$  NMR spectroscopy. Indeed, without additional splitting from NMR-active phosphorus or metal nuclei, complexes with a  $P_4$  ligand exhibit a well-resolved  $AB_3$ -system. The signal of the  $P_\alpha$  atom shifts by 200–250 ppm, whereas the position of the signal from  $P_\beta$  almost coincides with that for the free white phosphorus molecule.



[M] = (triphos)Re(CO)<sub>2</sub>(OTf) (**a**), Cp\*Re(CO)<sub>2</sub> (**b**), Cp\*Ru(PEt<sub>3</sub>)<sub>2</sub>(OTf) (**c**).

It has been suggested<sup>42</sup> that transition metal complexes containing an intact  $P_4$  molecule as a ligand are stable only when bulky ligands are present near the metal atom. The change in the ligand environment of rhenium changes the structure of the final reaction products. The reaction of white phosphorus with the 16-electron intermediate  $Cp^*Re(CO)_2$ , generated from the corresponding dimer **28**, gives a mixture of rhenium complexes **29** and **30**, differing in coordination number and, hence, in the type of coordination of the  $P_2$  ligand.<sup>43,44</sup>



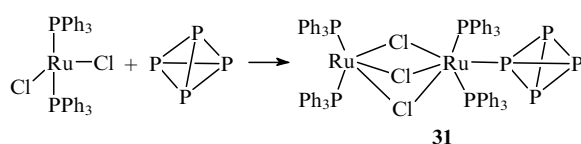
Thus, these examples demonstrate the important role of steric factors for realising of a particular route of transformation of white phosphorus in the presence of transition metal complexes.

## 5. Derivatives of Group VIIIB metals

Published data on the reactions of white phosphorus with group VIIIB metal derivatives are very abundant. The ready availability of the initial compounds, the ease of processing and the stability of the final products are the factors that lead to success in these studies. Almost all types of phosphorus intermediates resulting from cleavage of the  $P_4$  tetrahedron followed by aggregation of the phosphorus species have been stabilised in the coordination sphere of Group VIIIB metals. These complexes were isolated and characterised by various physicochemical methods. In addition, Group VIIIB metals allowed researchers to demonstrate the relationship between the structure of the starting metal complexes (the presence of vacant coordination sites, steric and electronic characteristics of the ligands) and the structure of the metal-coordinated phosphorus fragments.

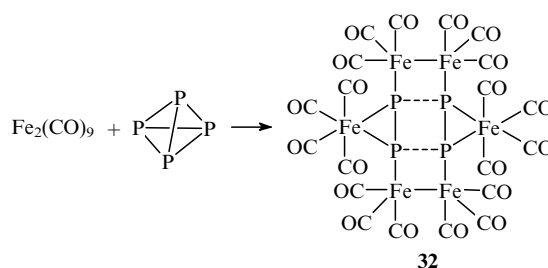
### a. Iron group metal derivatives

As noted above, the  $P_4$  molecule can act as a  $\eta^1$ -ligand when bulky ligands are present in the metal atom environment.<sup>41</sup> The first binuclear complex **31**, containing a  $\eta^1$ - $P_4$  ligand, has been prepared<sup>45</sup> in a study of the hydrogenation of white phosphorus in the presence of a homogeneous catalyst, bis(triphenylphosphine)ruthenium(II) chloride.

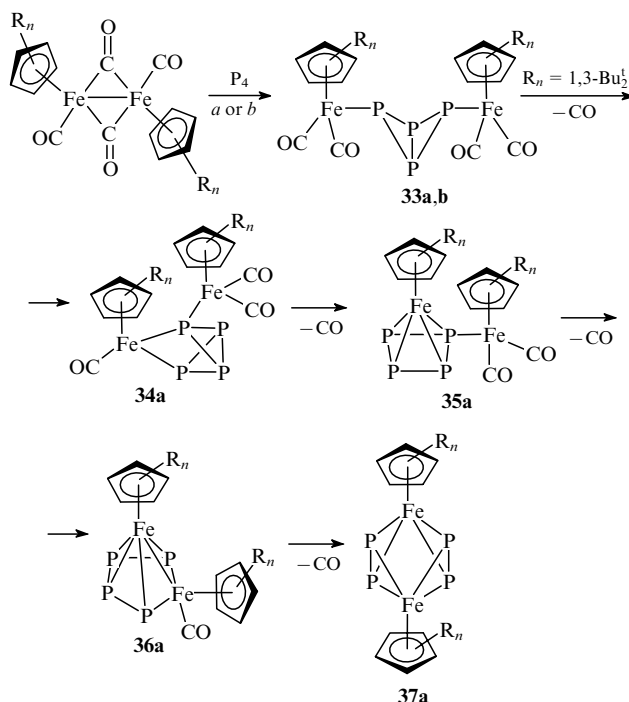


The poor solubility and the low stability of compound **31** precluded<sup>45</sup> its full characterisation; only its  $^{31}P$  NMR spectrum was reported.

Thermolysis of a mixture of white phosphorus and iron carbonyl  $Fe_2(CO)_9$  results in partial decarbonylation. Four phosphorus–phosphorus bonds are cleaved during the reaction. This gives cluster **32** containing two separated  $P_2$  fragments.<sup>46</sup>

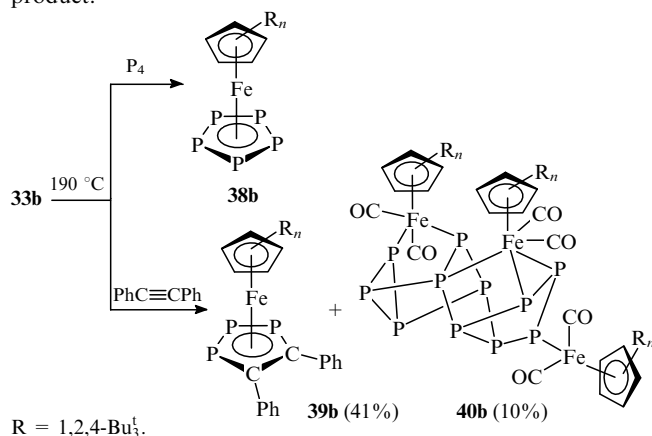


The most important and interesting results were obtained for the reactions of white phosphorus with cyclopentadienylcarbonyl complexes of iron group metals. The study by Scherer *et al.*<sup>47</sup> made a significant contribution to investigations of the activation of white phosphorus in the coordination sphere of transition metals and the mechanism of  $P_4$  cleavage. This study is devoted to the transformations of white phosphorus under the action of binuclear (cyclopentadienyl)carbonyliron complexes  $[Cp^RFe(CO)_2]_2$ , which contain sterically crowded ligands. It was shown that photolysis of  $[Cp''Fe(CO)_2]_2$  ( $Cp''$  is 1,3-di-*tert*-butylcyclopentadienyl) yields two 17-electron  $Cp''Fe(CO)_2$  fragments, and one  $P-P$  bond in the  $P_4$  molecule is cleaved to give complex **33a** with the composition  $[Cp''Fe(CO)_2]_2(\mu, \eta^{4,1}-P_4)$ . This complex loses one carbonyl group under the reaction conditions, being converted into the binuclear adduct **34a**, whose formula is  $\{Cp''Fe(CO)_2\}[\{Cp''Fe(CO)\}(\mu, \eta^{1,2}-P_4)]$  and in which the geometry of the  $P_4$  ligand is essentially preserved. The subsequent photochemical elimination of CO affords a 13-electron iron complex **35a**, in which the metal atom is easily inserted into the phosphorus–phosphorus bond to give a sandwich type complex **36a** with an almost planar five-membered  $P_4Fe$  ring. The elimination of a CO ligand from complex **36a** induces an intramolecular rearrangement of the  $FeP_4$  ring into triple-decker complex **37a**,  $[\{Cp''Fe\}_2(\mu, \eta^{4,4}-P_4)]$ , in which the tetraphosphabutane fragment is connected to two equivalent  $\{Cp''Fe\}$  residues.

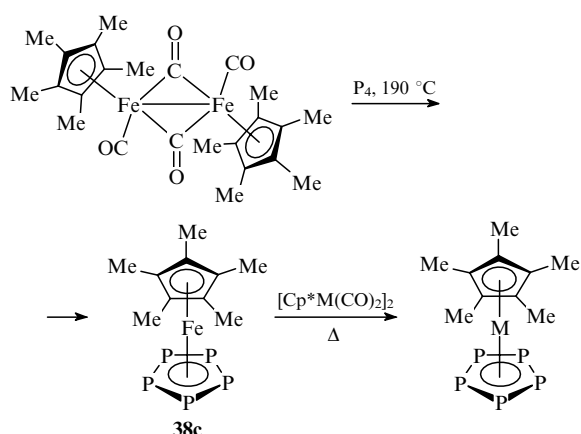


(a) *hν*; (b) toluene, 110 °C, 2 min; R = 1,3- $Bu_2^t$  (a), 1,2,4- $Bu_3^t$  (b).

The structure of the binuclear complex **33**, containing bicyclo[1.1.0]tetraphosphabutane as the ligand and first proposed on the basis of spectroscopic data,<sup>47–49</sup> was recently proved by the X-ray diffraction of **33b** ( $R_n = 1,2,4\text{-Bu}_3^1$ ). It has been shown<sup>50</sup> that the process considered above can be terminated after the formation of compound **33** by introducing one more *tert*-butyl substituent into the cyclopentadienyl ring of the initial complex. In this case, the reaction with white phosphorus proceeds in toluene on heating to 110 °C over a period of 2 min. The resulting binuclear complex **33b** can react with excess white phosphorus at 190 °C to give 1,2,4-tri-*tert*-butylpentaphosphaferrocene **38b**.<sup>51</sup> Under these conditions, compound **33b** and diphenylacetylene form sandwich iron complex **39**, in which one ligand is 4,5-diphenyl-1,2,3-triphenylphosphacyclopentadiene, an isolobal analogue of the cyclo-P<sub>5</sub> ligand. In the last-mentioned reaction, polynuclear phosphorus-containing complex **40** was also isolated as a side product.



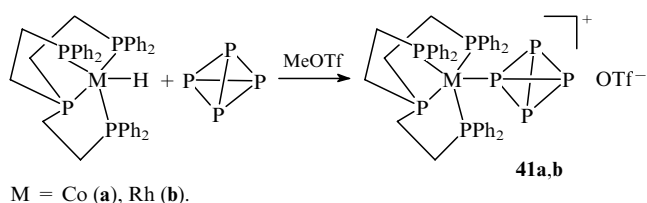
The introduction of five methyl substituents instead of the *tert*-butyl groups into the cyclopentadienyl ring of the initial Fe complex changes crucially the process route. Thermolysis of a mixture of white phosphorus and bis(pentamethylcyclopentadienyl)dicarbonyliron [ $\text{Cp}^*\text{Fe}(\text{CO})_2$ ]<sub>2</sub> in xylene affords pentamethylpentaphosphaferrocene  $\text{Cp}^*\text{FeP}_5$  in ~15% yield. This reaction has become an important stage of development of the organometallic chemistry of highly reactive phosphorus intermediates.<sup>52, 53</sup>



Raising the reaction temperature to 190 °C increased the yield of the target product **38c** to 80%.<sup>54</sup> The ruthenium and osmium sandwich compounds containing a pentaphosphacyclopentadienyl fragment were obtained in moderate yields on heating complex **38c** with bis(pentamethylcyclopentadienyl)dicarbonylmetals [ $\text{Cp}^*\text{M}(\text{CO})_2$ ]<sub>2</sub> ( $M = \text{Ru, Os}$ ) at 220–250 °C.<sup>55</sup>

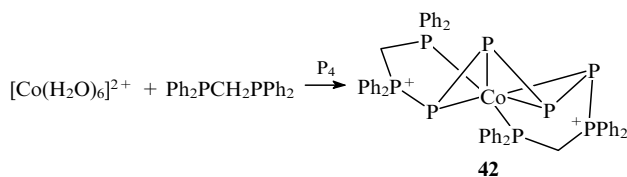
## b. Derivatives of cobalt group metals

As shown above, transition metal complexes containing an intact P<sub>4</sub> molecule are stable only in the presence of bulky ligands at the metal atom.<sup>42</sup> Derivatives of cobalt and rhodium hydrides with the tris[2-(diphenylphosphino)ethyl]phosphine ligand are convenient starting compounds for the preparation of complexes containing a P<sub>4</sub> molecule. The reductive elimination of the hydride ion on treatment with methyltrifluoromethanesulfonate (MeOTf) affords a coordinatively unsaturated intermediate, which coordinates white phosphorus under mild conditions giving rise to cationic complexes **41a,b**, containing an intact P<sub>4</sub> molecule.<sup>56, 57</sup>



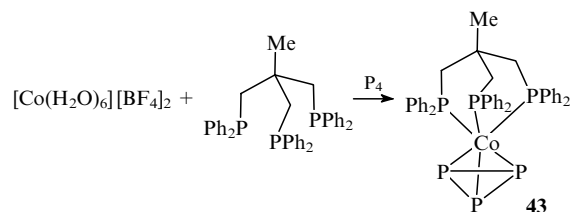
Like W and Mo derivatives, complexes **41a,b** are stable only at low temperatures (< –40 °C).

The use of transition metal complexes containing other phosphines as ligands in reactions with white phosphorus results in the generation of diverse phosphorus fragments which can be stabilised in a metal coordination sphere. For example, in the presence of bis(diphenylphosphino)methane, the aqua complexes of  $\text{Co}(\text{BF}_4)_2$  are converted into mononuclear complex **42**, containing an unusual P<sub>6</sub> ligand formed by four phosphorus atoms of the P<sub>4</sub> molecule and two phosphorus atoms of the phosphine.<sup>58</sup>

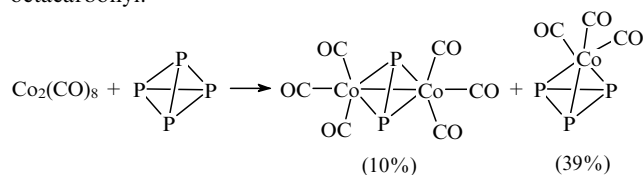


An X-ray diffraction study of complex **42** has shown that all atoms of the P<sub>4</sub> fragment are coordinated to cobalt. The phosphorus–phosphorus bond lengths are 2.17–2.19 Å, *i.e.*, they are shorter than the bond length in P<sub>4</sub> (2.21 Å).

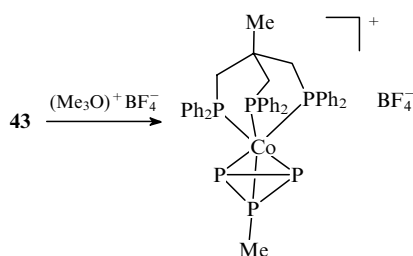
The introduction of 1,1,1-tris(diphenylphosphinomethyl)ethane into this reaction results in cobalt compounds **43**, containing a cyclo-P<sub>3</sub> fragment.<sup>59</sup>



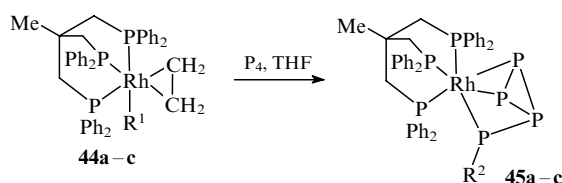
Cobalt complexes containing similar phosphorus ligands are also formed on treatment of white phosphorus with dicobalt octacarbonyl.<sup>60, 61</sup>



Using complex **43**, it has been demonstrated that a phosphorus–carbon bond can be formed in these systems by treatment with trimethylxonium tetrafluoroborate, resulting in the methylation of one phosphorus atom; the structure of the triphosphacyclopentane fragment remains unchanged.<sup>62</sup>

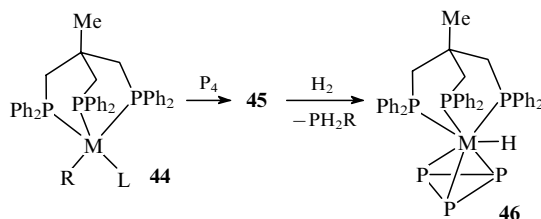


A scheme for the formation of the cyclo- $P_3$  fragment upon the destruction of  $P_4$  has been proposed after an investigation of the reaction of white phosphorus with rhodium and cobalt compounds.<sup>63,64</sup> It was shown that on treatment with rhodium complexes **44a,b** under mild conditions, the  $P_4$  tetrahedron is converted into an unusual  $\eta^{2:1}\text{-}P_4R$  ligand, which is stabilised in the coordination sphere of the metal. A similar Rh complex **45c** has been obtained from hydride derivative **44c**. The same transformations are known for iridium.



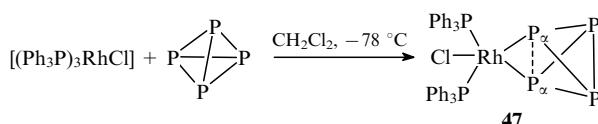
$R^1 = R^2 = \text{Me}$  (**a**),  $\text{Ph}$  (**b**);  $R^1 = \text{H}$ ,  $R^2 = \text{Et}$  (**c**).

These reactions are among the first examples of the formation of compounds with  $P\text{--}C$  bonds from white phosphorus by the participation of a metal complex; they also represent the first examples of metal-mediated direct transfer of an organic fragment to phosphorus coordinated as a tetrahedron. Hydrogenation of **45** yields alkylphosphine  $\text{PH}_2R$  and a stable non-reactive compound **46** containing the cyclo- $P_3$  ligand.<sup>42</sup>



$M = \text{Rh, Ir}$ ;  $L = \text{H}_2$ ,  $R = \text{H}$ ;  $L = \text{C}_2\text{H}_4$ ;  $R = \text{H, Me, Et, Ph}$ .

The generation of a highly reactive bicyclo[1.1.0]tetraphosphabutane and its subsequent stabilisation in a metal coordination sphere is observed in the reaction of  $P_4$  with Wilkinson's catalyst or other square planar  $\text{Rh(I)}$  or  $\text{Ir(I)}$  complexes.<sup>65,66</sup> At low temperatures, one triphenylphosphine molecule is eliminated to give rhodium complex **47** containing a  $\eta^2\text{-}P_4$  fragment.

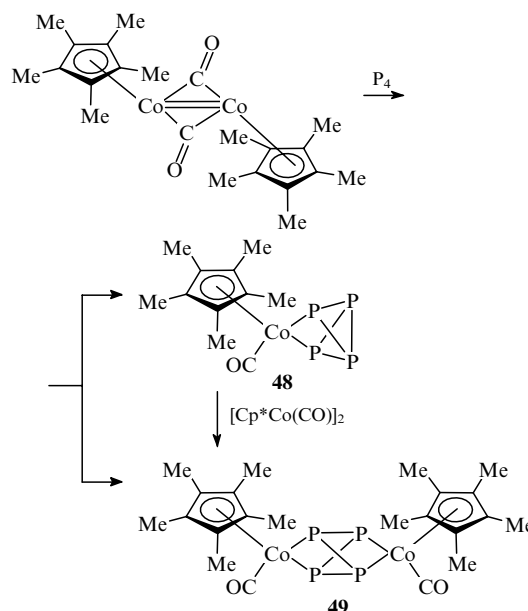


This reaction can formally be considered as an oxidative addition of a white phosphorus molecule with a simultaneous increase in the rhodium coordination number.

The structure of (bicyclo[1.1.0]tetraphosphabutane)bis(triphenylphosphine)rhodium **47** was proved by X-ray diffraction. The  $\eta^2$ -coordination of the  $P_4$  fragment results in an increase in the  $P_\alpha\text{--}P_\alpha$  bond length to 2.4616 Å. This type of coordination was previously predicted theoretically by Albright *et al.*<sup>67</sup> for the model complex  $[(\text{PH}_3)_2\text{ClRhP}_4]$ , in which the  $\eta^2$ -coordination of

the  $P_4$  fragment proved to be 15 kcal mol<sup>-1</sup> more favourable than the  $\eta^1$ -coordination.<sup>67</sup> However, the computation data do not provide an unambiguous answer to the question of whether or not the structure of the white phosphorus molecule is retained or whether the oxidative addition takes place due to cleavage of the phosphorus–phosphorus bond.

On the basis of experimental data, one can conclude that the initial formation of bicyclo[1.1.0]tetraphosphabutane fragment is a general step in the opening of the white phosphorus molecule on treatment with transition metal derivatives. The formation of metal complexes is the result of the subsequent transformation of this intermediate and depends on the reaction conditions (first of all, on the reactant ratio). The  $\eta^2$ -coordination of the  $P_4$  fragment, arising from the cleavage of one  $P\text{--}P$  bond in the  $P_4$  tetrahedron of metal complex **48**, is observed upon reaction of the white phosphorus with (pentamethylcyclopentadienyl)carbonylcobalt  $[\text{Cp}^*(\text{CO})_2](\text{Co}=\text{Co})$ .<sup>68</sup> This reaction may also involve the simultaneous cleavage of two  $P\text{--}P$  bonds, giving rise to complex **49** with a bridging  $\mu, \eta^{2:2}$ -tetraphosphacyclobutane ligand. Note that complex **49** was obtained in 30% yield on treatment of compound **48** with an excess of the initial metal complex.<sup>68</sup>

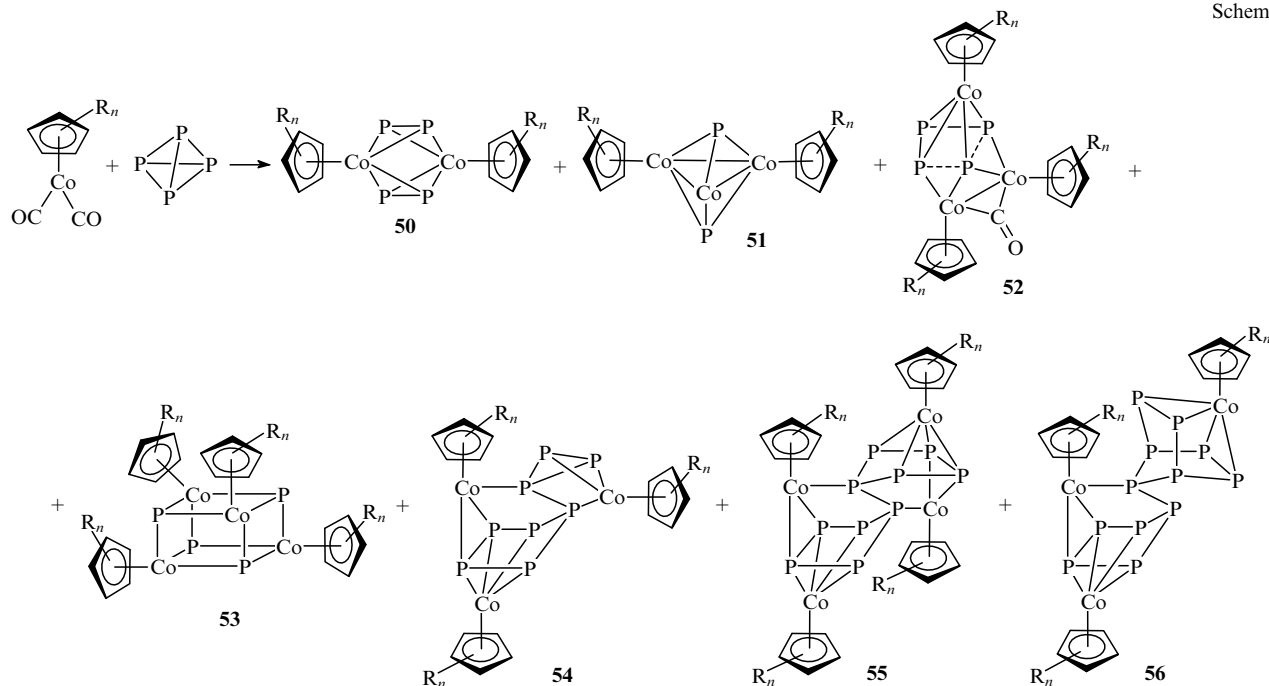


On introduction of a similar mononuclear cobalt complex into the reaction with  $P_4$ , complete decarbonylation of the metal atom takes place, ultimately giving a series of compounds. The reaction affords both the complexes **50–53**, with highly reactive phosphorus ligands, and products of their further transformations containing  $P_8$ ,  $P_{10}$  and  $P_{12}$  type polyphosphorus fragments as ligands, compounds **54**, **55** and **56**, respectively (Scheme 1).<sup>69,70</sup> The latter were isolated from the reaction mixture in low yields (< 5%).

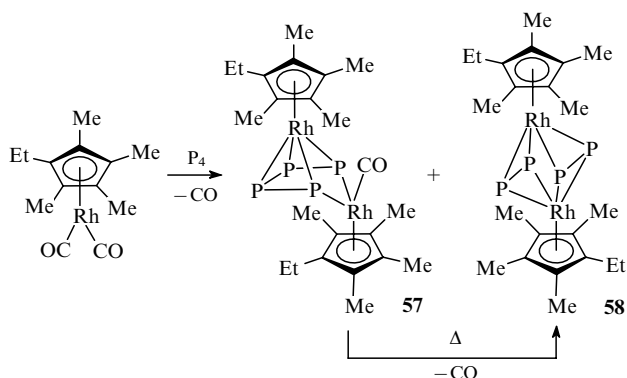
A similar chemical behaviour for white phosphorus was found in its joint thermolysis with rhodium and iridium complexes  $[\{\text{Cp}^*\text{M}(\text{CO})_n\}_m]$  ( $m + n = 3$ ;  $M = \text{Rh, Ir}$ ).<sup>17,68,71–76</sup>

A study of the reaction of  $P_4$  with rhodium derivatives has provided one more step towards understanding the cleavage of  $P\text{--}P$  bonds in metal coordination spheres and elucidating the relationship between the structures of the resulting phosphorus ligands and the initial metal complexes.<sup>17</sup> The thermolysis of white phosphorus in the presence of (tetramethylethylcyclopentadienyl)dibondylrhodium was found to give complex **57**, containing two non-equivalent rhodium atoms. The long-term heating of compound **57** induces the loss of CO, resulting in binuclear complex **58**, in which the  $P_4$  fragment splits into two  $P_2$  fragments stabilised by two rhodium atoms.

Scheme 1



$R_n = 1,3\text{-Bu}_2^1, 1,2,4\text{-Bu}_3^1, \text{Me}_3\text{Si}.$



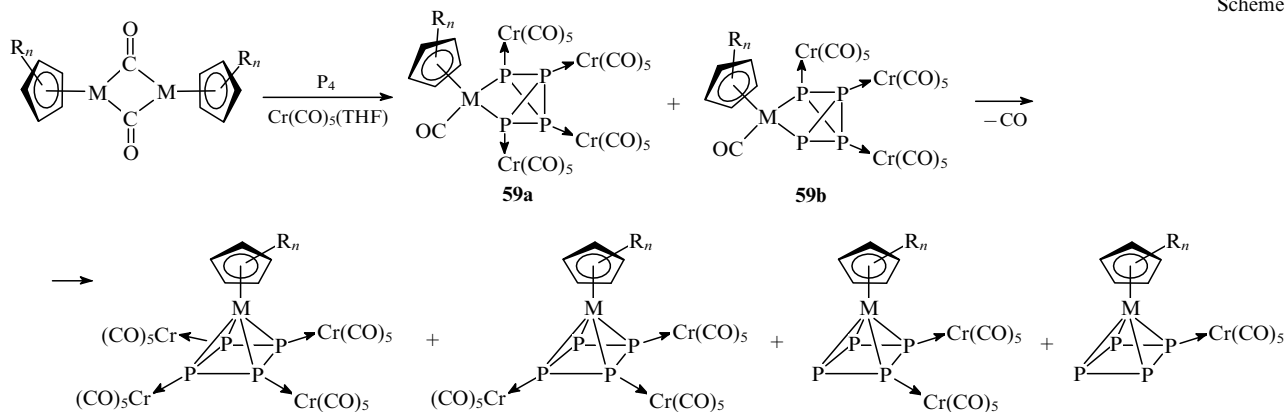
Fuller information on the pathways of cleavage of the  $P_4$  molecule, resulting in one or another phosphorus ligand, has been gained from a study of the reaction of the cyclopentadienylcar-

bonyl complexes of cobalt group metals with white phosphorus in the presence of  $\text{Cr}(\text{CO})_5(\text{THF})$ . It has been found<sup>74, 77, 78</sup> that the process starts with the generation of bicyclo[1.1.0]tetraphosphabutane, which forms heteropolynuclear complexes of type **59a,b** with transition metal compounds. Analogous cobalt complexes have also been isolated in the absence of  $\text{Cr}(\text{CO})_5(\text{THF})$ .<sup>68</sup>

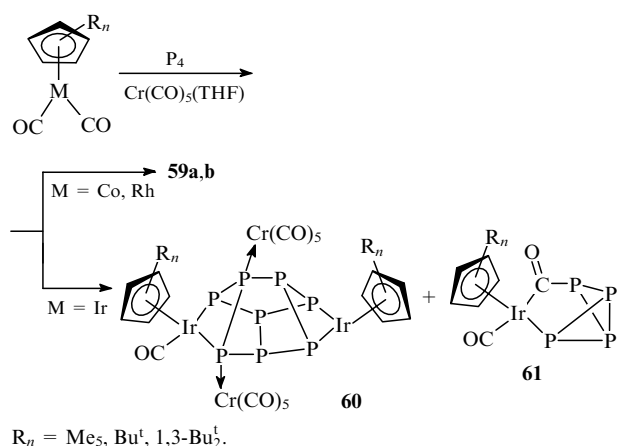
The decarbonylation of polynuclear complexes **59a,b** gives four types of coordination compound with a planar tetraphosphacyclobutane fragment, which has not been observed previously for cobalt group metals (Scheme 2). The product of the coordination of four  $\text{Cr}(\text{CO})_5$  molecules is the predominant product.

In complex **59a**, the bicyclo[1.1.0]tetraphosphabutane fragment is a 10-electron-donor ligand, which is its maximum value. In the case of iridium derivatives, in addition to complex **60**, the product of inserting the carbonyl group into the metal–phosphorus bond, compound **61**, was isolated quite unexpectedly (yield 58%).<sup>79</sup>

Scheme 2

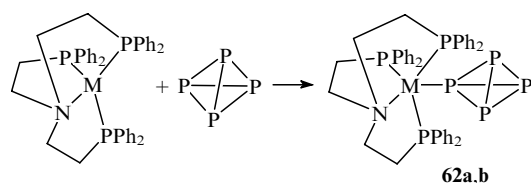


$R_n = \text{Me}_5, \text{Bu}^1, 1,3\text{-Bu}_2^1; \text{M} = \text{Co}, \text{Rh}, \text{Ir}.$



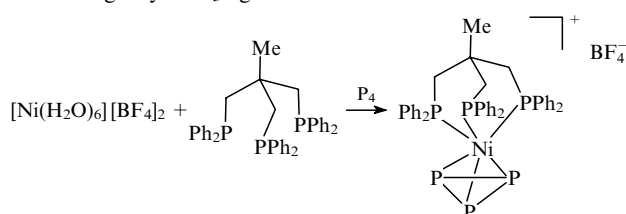
### c. Derivatives of nickel group metals (Ni, Pd, Pt)

Derivatives of nickel group metals containing a white phosphorus molecule as a ligand were the first representatives of metal complexes of this class.<sup>6, 7, 15, 80–85</sup> The  $[(\text{NR}_3)\text{M}(\eta^1\text{-P}_4)]$  complexes, where  $\text{NR}_3$  is tris(2-diphenylphosphinoethyl)amine,  $\text{M} = \text{Ni}$  (**62a**)<sup>86</sup> or  $\text{Pd}$  (**62b**),<sup>87</sup> were obtained in the late 1970s by Sacconi and co-workers, who studied the reactions of white phosphorus with nickel and palladium derivatives,  $[(\text{NR}_3)\text{M}]$ , which are strong Lewis acids.

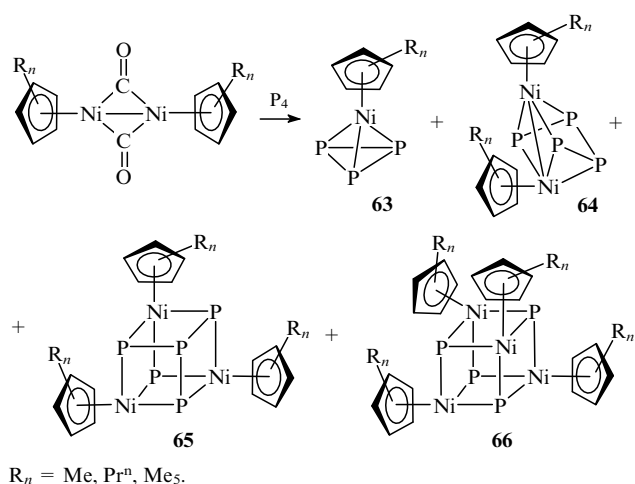


The structure of nickel complex **62a**, relatively insensitive to oxidation in the solid state, was proved by X-ray diffraction,<sup>86</sup> which confirmed the presence of  $\eta^1$ -coordination of a phosphorus molecule to the metal. Due to coordination of only one phosphorus atom, the  $\text{P}_4$  tetrahedron is converted into a trigonal pyramid, which shows itself as a change in the  $\text{P}_\alpha\text{-P}_\beta$  and  $\text{P}_\beta\text{-P}_\gamma$  bond lengths (see below).

Changes in the steric and electronic parameters of ligands surrounding the nickel atom influence the route of the reaction between nickel complexes and white phosphorus. The reaction of  $\text{P}_4$  with nickel tetrafluoroborate in the presence of 1,1,1-tris(diphenylphosphinomethyl)ethane results in a cationic complex containing a cyclo- $\text{P}_3$  ligand.<sup>59</sup>



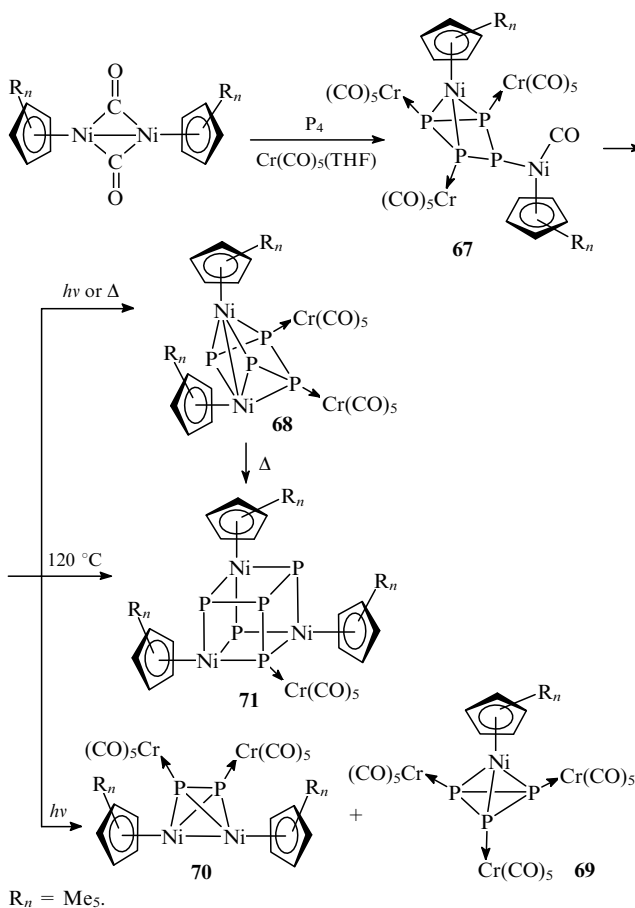
The transformation of a  $\text{P}_4$  molecule in the coordination sphere of a metal with a 15-electron configuration has been studied in relation to nickel (cyclopentadienyl)carbonyl complexes. Thermal activation of white phosphorus under the action of (cyclopentadienyl)carbonylnickel dimer results in the formation of a mixture of products containing sandwich-type 18-electron complex **63**, binuclear complex **64** with an open-chain  $\text{P}_4$  fragment, and two organometallic 'cubanes': **65** with separated  $\text{P}_4$  and  $\text{P}_1$  fragments and **66** with four  $\text{P}_1$  fragments.<sup>88, 89</sup> Complex **65** is the major product of this reaction (yield 58%).



In order to elucidate the mechanism of complexation of  $[\text{Cp}^R\text{Ni}(\text{CO})_2]$ , this reaction was investigated in the presence of a pentacarbonyl chromium complex. Exposure of the reaction mixture to the UV light afforded complex **67**, containing the tetraphosphacyclobutane ligand in an unusual distorted square conformation (Scheme 3).<sup>90, 91</sup> Owing to the additional stabilisation by bulky  $\text{Cr}(\text{CO})_5$  fragments, intermediate **67** was isolated and studied.<sup>90</sup>

It was found that further photolysis of complex **67** was accompanied by elimination of chromium hexacarbonyl and the simultaneous rupture of one  $\text{P-P}$  bond of the tetraphosphacyclobutane fragment, giving rise to complex **68** with an open-chain  $\text{P}_4$  substituent. Heteropolynuclear nickel complexes **69** and **70**, containing cyclo- $\text{P}_3$  and  $\text{P}_2$  ligands, respectively, were isolated as

Scheme 3

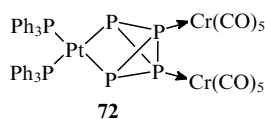


the minor products. The formation of complex **70** was attributed<sup>90</sup> to the dimerisation of the highly reactive intermediate  $[\text{Cp}^*\text{Ni}\equiv\text{P}\rightarrow\text{Cr}(\text{CO})_5]$ .

Thermolysis of complex **67** can also yield compound **68**. This rearranges at high temperature to cubane **71** with separated  $\mu_3\text{-P}$  and tridentate  $\text{P}_4$  ligands.<sup>90</sup>

It has been noted above that the stabilisation of  $\text{P}_3$  or  $\text{P}_4$  fragments in the coordination sphere of transition metals is possible only in the presence of bulky ligands (*e.g.*, triphos) at the metal atom. The stabilising role of the  $\text{Cr}(\text{CO})_5$  group has also been found for platinum derivatives containing a  $\text{P}_4$  ligand in the coordination sphere.

The oxidative addition of white phosphorus to platinum(0) complexes in the presence of  $\text{Cr}(\text{CO})_5(\text{THF})$  allowed the preparation of compound **72**, in which the bicyclo[1.1.0]tetraphosphabutane fragment acts as a  $\text{P}_4^{2-}$  ligand, stabilised *via* coordination to two  $[\text{Cr}(\text{CO})_5]$  groups.<sup>92</sup>



Thus, the route of cleavage of the  $\text{P}_4$  tetrahedron has been elucidated as a result of studies into the transformations of a white phosphorus molecule under the action of transition metal complexes, and into the structures of phosphorus intermediates thus generated and stabilised in metal coordination spheres (Table 1). In addition, factors responsible for the formation of particular types of phosphorus species were revealed.

In summary, one can represent the general scheme of cleavage and subsequent transformation of the white phosphorus molecule in the coordination sphere of a transition metal. The presence of four lone electron pairs (LEP) in the initial molecule accounts for the formation of complexes containing a  $\text{P}_4$  fragment at the metal atom. When additional bulky ligands (for example, triphos) are present, these complexes can be isolated in a pure state. A small steric bulk of ligands and additional vacant coordination sites at the metal atom dictate the pathway of  $\text{P}-\text{P}$  bond cleavage in  $\text{P}_4$  during its coordination to transition metal complexes, accompanied by the formation of bicyclo[1.1.0]tetraphosphabutane stabilised in the metal coordination sphere. The cleavage of the  $\text{P}-\text{P}$  bond in this product furnishes two types of phosphorus species, tetraphosphacyclobutadiene and triphosphacyclop propane. The rupture of  $\text{P}-\text{P}$  bonds in these intermediates yield a series of highly reactive phosphorus-containing fragments, many of which have also been stabilised in a metal coordination sphere. This pathway is simplified, as it does not include the aggregation processes of phosphorus intermediates. These processes afford complex polyphosphorus ligands  $\text{P}_n$  ( $n < 14$ ), which can also be isolated as complexes with transition metals.

The reactions of organic compounds with transition metal complexes containing  $\text{P}_n$  species ( $n \leq 4$ ) with unsubstituted phosphorus atoms as ligands have been barely studied as yet. These reactions result in  $\text{P}-\text{C}$  and  $\text{P}-\text{E}$  bonds (where  $\text{E} = \text{O}, \text{S}, \text{N}$ , *etc.*). This is undoubtedly a topical problem. The fact is that all complexes described in this Section are relatively stable. The use of these compounds as efficient catalysts of the reactions of white phosphorus with organic substrates implies the presence of coordinative or electronic unsaturation of the metal atom. Hence, less stable transition metal complexes with phosphorus intermediates should become objects of investigation. These complexes are expected to be highly reactive towards organic and organoelement substrates used for the synthesis of organophosphorus compounds directly from white phosphorus.

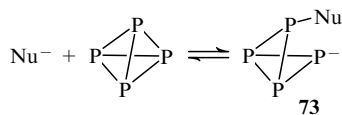
**Table 1.** Types of phosphorus species formed from the  $\text{P}_4$  tetrahedron and stabilised in a metal coordination sphere.

| Type of species | Examples of metal complexes |
|-----------------|-----------------------------|
|                 |                             |
|                 |                             |
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### III. Reactions of white phosphorus with nucleophilic and electrophilic reagents

The reactions of elemental phosphorus with nucleophilic reagents have been studied in the most detail. Relying on abundant experimental data, Brown and Hudson<sup>93-97</sup> considered some theoretical aspects and rules for these processes. The phosphorus atoms in the  $\text{P}_4$  tetrahedron are known to exhibit weak nucleophilic properties, as was confirmed by quantum-chemical calculations.<sup>98</sup> This is attributable to the fact that the electron pair of each phosphorus atom is localised, in the first approximation, in the  $3s$  orbital, *i.e.*, it is arranged as a sphere around the nucleus. In the partially opened  $\text{P}_4$  structure, the phosphorus atoms become more nucleophilic. However, due to ring strain and the instability of the  $\text{P}-\text{P}$  bond, the atoms possess strong electrophilic properties. Attack at the  $\text{P}_4$  molecule by a nucleophilic reagent ( $\text{Nu}^-$ ) yields the phosphide anion **73**, which is both a strong nucleophile and strong base:<sup>93</sup>

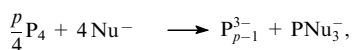
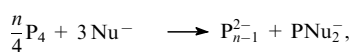
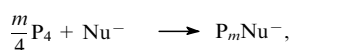




In the absence of electrophilic reagents, the equilibrium of this reaction is shifted towards the starting compounds for almost all types of nucleophiles, except for the very strong ones, such as carbanions. Due to its basic properties ( $\text{p}K_{\text{a}}$  of the corresponding acid is about 29), the phosphide anion **73** is rapidly protonated in a proton-donating medium, giving rise to an unstable intermediate. For example, if a hydroxide or alkoxide anion is used as the nucleophile, this intermediate spontaneously decomposes with evolution of hydrogen, phosphine, hypophosphite anions and phosphite anions.<sup>99</sup> In order to eliminate this undesirable process, it is necessary to use an electrophilic reagent capable of competing with the proton. This was attained in the reactions of  $\text{P}_4$  with organometallic compounds in the presence of alkyl halides;<sup>100</sup> with the hydroxide ion in the presence of aldehydes;<sup>101</sup> with acrylonitrile and other  $\alpha,\beta$ -unsaturated compounds;<sup>102</sup> with disulfides;<sup>103</sup> and with alkoxide ions in a mixture of an alcohol and tetrachloromethane.<sup>93–96, 104</sup> Repeated nucleophilic attack followed by the capture of the phosphide anion by an electrophilic reagent allows one to obtain diverse products under mild conditions.

It is noteworthy that in the vast majority of cases, the rupture of the P–P bonds in  $\text{P}_4$  proceeds by a pattern much more complicated than merely the successive addition of nucleophilic and electrophilic reagents (the latter may be represented by the white phosphorus itself). It was shown<sup>105, 106</sup> that the formation of oligomeric phosphides is a general process accompanying the cleavage of the  $\text{P}_4$  molecule. The negative charge on the phosphorus atom, which results from rupture of the first P–P bond on treatment with a nucleophilic reagent, can be stabilised due to fast interaction with the second  $\text{P}_4$  molecule, *etc.* The formation of dark solid precipitates with a high content of phosphorus has been observed in the reaction of  $\text{P}_4$  with disulfides,<sup>103</sup> phenyllithium and other reagents.<sup>102, 107</sup>

The earliest attempts<sup>100</sup> to determine the structure of the intermediate phosphorus oligomers resulting from the attack by carbanions on  $\text{P}_4$  suggest that these polyphosphides have a cross-linked structure. More recent studies attest to even more complex reaction pathways, involving opening of the  $\text{P}_4$  molecule under the action of nucleophilic reagents<sup>108</sup> followed by disproportionation and elimination of polyphosphide residues.



where  $m > n > p$ .

These transformations have been studied, taking reactions of  $\text{P}_4$  with the  $\text{CN}^-$  and  $\text{Ph}_2\text{P}^-$  anions and other nucleophiles as examples, in order to elucidate the factors that would suppress disproportionation.<sup>108</sup> The selection of the optimal conditions ensures, in some cases, the selective formation of the target products from the intermediate phosphorus oligomers.

### 1. Reactions of white phosphorus with alkali metals and magnesium

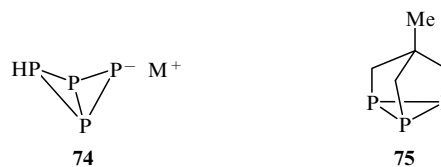
Studies of the reactions between white phosphorus and alkali metals and magnesium clearly demonstrated the difficulties faced when conducting these seemingly simple reactions. As in the case of transition metal complexes, the product structure is determined by a number of factors, first of all, reactant ratio.

Thus heating a mixture of white phosphorus and sodium (atomic ratio 3 : 1) in THF or dimethoxyethane in the presence of a

phase transfer catalyst, 18-crown-6 ether, resulted in a mixture of compounds, from which disodium hexadecaphosphide  $\text{Na}_2\text{P}_{16}$  was isolated by partial crystallisation.<sup>105</sup> A detailed investigation of the reaction mixture showed the formation of an isolobal analogue of sodium cyclopentadienide ( $\text{NaCp}$ ), namely, sodium pentaphosphacyclopentadienide  $\text{NaP}_5$ ,<sup>109</sup> stable only in solution. An alternative method for the preparation of alkali metal pentaphosphacyclopentadienides  $\text{MP}_5$  consists of the reaction of white or red phosphorus with alkali metal dihydrophosphides  $\text{MPH}_2$  (in 5 : 1 molar ratio).<sup>110, 111</sup> The reaction of white phosphorus with sodium in the presence of catalytic amounts of dibenzo-18-crown-6 ether is a convenient method for the synthesis of  $\text{NaP}_5$ .<sup>112</sup> Note that the pentaphosphacyclopentadienide anion  $\text{P}_5^-$  is a new and promising ligand in organometallic chemistry,<sup>109, 113</sup> as has been mentioned in a previous subsection.

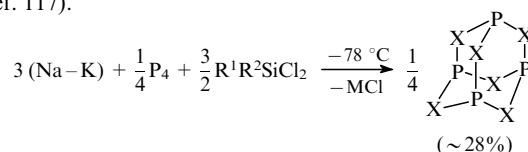
The formation of a series of polyphosphides in the reactions of white phosphorus with alkali metals is a general process and depends on many factors, in particular, the boiling point of the solvent. The use of solvents with boiling points lower than the melting point of the alkali metal facilitates the formation of polyphosphides.<sup>114</sup> In particular, the fraction of polyphosphides can be reduced and, hence, the yields of the target products increased by using a Na–K alloy, the melting point of which is lower than the melting points of the pure metals.

For example, white phosphorus reacts with the Na–K alloy (1 : 3) or with Li metal in the presence of naphthalene to give bicyclo[1.1.0]tetraphosphine salts **74**.<sup>106</sup>



Phosphine **75**, having a nortricyclane structure, has been isolated<sup>115</sup> in a study of the reaction of  $\text{P}_4$  with a Na–K alloy in the presence of 1,3-dibromo-2-bromomethyl-2-methylpropane  $\text{MeC}(\text{CH}_2\text{Br})_3$ . Note that phosphine **75** reacts with metal carbonyls  $\text{M}(\text{CO})_5(\text{THF})$  ( $\text{M} = \text{Cr}, \text{W}$ ) under mild conditions to form metal complexes in which the metal is coordinated to one, two, or three phosphorus atoms  $\text{MeC}(\text{CH}_2\text{P})_3[\text{M}(\text{CO})_5]_n$  ( $n = 1, 2, 3$ ).

The reaction of white phosphorus with a Na–K alloy has been successfully used to prepare silylphosphines, which are basic reagents for the preparation of diverse derivatives of trivalent phosphorus. Thus treatment of the reaction mixture with chlorotrimethylsilane resulted in the isolation of tris(trimethylsilyl)phosphine, which is widely used in the chemistry of low-coordinate phosphorus compounds.<sup>116</sup> The replacement of chlorotrimethylsilane in this reaction by dichlorodimethylsilane allowed the preparation of silylphosphine  $(\text{Me}_2\text{Si})_3\text{P}_4$  (yield ~1%) with a nortricyclane structure. Optimisation of the reaction conditions, first of all, changing the reactant ratio, markedly increased the yield of the target silylphosphine. The introduction of a Na–K alloy into the reaction with white phosphorus in a 1 : 3 atomic ratio and subsequent treatment of the reaction mixture with  $\text{R}^1\text{R}^2\text{SiCl}_2$  at  $-78^\circ\text{C}$  opened up the way to the synthesis of silylphosphines having the adamantane structure  $(\text{R}^1\text{R}^2\text{Si})_6\text{P}_4$  (see Ref. 117).

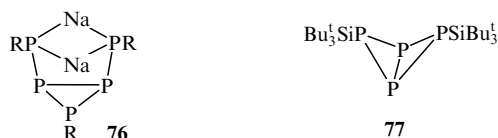


$\text{X} = \text{R}^1\text{R}^2\text{Si}$  ( $\text{R}^1, \text{R}^2 = \text{Me}, \text{Et}, \text{Ph}$ ).

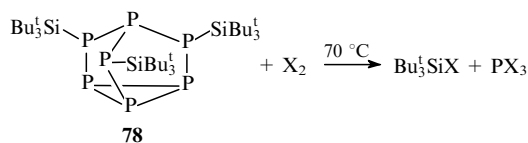
This method was successfully used for the preparation of both the silicon analogues of adamantane, such as  $[\text{R}(\text{Me})\text{Si}]_6\text{P}_4$ , containing diverse functional groups (for example,  $\text{R} = \text{CH}_2 = \text{CH}$ ), mixed silylphosphines  $(\text{MeHSi})(\text{Et}_2\text{Si})_5\text{P}_4$ .<sup>118</sup>

However, due to steric and electronic factors, this approach cannot be applied to the synthesis of silaphosphaadamantanes containing *tert*-butyl and phenyl groups at the silicon atom.<sup>118</sup>

The reactions of white phosphorus with sodium tris(*tert*-butyl)silicide ( $\text{Bu}_3^t\text{SiNa}$ ) and hexakis(*tert*-butyl)disilane have been proposed<sup>119</sup> as an alternative pathway to silylphosphines containing a bulky *tert*-butyl group. These reactions furnish a number of silylphosphines containing a tris(*tert*-butyl)silyl group:  $\text{Na}_2\text{P}_4(\text{SiBu}_3)_2$ ,  $\text{NaP}_3(\text{SiBu}_3)_2$ ,  $\text{Na}_2\text{P}_5(\text{SiBu}_3)_2$  (compound **76**,  $\text{R} = \text{Bu}^t$ ) and  $\text{Na}_2\text{P}_7\text{SiBu}_3$ .

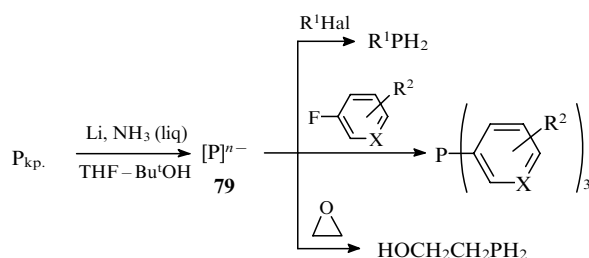


The reaction of  $\text{P}_4$  with hexakis(*tert*-butyl)disilane presumably proceeds by a free-radical mechanism. The  $\text{Bu}_3^t\text{Si}^\cdot$  radical is generated on thermal decomposition of  $(\text{Bu}_3^t\text{Si})_2$  ( $T > 100^\circ\text{C}$ ) and reacts with white phosphorus, giving rise to silylphosphines  $(\text{Bu}_3^t\text{Si})_2\text{P}_4$  and  $(\text{Bu}_3^t\text{Si})_3\text{P}_7$  (compounds **77** and **78**, respectively).<sup>119</sup> Heptaphosphine **78** has a nortricyclane structure and is distinguished by a high thermal stability. The steric crowding of the  $\text{Bu}_3^t\text{Si}$  groups results in an increase in the exocyclic angles at the equatorial phosphorus atoms but scarcely influences the structure of the phosphorus  $\text{P}_7$ -skeleton of the molecule. On treatment with chlorine or bromine at  $70^\circ\text{C}$ , heptaphosphine **78** decomposes to give phosphorus trihalides and halosilanes.<sup>119</sup>



$\text{X} = \text{Cl}, \text{Br}$ .

Yet another method for decreasing the fraction of polyphosphides in the reaction products and increasing the yield of the target compounds in the reaction of white phosphorus with alkali metals is to conduct the process in liquid ammonia.<sup>120</sup> A good solubility of both reactants in liquid ammonia is favourable for high product yields. It was shown<sup>121</sup> that the reaction of white phosphorus with sodium metal in liquid ammonia yields the previously unknown 1,3-diaminotriphosphine  $\text{H}_2\text{NPH}$ .  $\text{PHPHNH}_2$ , which is stable only in solution. Of the three possible diastereomers, only the *erythro,erythro*-isomer, with the transoid arrangement of the  $\text{NH}_2$  groups, was isolated. The reduction of white phosphorus with lithium metal in liquid ammonia results in a complex mixture of polyphosphides. On treatment of red phosphorus with lithium under these conditions, phosphide anion **79** is generated *in situ*. This anion is a convenient reagent for the synthesis of diverse compounds of trivalent phosphorus.<sup>122</sup>



$\text{R}^1 = n\text{-C}_9\text{H}_{19}, \text{PhCH}_2, \text{cyclo-C}_5\text{H}_9; \text{X} = \text{CH}, \text{N}$ .

When the phosphide anion **79** reacts with alkyl halides, primary phosphines are formed in high yields,<sup>123</sup> while the reaction with alkyl fluorides gives symmetric triarylphosphines (yields 36%–60%).<sup>124</sup> Note that the latter can contain functional

substituents, including phosphonodiimide, sulfonamide, 2-oxazole and nitrile groups.

Phosphine  $\text{HOCH}_2\text{CH}_2\text{PH}_2$  was isolated in 27% yield from the reaction of the phosphide anion **79** with oxirane at  $-33^\circ\text{C}$ .<sup>125</sup> With a sterically crowded oxirane, 7-oxabicyclo[4.1.0]heptane, a good yield of the target phosphinoethanol (60%) was attained when the reaction was carried out at high temperature ( $40^\circ\text{C}$ ).<sup>126</sup>

An interesting version of the activation of elemental phosphorus has been reported by Bornancini *et al.*<sup>127</sup> They proposed using radiation for initiating the reactions of sodium phosphides and aryl halides. A series of symmetrical and asymmetrical triarylphosphines were prepared in good yields using this approach.

The development of methods for the synthesis of polycyclic organophosphines<sup>128,129</sup> has resulted in the synthesis of the first representative of this class of compound, tetraisopropyltetradecaphosphine  $\text{P}_{14}\text{Pr}_4^i$ . It is formed in the reaction of white phosphorus with magnesium metal in the presence of  $\text{Pr}^i\text{PCl}_2$ .<sup>130</sup> The first stage of the process affords a mixture of polyphosphines  $\text{P}_9\text{Pr}_5^i$  and  $\text{P}_7\text{Pr}_5^i$ , and isopropylphosphines with high phosphorus contents. Further thermolysis of the reaction mixture gives, in addition to  $\text{P}_9\text{Pr}_5^i$  and  $\text{P}_7\text{Pr}_5^i$ , a substantial amount of less alkylated phosphorus derivatives containing more than 9 phosphorus atoms in each molecule (including  $\text{P}_{14}\text{Pr}_4^i$ ). As a result of systematic research, both stages were optimised. This unusual synthetic approach has been successfully used for the synthesis of a number of polycyclic organophosphines such as  $\text{P}_{11}\text{Pr}_3^i$  (see Ref. 131),  $\text{P}_{11}\text{Pr}_5^i$  (see Refs 132, 133),  $\text{P}_{12}\text{Pr}_4^i$  (see Refs 134, 135),  $\text{P}_{13}\text{Pr}_5^i$  (see Ref. 136),  $\text{P}_{18}\text{Pr}_6^i$  (see Ref. 137),  $\text{P}_{18}\text{Pr}_4^i$  (see Ref. 138),  $\text{P}_{20}\text{Pr}_6^i$  (see Ref. 139) and  $\text{P}_{14}\text{Pr}_4^i$  (see Ref. 131). The reaction of  $\text{PET}_5$  with  $\text{PCl}_3$  in the presence of magnesium metal can be used as an alternative method for the preparation of compounds of this class.<sup>140</sup>

Thus, the reaction of white phosphorus with alkali metals, magnesium and C-electrophiles can be used to prepare OPCs with different oxidation states of phosphorus. However, the scope of this method is limited due to oxidative elimination processes. Metal phosphides formed upon interaction of white or red phosphorus with alkali metals react with alkyl (or aryl) halides to give not only compounds with the  $\text{P}-\text{C}$  bonds, but also polyphosphines, which reduces the yield of the target product.

The oxidative elimination and formation of polyphosphines can be suppressed by using organic derivatives of alkali and alkaline earth metals as nucleophilic agents.

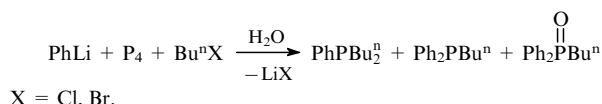
## 2. The reactions of white phosphorus with organolithium and organomagnesium compounds

The use of organolithium compounds ensured the first synthesis of organophosphorus derivatives with  $\text{P}-\text{C}$  bonds directly from white phosphorus.<sup>100</sup> It was suggested that the reaction yields a mixture of alkali metal phosphides and triphenylphosphine:



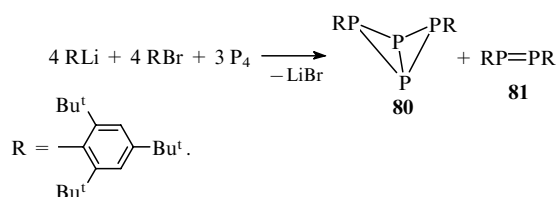
However, only traces of triphenylphosphine  $\text{Ph}_3\text{P}$  and diphenylphosphine were isolated after hydrolysis of the reaction mixture, unsubstituted phosphine was not even detected, while phenylphosphine was formed as the major product. The yields of primary phosphines in the reaction of  $\text{P}_4$  with  $\text{Bu}^n\text{Li}$  and  $\text{PhLi}$  were 9% and 40%, respectively, while those for reactions with  $\text{Bu}^n\text{MgBr}$  and  $\text{PhMgBr}$  were 5%–7%.<sup>100</sup>

The use of a combination of reactants — carbanions generated from organometallic compounds and electrophiles (for example, alkyl halides) — increased the overall yield of organophosphorus compounds to 70%–80%.<sup>100</sup> The reaction of white phosphorus with phenyllithium in the presence of alkyl halides affords, after hydrolysis, a mixture of tertiary phosphines and their oxides.



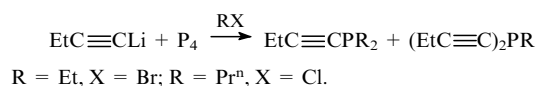
This reaction gives organopolyposphines as intermediates; most likely, these are cross-linked polymeric phosphorus fragments. Their composition is determined by the reactant ratio. Hydrolysis of these polyphosphines proceeds much more readily than the decomposition of lithium phenyl polyphosphide; therefore, the total yield of OPCs does not depend on the nature of the alkali metal. On changing the reactant ratio (increasing in the proportion of phosphorus), the reaction gives tetrabutylcyclotetraphosphine, resulting from the rupture of two P–P bonds in the  $P_4$  tetrahedron<sup>100</sup>

The introduction of sterically hindered 2,4,6-tri-*tert*-butylphenyllithium and 2-bromo-1,3,5-tri-*tert*-butylbenzene into the reaction with phosphorus affords a mixture of bis(2,4,6-tri-*tert*-butylphenyl)bicyclotetraphosphine (**80**) and bis(2,4,6-tri-*tert*-butylphenyl)diphosphene (**81**) in moderate yields.<sup>107</sup>

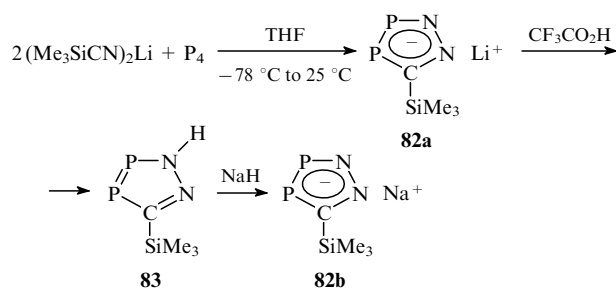


Compound **80** is unstable in air and decomposes in chlorinated hydrocarbons. Attempts to convert it into stable compounds of four-coordinate phosphorus by treatment with elemental sulfur or trimethylsilyl azide failed.

It was found<sup>141, 142</sup> that the but-1-ynylphosphide and di(but-1-ynyl)phosphide anions were generated in the reaction of white phosphorus with but-1-ynyllithium in liquid ammonia; these anions reacted with alkyl halides  $\text{RHal}$  ( $\text{R} = \text{Et}, \text{Pr}^n$ ) to give mixtures of approximately equal amounts of but-1-ynyldialkylphosphines  $\text{EtC}\equiv\text{CPR}_2$  and alkyldi(but-1-ynyl)phosphines  $(\text{EtC}\equiv\text{C})_2\text{PR}$ .<sup>141, 142</sup> The overall yield of phosphines was 15%–20%.

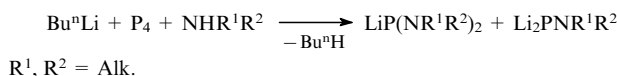


The discovery of pentaphosphaferrocenes<sup>83</sup> and the development of methods for the preparation of the pentaphosphacyclopentadienide ion<sup>109, 111</sup> have stimulated research into the transformation processes of white phosphorus aimed at the construction of new ligands containing several phosphorus atoms in the molecule. It was suggested that the carbene anion  $\text{RC}^-$  can be inserted into a  $\text{P}_4$  molecule, yielding directly the  $[\text{RCP}_4]^-$  ion, owing to stabilisation of the aromatic phosphorus-containing heterocycle.<sup>143</sup> This was confirmed in a study of the reaction of white phosphorus with lithium (trimethylsilyl)diazomethanide. The salt with the previously unknown 1,2,3,4-diazaphospholide anion **82a**, formed during the formal [3+2]-cycloaddition of the  $\text{P}\equiv\text{P}$  fragment to the diazomethyl anion, was isolated as the only reaction product.



The protonation of lithium salt **82a** with trifluoroacetic acid at low temperature produces stable 2*H*-1,2,3,4-diazadiphosphole **83**, which was converted into Na salt **82b**.<sup>143</sup>

The use of dialkylamines as nucleophilic reagents in the reaction of white phosphorus with  $\text{Bu}^n\text{Li}$  results in a mixture of equimolar amounts of lithium dialkylaminophosphide and dilithioalkylaminophosphide.<sup>144</sup>

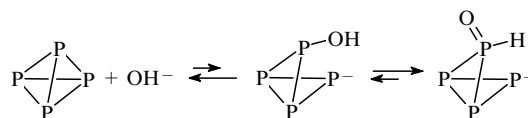


In this case, amine is probably first deprotonated to the amide anion, which then attacks the white phosphorus molecule. The formation of a mixture of two products is attributable to different extents of nucleophilic attack.

### 3. The reactions of white phosphorus with electrophilic reagents in the presence of hydroxide ions

The reactions of elemental phosphorus with electrophiles in the presence of the hydroxide anion are well studied processes. The simple procedures, mild conditions, ready availability of the initial reactants and the easy isolation and identification of products are the reasons for the fast progress in this field of chemistry of elemental phosphorus.

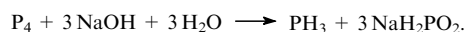
As shown above, the first stage in the cleavage of the  $\text{P}_4$  molecule under the action of nucleophilic reagents gives bicyclo[1.1.0]tetraphosphabutane derivatives; in the absence of electrophiles, the equilibrium is shifted towards the starting compounds. In the presence of the hydroxide ion, this equilibrium can be represented as follows:



In our opinion, the prototropic tautomerism inherent in the  $\text{P}(\text{III})$  intermediates generated *in situ* predetermines the formation of four-coordinate phosphorus compounds in this process. Simultaneously, the tautomeric equilibrium is favourable for the stabilisation of bicyclo[1.1.0]tetraphosphabutane derivatives, which makes it possible to accomplish the reactions of white phosphorus with nucleophilic reagents in the presence of electrophiles under relatively mild conditions.

The combined action of nucleophilic and electrophilic reagents on white phosphorus often allows one to accomplish the consecutive rupture of all P–P bonds and to obtain the target product. However, nucleophilic cleavage of the  $\text{P}_4$  tetrahedron in the absence of electrophiles specially added to the reaction mixture is also of interest in itself, and deserves special consideration. These reactions may underlie the synthesis of unknown polyphosphorus structures thus providing new information on the reactivity of white phosphorus.

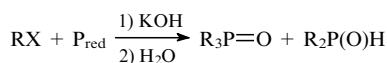
The nucleophilic cleavage of white phosphorus on treatment with NaOH in water (or in a high-molecular-weight alcohol with surfactant additives) results in the formation of high-purity phosphine  $\text{PH}_3$ .<sup>145–147</sup>



The reaction of white phosphorus with  $\text{H}_2\text{O}$  in the presence of HI proceeds with  $\text{PH}_3$  evolution to give phosphorous acid  $\text{H}_3\text{PO}_3$ .<sup>148</sup> Recall that disproportionation of phosphorous acid to phosphine  $\text{PH}_3$  and phosphoric acid is a well-known reaction.<sup>149</sup>

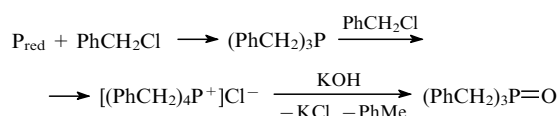
The reaction of elemental phosphorus with electrophilic agents in the presence of strong alkalis (so-called superbasic media) is a convenient way for the preparation of OPCs.<sup>1, 150–160</sup> The most important work on the arylation and alkylation of elemental phosphorus was carried out by Trofimov and co-workers.<sup>150–159</sup> As a rule, these reactions are carried out in the presence of alkali metal hydroxides in aprotic solvents (HMPTA, DMSO) or under phase transfer catalysis conditions. Tertiary phosphines

and phosphine oxides are formed as major products in total yields of 40%. Note that trialkylphosphines cannot be isolated, even when the process is conducted under conditions that absolutely rule out contact with atmospheric oxygen.

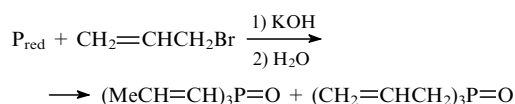


R = Et, Pr<sup>n</sup>, Bu<sup>n</sup>, n-C<sub>5</sub>H<sub>11</sub>, n-C<sub>8</sub>H<sub>17</sub>; X = Cl, Br, I.

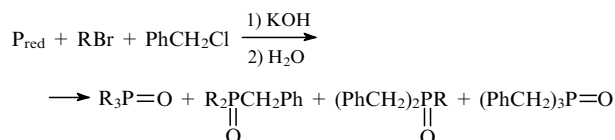
On heating a suspension of red phosphorus in the KOH–DMSO (or HMPTA) system in the presence of benzyl chloride to 70–80 °C, tribenzylphosphine oxide is formed as the major product (yield 65%). Small amounts of tribenzylphosphine and tetrabenzylphosphonium chloride were also isolated.<sup>151</sup> Since the phosphonium salt and toluene were detected in the reaction mixture, the known decomposition of phosphonium hydroxide could form an alternative route to phosphine oxide.<sup>151</sup>



Allyl halides react with red phosphorus at elevated temperatures in a similar way, resulting in tris(prop-1-enyl)phosphine oxide and tris(prop-2-enyl)phosphine oxide in 35% and 30% yields, respectively.<sup>152, 153</sup>



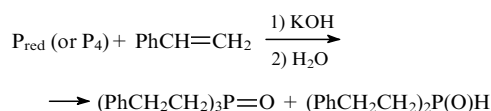
The simultaneous phosphorylation of alkyl bromides and benzyl chloride with red phosphorus was carried out in the development of a one-step method for the synthesis of asymmetrical tertiary phosphine oxides, which are difficult to obtain by other methods. The yield of these products was found to depend, first of all, on the ratio of the initial organyl halides.<sup>161</sup>



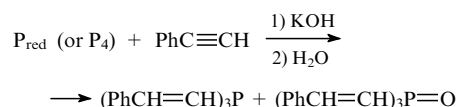
R = Alk.

Since alkyl bromides are subject to side dehydrobromination and hydrolysis under these conditions, and are less reactive than benzyl chloride, the use of a two- to three-fold excess of RBr has been proposed for increasing the yield of asymmetric tertiary phosphine oxides.

In superbasic media KOH–HMPTA(DMSO), unsaturated compounds, namely acrylonitrile, acrylamide, ethyl acrylate, vinylphosphonate, styrene, 4-vinylpyridine and acetylene derivatives, can be used as electrophilic reagents (Refs 125, 141, 144, 155–159, 162–164). For example, the reaction of phosphorus with styrene gave tris(2-phenylethyl)phosphine oxide (yield 60%) with bis(2-phenylethyl)phosphinous acid as the minor product.<sup>155</sup>

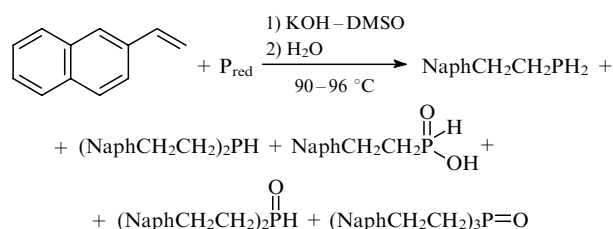


In the case of phenylacetylene, in conformity with the rule for addition of nucleophiles to alkynes,<sup>165</sup> tris[(Z)-styryl]phosphine is formed stereoselectively in 55% yield.<sup>156–158</sup> Tris[(Z)-styryl]phosphine oxide was obtained as a by-product.



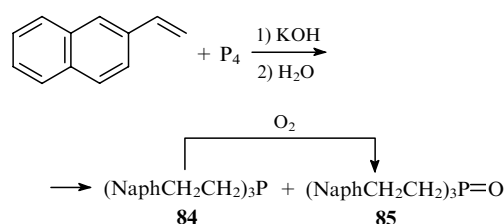
To increase the yield of the target products, it has been proposed to carry out additional activation of elemental phosphorus by using ionising radiation (X-ray or γ electromagnetic radiation); the degree of conversion of red phosphorus reached 97%.<sup>166, 167</sup> The researchers believe that on irradiation, non-paramagnetic cationic and anionic defects appear in the P<sub>red</sub> layered polymeric structure; these are converted into radical paramagnetic defects,<sup>168</sup> which are responsible for the high activity of elemental phosphorus.

The introduction of 2-vinylnaphthalene into the reaction with elemental phosphorus allows one to synthesise previously unknown phosphines and phosphine oxides with bulky radicals that are promising ligands for metal complex catalysts. In the case of red phosphorus, the reaction takes place on heating of the reactants to 90–96 °C in a superbasic medium, KOH–DMSO. The reaction yields a mixture of compounds: primary and secondary phosphines, phosphinic acid and phosphine oxide, in a total yield of up to 40%.<sup>169</sup>

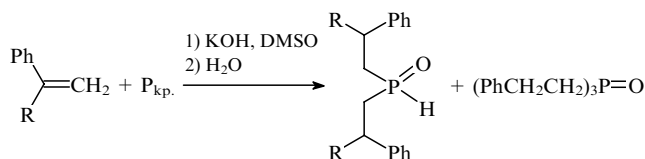


Naph is 2-naphthyl.

The degree of conversion of white phosphorus in this reaction is twice as high as the degree of conversion of P<sub>red</sub>. In addition, an increase in the content of 2-vinylnaphthalene in the initial mixture results in a higher reaction selectivity, and in the formation of tertiary phosphine **84** and phosphine oxide **85** in a 1 : 5 ratio as the major products (total yield 63%). After treatment of the reaction mixture with atmospheric oxygen, phosphine oxide **85** was isolated in 58% yield.<sup>169</sup>



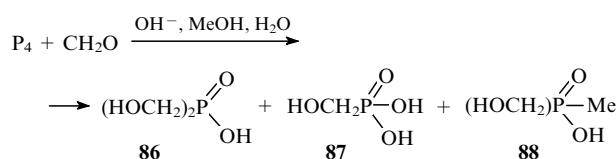
A convenient method for the preparation of phosphinous acids has been developed on the basis of reactions of red phosphorus with arylalkenes in aprotic solvents in the presence of strong bases.<sup>162</sup> This reaction with styrenes affords tris- and bis(2-phenylethyl)phosphine oxides in yields of up to 20%.



R = H, Me.

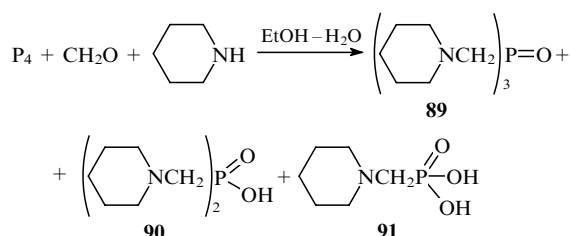
Under similar conditions, tris(2,2-dialkoxyethyl)phosphine oxides [(RO)<sub>2</sub>CHCH<sub>2</sub>]<sub>3</sub>PO were obtained from red phosphorus and 1,1-dialkoxy-2-bromoethanes (RO)<sub>2</sub>CHCH<sub>2</sub>Br (R = Et, Bu<sup>n</sup>), the product yields being moderate (15% and 8%, respectively).<sup>163</sup>

The use of formaldehyde as an electrophilic reagent in the reaction with white phosphorus results in a mixture of bis(hydroxymethyl)phosphinic (**86**), hydroxymethylphosphonic (**87**) and methyl(hydroxymethyl)phosphinic (**88**) acids.<sup>101, 144</sup>



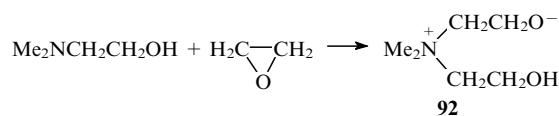
A method for the preparation of methylphosphonic acids, which have found wide use as fire retardants, has been developed on the basis of the reaction of white phosphorus with methyl chloride in the presence of KOH. Phosphonium salts were employed as phase transfer catalysts.<sup>170</sup>

By using organic bases (first of all, primary and secondary amines), one can prepare a series of organic phosphorus derivatives under mild conditions. For instance, white phosphorus reacts with formaldehyde in the presence of piperidine, giving rise to a mixture of tris(piperidinomethyl)phosphine oxide (**89**), bis(piperidinomethyl)phosphinic acid (**90**) and piperidinomethylphosphonic acid (**91**).<sup>171, 172</sup>

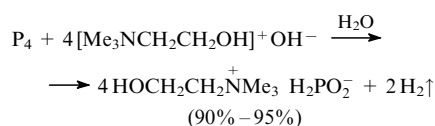


When linear amines, for example,  $\text{Me}_2\text{NH}$  and  $\text{Et}_2\text{NH}$ , are used, the reaction affords also tertiary phosphine.<sup>102</sup> The product yields depend on the starting reactant ratio, the nature of the solvent and the pH of the medium. It was found<sup>102</sup> that  $\text{P}_4$  reacts with *N*-hydroxymethyldialkylamine, formed in the primary reaction between amine and aldehyde. The process starts with nucleophilic attack by the  $\text{R}_2\text{NCH}_2\text{O}$  on the white phosphorus molecule, and is accelerated by the presence of basic catalysts.

This hypothesis has been confirmed in a study of the chemical behaviour of white phosphorus towards alcohol-oxirane mixtures in the presence of inorganic and organic bases.<sup>173–176</sup> The reactions of oxiranes (in particular, ethylene oxide) with *N,N*-dimethylethanamine were found to afford betaine **92**, which can react with white phosphorus.



$\beta$ -Hydroxyethyltrimethylammonium hydroxide (choline) was used as the model compound in the reaction with  $\text{P}_4$ ; this gave  $\beta$ -hydroxyethyltrimethylammonium hypophosphite.<sup>177</sup>

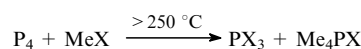


If ethylene oxide and trimethylamine are added consecutively to white phosphorus, the same products are formed as in the reaction with choline.<sup>177</sup>

#### 4. Reactions of white phosphorus with alkyl halides

Since elemental phosphorus has weak nucleophilic properties, the reaction of both of its allotropes with organic halides usually take place under drastic conditions.

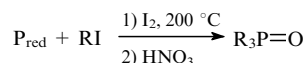
White phosphorus reacts with alkyl or aryl halides at a temperature of  $>250^\circ\text{C}$  to give phosphorus halides and phosphonium salts.<sup>178</sup>



$\text{X} = \text{Cl}, \text{Br}$ .

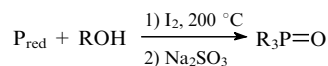
The introduction of alkyl iodides into this reaction, or conducting the process in the presence of elemental iodine, increases the yield of the target products.

Heating red phosphorus and lower alkyl iodides  $\text{RI}$  ( $\text{R} = \text{Me}, \text{Et}, \text{Bu}^n$ ) in an autoclave at  $200^\circ\text{C}$  in the presence of traces of iodine or diphosphorus tetraiodide, followed by treatment of the reaction mixture with dilute nitric acid, affords tertiary phosphine oxides:  $\text{Me}_3\text{PO}$  (yield 54%),  $\text{Et}_3\text{PO}$  (56%) and  $\text{Bu}_3\text{PO}$  (66%).<sup>179–181</sup> The separation of this process into two steps, that is, heating of catalytic amounts of alkyl iodide with red phosphorus in the presence of  $\text{I}_2$  or the salt  $[\text{IR}_3\text{PP}^+\text{R}_3]\text{I}_5^-$  to  $180\text{--}230^\circ\text{C}$  and the subsequent addition of excess alkyl iodide, increases the yield of trialkylphosphine oxides.<sup>179</sup> For example, the yield of triethylphosphine oxide reaches 88%. The researchers believe that the process follows an ionic mechanism as no free radicals were detected during the reaction and UV irradiation or the addition of benzoyl peroxide did not influence the reaction rate.



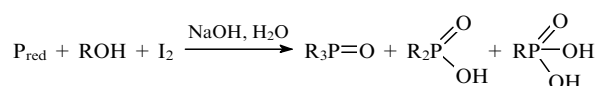
$\text{R} = \text{Me}, \text{Et}, \text{Bu}^n$ .

Alcohols are suitable as alkylating agents for red phosphorus. The reaction occurs in the presence of iodine under drastic conditions. After treatment of the reaction mixture with an aqueous solution of sodium sulfite, the yield of phosphine oxide reaches 80%.<sup>182</sup>



$\text{R} = \text{Alk}$ .

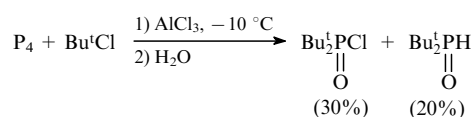
Under alternative conditions, for example, refluxing the reaction mixture in aqueous alkali, phosphinic and phosphonic acids are formed together with phosphine oxides.<sup>183</sup>



$\text{R} = \text{Alk}$ .

A similar reaction carried out using unsaturated compounds (fluorinated acetylene and ethylene derivatives) as the alkylating agents affords tertiary phosphines — diphosphabicyclooctatrienes (yields  $<30\%$ ).<sup>183</sup>

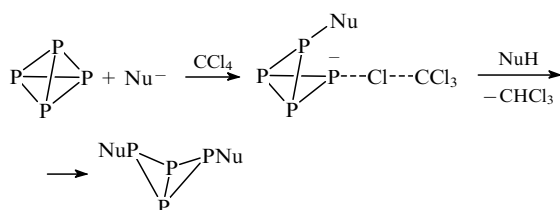
In the presence of catalysts (aluminium halides), the reactions between alkyl halides and white phosphorus can be carried out under mild conditions.<sup>184</sup> For example, white phosphorus dissolved in carbon disulfide reacts with *tert*-butyl chloride in the presence of Lewis acids, even at  $-10^\circ\text{C}$ . After hydrolysis of the reaction mixture, di(*tert*-butyl)phosphine oxide and di(*tert*-butyl)phosphinic acid chloride were isolated.



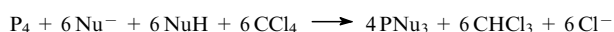
Other alkyl chlorides have also been used in this reaction. It has been suggested<sup>184</sup> that aluminium chloride polarises the  $\text{C}-\text{Cl}$  bond leading to the formation of a carbocation. The addition of the carbocation to a white phosphorus molecule results in a new cation, in which the phosphorus–phosphorus



A more efficient procedure for the preparation of phosphorus derivatives with P–heteroatom bonds has been proposed by Lemann<sup>194</sup> and by Brown and Hudson.<sup>93–96</sup> It is based on the assumption that the reaction of white phosphorus with disulfides can be considered as a redox process. Since the forward reaction of white phosphorus with disulfides takes place only under drastic conditions, the reaction is carried out in CCl<sub>4</sub> in the presence of strong nucleophiles. Tetrachloromethane is known to form charge transfer complexes (CTC) with nucleophiles. White phosphorus possesses weak nucleophilic properties; therefore, before introduction into the reaction with CCl<sub>4</sub>, it was converted into a rather stronger nucleophile<sup>194</sup> by treatment with, for example, alkoxide anions. The bicycletetraphosphide type anion **73**, formed during this process, forms a CTC with CCl<sub>4</sub>. On treatment with protic reagents, this complex decomposes to give chloroform and bicycletetraphosphine.

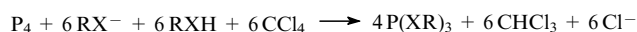


By repeating this process several times, consecutive rupture of all P–P bonds in the P<sub>4</sub> tetrahedron can be attained to give trivalent phosphorus derivatives.



If the PNu<sub>3</sub> derivatives are relatively strong nucleophiles, they can be oxidised by CCl<sub>4</sub> in the presence of protic reagents to give four-coordinate phosphorus compounds.<sup>194</sup>

The side reactions in the synthesis of trialkyl phosphites or trialkyl trithiophosphites can be suppressed by using a two-fold excess of alkoxide or thiolate ion with respect to the stoichiometric amount. The use of an equivalent amount of alkoxide decreases the yields of trialkyl phosphite due to the formation of dialkyl phosphite (RO)<sub>2</sub>PHO. The formation of dialkyl phosphite can be attributed to either protonation of the initial phosphide anion or cleavage of trialkyl phosphite to dialkyl phosphite and alkyl halide on treatment with acids.<sup>96</sup> The optimal reaction conditions are as follows: a large excess of CCl<sub>4</sub>, a two-fold amount of the alkoxide, room temperature, vigorous stirring and a short residence time.

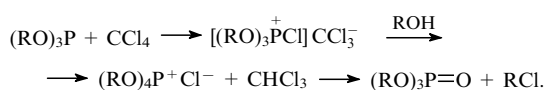


X = O: R = Me (82%), Et (76%), Bu<sup>n</sup> (58%) (see<sup>101</sup>);

X = S: R = Alk (<90%) (see<sup>94</sup>).

The key problem faced by this procedure is related to the purification of trialkyl phosphites, which form stable azeotropic mixtures with excess alcohol and CCl<sub>4</sub>. On repeated distillation of these mixtures, products of decomposition of trialkyl phosphites are formed.

An increase in the residence time results in the formation of trialkyl phosphate *via* the reaction of phosphite and CCl<sub>4</sub> in alcohol.<sup>96</sup>

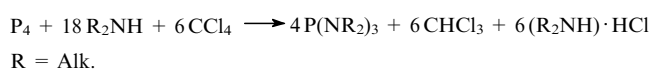


Under similar conditions, P<sub>4</sub> does not react with phenoxide and thiophenoxide ions. Relying on this fact, Brown *et al.*<sup>93–96</sup> made an unreasonable assumption that transformations of white phosphorus could be induced only by highly basic nucleophiles. Lemann and co-workers<sup>194</sup> demonstrated that it is nucleophilicity of the PhO<sup>-</sup> and PhS<sup>-</sup> anions rather than their basicity that plays the crucial role, the variation in the anion concentration having

only a minor influence on the reaction rate. The use of bipolar aprotic solvents and a base (for example, Et<sub>3</sub>N) to increase the nucleophilicity of these anions allowed the researchers to synthesise triphenyl phosphite (yield <50%) and triphenyl trithiophosphite (<80%).<sup>194</sup>

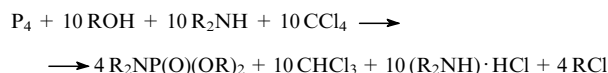
Despite the formal resemblance of the reactions giving trialkyl phosphite and its thio analogue in the P<sub>4</sub>–CCl<sub>4</sub>–RXH–NEt<sub>3</sub> system (X = O, S), these reactions were found to be quite different,<sup>194,195</sup> the rate of reaction of P<sub>4</sub> with thiols proving to be much higher. The difference between the reaction mechanisms is due to the fact that thiol can be rapidly oxidised to form disulfide. This species is not nucleophilic enough to cleave the P–P bond but it can be involved in the acid–base reaction with triethylamine to generate thiolate ions, which initiate the decomposition of P<sub>4</sub>.

The method based on the reaction of white phosphorus with proton-containing compounds in the presence of CCl<sub>4</sub> and a nucleophilic reagent has been successfully used to prepare triaminophosphines. A secondary amine functions as both a proton-donating reagent and a base.<sup>194</sup>



The target product, tris(dialkylamino)phosphine, is a strong base and can form stable quasi-phosphonium salts with [(R<sub>2</sub>N)<sub>3</sub>PCl]<sup>+</sup> and [(R<sub>2</sub>N)<sub>3</sub>PCCl<sub>3</sub>]<sup>+</sup> cations.

Phosphoramidates were prepared by the reaction of white phosphorus with a mixture of dialkylamine and alcohol.<sup>194</sup>

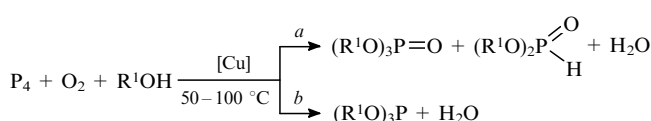


Due to the formation of by-products (R<sub>2</sub>N)<sub>2</sub>P(O)(OR), (RO)<sub>3</sub>PO and (R<sub>2</sub>N)<sub>3</sub>PO, the yield of the target phosphoramidates did not exceed 50%.<sup>194</sup>

An original method has been proposed for the preparation of phosphorus derivatives with P–X bonds (X = S, O and N) using transition metal, first of all copper(II), salts as oxidants.<sup>196–206</sup>

As shown above (see Section II), the white phosphorus molecule can be either a η<sup>1</sup>- or η<sup>2</sup> ligand. In the former case, the P<sub>4</sub> tetrahedron is converted into a trigonal pyramid arranged with its vertex towards the metal atom, which is manifested by an increase in the P<sub>α</sub>–P<sub>β</sub> bond length to 2.20 Å compared to the P<sub>β</sub>–P<sub>β</sub> bond lengths (2.09 Å). In the latter case, the length of the P–P bond that is coordinated to the metal atom (2.46 Å) increases to a greater extent than the bond length in the free phosphorus molecule, thus providing more appreciable loosening of the orbitals of the P<sub>4</sub> molecule. It has been suggested<sup>2</sup> that coordinatively saturated Cu(II) compounds containing donor ligands such as Cl<sup>-</sup>, Br<sup>-</sup>, SO<sub>4</sub><sup>2-</sup> and RCO<sub>2</sub><sup>-</sup>, incapable of the η<sup>2</sup>-coordination of tetrachlorophosphorus, possess lower catalytic activities than the coordinatively unsaturated complexes that display η<sup>1</sup>- and η<sup>2</sup>-binding modes.<sup>196–199</sup> This hypothesis is confirmed by the fact that the addition of pyridine to the former compounds sharply increases the reaction rate.

It was found<sup>196–199</sup> that the reaction of white phosphorus with alcohols proceeds selectively. The reaction takes place in the presence of copper(II) salts on moderate heating of the reactants dissolved in an aromatic hydrocarbon under an O<sub>2</sub> atmosphere.



R<sup>1</sup> = Me, Et, Pr<sup>n</sup>, Bu<sup>n</sup>, Bu<sup>i</sup>, n-C<sub>5</sub>H<sub>11</sub>, iso-C<sub>5</sub>H<sub>11</sub>, Ph, *p*-Tol.

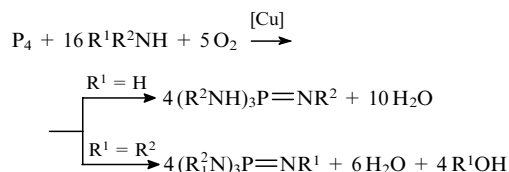
(a) [Cu] = CuCl<sub>2</sub>, CuBr<sub>2</sub>; (b) [Cu] = CuSO<sub>4</sub>, Cu(O<sub>2</sub>CR<sup>2</sup>)<sub>2</sub>

(R<sup>2</sup> = Me, Pr<sup>n</sup>, n-C<sub>17</sub>H<sub>35</sub>, Ar).

The reaction products depend on the copper(II) salt used. In the case of halides, phosphates and dialkyl (or diaryl) phosphites are mainly formed, while in the case of sulfates or carboxylates, the reaction gives trialkyl (or triaryl) phosphites.<sup>200</sup>

Under an inert atmosphere, copper(II) compounds react with white phosphorus in arene–alcohol solutions and are reduced to copper(I) salts or copper metal, which, in turn, can be oxidised by air oxygen to divalent copper.

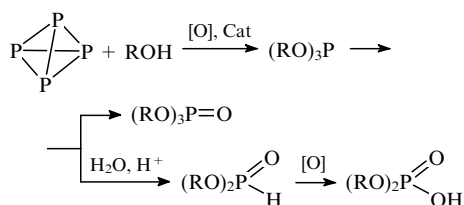
Copper(II) complexes exhibit high catalytic activities in the oxidative coupling of  $P_4$  with primary and secondary amines<sup>201,202</sup> to give phosphazeno compounds. Amines react with  $P_4$  one or two orders of magnitude faster than alcohols. Under an argon atmosphere, white phosphorus reduces Cu(II) to Cu(0).



$R^1 = H$ ;  $R^2 = Et, Cy, PhCH_2$ ;  $R^1 = R^2 = Et, Cy, PhCH_2$ .

The reactions of red phosphorus with alcohols in the presence of copper(II) salts afford trialkyl phosphates and dialkyl phosphates.<sup>202–205</sup> The process is carried out either under an inert gas or in the presence of atmospheric oxygen. In the latter case, oxygen and red phosphorus are consumed only by the formation of organic phosphates, whose yields based on the reactants are ~100%. The oxidative P–O coupling of red phosphorus with glycols in dioxane results in linear and cyclic alkylene phosphates.

Subsequently, other procedures for oxidative alkoxylation of white phosphorus have been proposed.<sup>206</sup> In these reactions, a co-oxidant and a catalyst are used in addition to the oxidant (oxygen or  $NaBrO_3$ ).



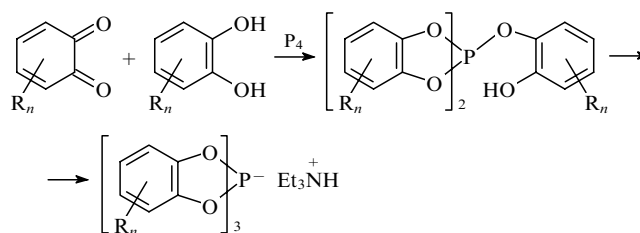
$[O] = O_2, NaBrO_3 + \text{co-oxidant} (CuCl_2, NaNO_2, FeCl_3, C_6H_4O_2)$ ;  
Cat =  $PdCl_2, Ru(OH)Cl_3, RuCl_3 \cdot 6 H_2O$ .

The oxidation of elemental phosphorus with oxygen in the presence of organic compounds yields a number of derivatives. In a study of the oxidation mechanism of white phosphorus in the presence of phenol in water, 17 reaction products have been detected, phosphonic acids being the major components.<sup>206,207</sup> In some cases, the researchers were able to attain selectivity in the formation of particular compounds. For example, white phosphorus is rapidly and selectively oxidised by air oxygen to give trialkyl phosphate from benzene–alcohol mixtures in the presence of iodine and sodium nitrite at 20–60 °C.<sup>208</sup>

Slow oxidation of white phosphorus with oxygen in ethylenediamine results in ethylenediammonium monophosphate  $[H_3NCH_2CH_2NH_3]^+[PHO_3]^-$  (see Ref. 209).

Benzoquinones can be used as oxidants in the synthesis of phosphoranes. For example, phosphoranes  $P(O_2C_6R)_2X$  ( $R = Cl_4, Br_4, Bu^t_2H_2$ ;  $X = Br, SePh$ ) were formed as the major products in the reaction of white phosphorus with *o*-benzoquinones, performed in the presence of bromine or diphenyl diselenide.<sup>210</sup> Studies of these reactions by EPR spectroscopy showed the presence of *o*-semiquinone radicals. Exposure to UV radiation

or thermolysis of a mixture of white phosphorus and substituted *o*-benzoquinone in the presence of catechol derivatives also yielded phosphoranes.<sup>211</sup>



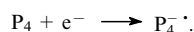
$R_n = H, 3,5-Bu^t_2, 3,6-Bu^t_2, 3,4,5,6-Cl_4, 4-Ph_3C$ .

The addition of anhydrous copper(II) chloride substantially accelerates this reaction and increases the yield of phosphoranes to 40%–60%; copper(II) being reduced to copper(I).

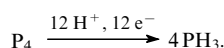
#### IV. Electrochemical methods for the synthesis of organophosphorus compounds from elemental phosphorus

Studies of the electrochemical behaviour of white phosphorus and the scope of applicability of electrochemistry for the synthesis of OPCs are in their infancy; therefore, the number of relevant papers is relatively small. The major contribution to the development of this line of chemistry was made by the Russian scientific groups headed by A P Tomilov and Yu M Kargin.

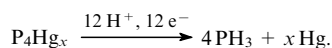
It has been shown<sup>212</sup> that electrochemical reduction of white phosphorus in an aprotic medium at a mercury dropping electrode is irreversible (half-wave potential  $E_{1/2} = -1.55$  V vs. mercury pool in DMF). The calculated number of accepted electrons depends on the concentration of  $P_4$ . It was suggested that the first stage of reduction is a one-electron transfer to give a radical anion:



In the presence of active proton donors, which rapidly protonate the intermediate anions, all P–P bonds in the white phosphorus molecule are cleaved to give phosphine.

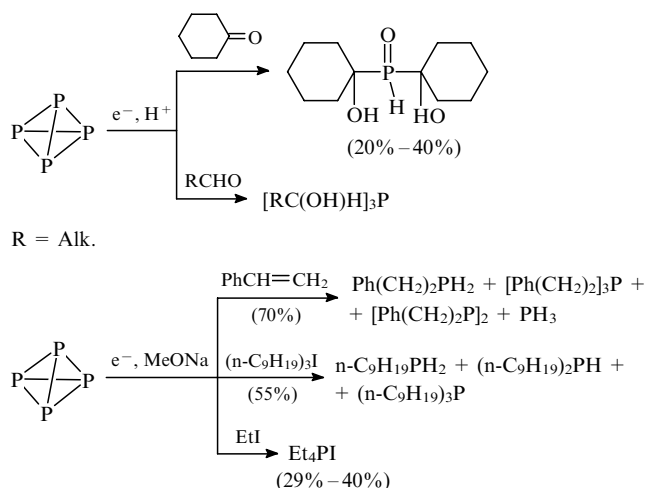


In alcohol solutions, white phosphorus is reduced *via* the intermediate chemisorbed product  $P_4/(Hg)_x$ .<sup>213</sup>



The electrochemical hydrogenation of white phosphorus is of practical interest as a method for the synthesis of phosphine. This process has been studied in detail using a lead cathode.<sup>214,215</sup> The results of the study initiated an important field of OPC electro-synthesis, namely reduction of white phosphorus in a proton-donating medium at a cathode with high hydrogen overvoltage (a mercury or lead cathode). The process consists of a number of successive steps giving highly reactive phosphorus hydrides of type  $(PH)_x$  (see Ref. 214). The final phosphine and intermediate phosphorus hydrides can react with various compounds that have been added to the electrolyte and are electrochemically inactive in the potential region of the working electrodes; these include alkenes,<sup>216</sup> carbonyl compounds,<sup>217,218</sup> alkyl halides<sup>219</sup> and so on. These reactions yield mixtures of phosphines or individual phosphine oxides. Lower alkyl halides react with  $P_4$  to give quaternary phosphonium salts.





The electrolysis of an emulsion of  $P_4$  in DMF in the presence of *n*-butyl bromide<sup>220</sup> furnishes a complex mixture of organic phosphines and phosphine oxides with an overall yield of 29%. At the cathode, hydrogen is apparently evolved and phosphorus and  $Bu^+Br$  are reduced.

In the above reactions, a substantial portion of elemental phosphorus polymerises and alkylation proceeds only partially (by 20%–50%). The low yields and the complex compositions of the mixtures hamper the separation and purification of the products.

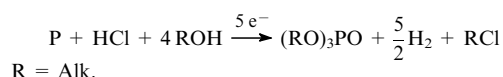
Electrochemical reduction of red phosphorus in alkaline solutions has been proposed for the synthesis of phosphine. It was found<sup>221</sup> that 15%–25% solutions of NaOH and a temperature range of 70–100 °C were the conditions of choice for the synthesis of  $PH_3$ . In more concentrated solutions, phosphorous and hypophosphorous acids were mainly formed. When a lead cathode was used, the yield of phosphine varied from 60% to 83%.<sup>221</sup>

The electrochemical oxidation of white phosphorus supported on porous conductive substrates in neutral or acidic media results in phosphoric and phosphorous acids.<sup>222</sup> It has been suggested that the reaction is accompanied by oxidation of phosphine formed upon disproportionation of white phosphorus.

In aqueous solutions of hydrogen halides<sup>223, 224</sup> (in some cases, with the addition of the organic solvents, benzene or chloroform<sup>224</sup>), indirect electrochemical oxidation of white phosphorus to phosphorous acid takes place. Apparently, in the first stage, phosphorus is oxidised by the elemental halogen evolved at the anode; this gives phosphorus halides, which are hydrolysed to give  $H_3PO_3$ .

The synthesis of phosphorous and hypophosphorous acids was performed by electrolysis of a suspension of red phosphorus in the presence of organic bases, ethylenediamine and triethylamine.<sup>224</sup> The influence of a number of parameters on the yield and product ratio, which depend on the amount of electricity passed, was studied. The process was intensive only at a temperature of > 70 °C, the degree of conversion of phosphorus being 40%–45%.

Of interest from both theoretical and practical standpoints was a study of the anodic oxidation of a suspension of red phosphorus in alcohols in the presence of hydrogen chloride.<sup>225</sup> In these experiments, electrolysis was carried out in an undivided cell; hydrogen being evolved at the cathode, and trialkyl phosphate and alkyl chloride at the anode. The process can be represented as follows:

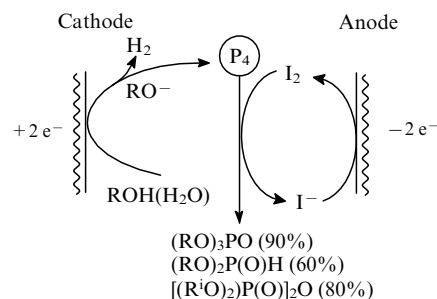


Chlorine evolved at the anode reacts with phosphorus and alcohol, giving the final products in 40%–70% yields. This

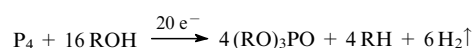
method is applicable only to primary aliphatic alcohols in an excess of hydrogen chloride; in other cases, the anodic process appears to yield compounds that cannot be isolated or identified.

An electrochemical procedure for the synthesis of OPCs from white phosphorus in an undivided cell was developed in the USA.<sup>226, 227</sup> The process is carried out in solutions of alcohols, phenols or mercaptans in the presence of nitrates, bicarbonates, *etc.* as the supporting electrolytes, and using either a mercury<sup>226</sup> or ferrophosphorus anode.<sup>227</sup> Hydrogen is evolved at the cathode, and the metal cation formed upon anode dissolution serves as the oxidant. However, the yields of triorganyl phosphates are relatively low (45%–50%). In addition, this method is environmentally unsafe due to its use of large amounts of mercury. No data on the mechanism of formation of the products have been reported in the publications cited.

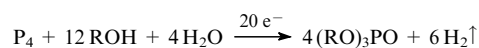
In recent years, new approaches to the synthesis of OPCs have been developed. They combine the advantages of conventional (homogeneous) chemistry in solution with electrochemistry, in which the reagents are generated at the electrodes directly in the reaction system.<sup>228–241</sup>



The following processes occur in an undivided cell: the formation of nucleophiles (alkoxide, hydroxide, phenoxide, amide or other anion) at the cathode and oxidation of halide ions (*e.g.*, iodide to iodine) at the anode.<sup>228–238, 240–243</sup> The halogen, together with the nucleophile, reacts with the  $P_4$  molecule to give various phosphorus compounds depending on the conditions of electrolysis. The general pattern of electrosynthesis of trialkyl phosphate from white phosphorus in anhydrous alcohol is as follows:



In the presence of water, optimal conditions are ensured and the yield of trialkyl phosphate becomes nearly quantitative.<sup>231, 233, 235–238</sup>



The proposed method for the electrosynthesis of trialkyl phosphates is almost waste-free. By varying the electrolysis conditions, the process can be directed towards the formation of other products, for example, tetraalkyl pyrophosphates.<sup>230, 232, 236–238</sup> The yield of these products depends on the structure of the aliphatic alcohol and the reactant ratio. In the case of linear aliphatic alcohols, a mixture of trialkyl phosphate and tetraalkyl pyrophosphate in ~2:3 ratio is formed, while the use of branched alcohols results in a similar mixture, but in a 1:9 ratio.

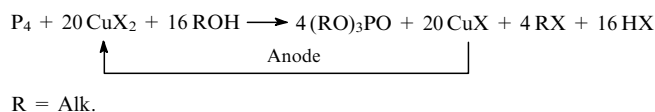
These studies provided an understanding of the mechanism of transformation of white phosphorus during the electrolysis of its solutions in aqueous alcohols in the presence of  $Et_4NI$ , and also made it possible to control this complex process. In the systems in question, cathodically generated nucleophile initiates the opening of the phosphorus rings, while halogen resulting from oxidation of the halide ion facilitates the replacement of the proton of the P–H bond. The halogen is regenerated during the electrolysis, and thus the cycle is completed. Owing to the high selectivity and rate of

these processes, phosphorus can be transformed into organophosphorus compounds with a high degree of conversion. Varying of the pH of the alcohol- and water-containing electrolyte can result in a substantial change in the composition of the cathodically generated species and, hence, in the routes of transformation of white phosphorus into target products.<sup>236, 237</sup> For example, in acidic solutions, hydrogen ions are reduced at the cathode instead of alcohol; therefore, no opening of the phosphorus rings induced by nucleophiles (alkoxide ions) takes place. In addition, dealkylation of the esters of trivalent phosphorus acids readily occurs under these conditions. Indeed, electrolysis of aqueous alcohol solutions of HBr (or HI) over a broad concentration range in the presence of an emulsion of white phosphorus gives dialkyl phosphite as the major product (yield 70%).

It was found that anodically generated phenothiazine and triarylamine radical cations can be used to cleave P<sub>4</sub> in alcohol solutions.<sup>234</sup>

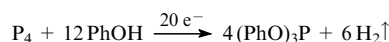
Thus, using the simple phosphorus–alcohol–water system as an example, a number of essential advantages of electrochemical methods over classical approaches of organic chemistry have been demonstrated. The use of electrochemistry allows one to synthesise OPCs from white phosphorus in high yields under mild conditions. This opens up the way to almost waste-free environmentally safe processes, allowing one to design a controlled chemical system in which the desired products can be obtained specifically by varying the conditions.

The oxidation of Cu(I) catalyst to Cu(II) during the preparation of trialkyl phosphates from white phosphorus,<sup>196–206</sup> considered above, can be carried out by an electrochemical process,<sup>239</sup> which would eliminate the explosion-prone oxidant O<sub>2</sub>. The important advantages of the electrochemical regeneration of the catalyst include a decrease in the number of components to the reaction system, the elimination of side reactions and an increase in the yield of the target products. Studies of the Cu–ROH–P<sub>4</sub> ternary system revealed an analogy with the behaviour of white phosphorus in the coordination sphere of copper or nickel. The redox properties of copper catalysts were found to change in the presence of white phosphorus: the Cu<sup>I</sup>/Cu<sup>0</sup> reduction wave shifting towards more positive potentials. The Cu<sup>I</sup>–P<sub>4</sub> complex is characterised by a smaller electrochemical gap, *i.e.*, it is more polarisable and reactive than the initial Cu(I) compound. The possibility of electrosynthesis of phosphorus-containing acid derivatives from P<sub>4</sub> and alcohol, promoted by copper(II) compounds which serve as charge transferring catalysts, was also demonstrated.

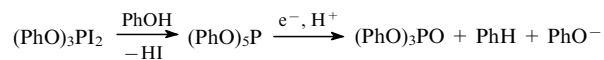


The use of electrochemical methods has extended the range of compounds that can be prepared directly from white phosphorus. For example, aromatic esters of phosphorus acids have been synthesised in good yields.<sup>237–242</sup> By varying the conditions of electrolysis, one can obtain either triaryl phosphites (by adding pyridine to the electrolyte) or triaryl phosphates in nearly quantitative yields.

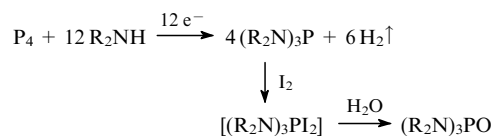
A study<sup>237, 240</sup> of the decomposition routes of white phosphorus during the electrolysis of phenol solutions of Et<sub>4</sub>Ni has confirmed the general rules of behaviour of P<sub>4</sub> molecule in alcohol media. Characteristic features of the subsequent transformations of the organophosphorus intermediates were also elucidated. It was found that rupture of all the P–P bonds in phosphorus oligomers produced the phosphite (PhO)<sub>3</sub>P. It was the first product formed in the reaction of white phosphorus with nucleophilic and electrophilic reagents generated at the electrodes.



It was shown experimentally for the first time<sup>237, 240</sup> that pentaphenoxyphosphorane formed at intermediate stages of the process undergoes cathodic reduction to triphenyl phosphite. This accounts for the quantitative transformation of triphenyl phosphite into the corresponding phosphate.

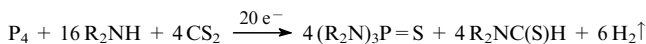


This accumulated experience has been used to develop a procedure for the electrosynthesis of phosphorotriamidates and thiophosphorotriamidates from white phosphorus under the action of amide anions R<sub>2</sub>N<sup>−</sup>, generated by the reduction of amines at the cathode with a low hydrogen overvoltage.<sup>237, 242, 243</sup> The electrolysis of amine in the presence of an emulsion of white phosphorus gave the corresponding phosphorotriamidate; the yields in DMF (62%) were substantially higher than those in acetonitrile (12%). Presumably, phosphorotriamidate is formed by hydrolysis of the intermediate triamidoiodophosphoranes.<sup>237, 243</sup>



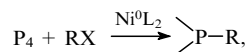
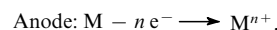
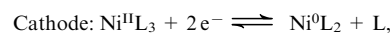
R = Alk.

Yet another route of transformation of (R<sub>2</sub>N)<sub>3</sub>P formed initially has been accomplished by conducting the electrolysis in the presence of carbon disulfide. This compound acts as a sulfur donor, the reaction yielding thiophosphorotriamidate (R<sub>2</sub>N)<sub>3</sub>P=S (major product) and thioformamide (minor product).<sup>237, 243</sup>



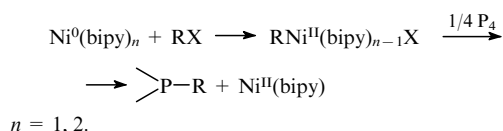
The methods described above are based on the combined treatment of white phosphorus with nucleophilic and electrophilic reagents in an undivided cell. In these reactions, one can obtain only esters or amides of phosphorus acids but not compounds with P–C bonds.

In recent years, a new efficient method for the selective electrosynthesis of compounds with P–C bonds from white phosphorus, using metal complexes as catalysts, has been developed.<sup>244–249</sup> The activation of white phosphorus followed by rupturing of the P–P bonds takes place in a system that ensures cyclic regeneration of the catalyst at an electrode. It was shown that by treatment with organic halides in the presence of electrochemically generated catalysts, namely Ni(0) complexes with 2,2'-bipyridine (bipy) ligands, white phosphorus can be converted into organic phosphines and phosphine oxides. The process scheme is as follows:<sup>246–249</sup>

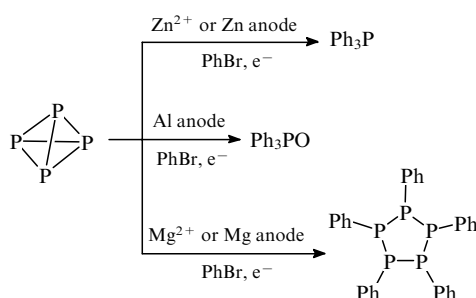


*n* = 2, 3; M = Mg, Zn, Al; L = bipy, Ph<sub>3</sub>P.

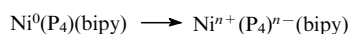
The electrocatalytic arylation of white phosphorus has been studied using preparative electrolysis and cyclic voltammetry.<sup>246–248</sup> Some stages of the catalytic cycle were simulated and studied separately. Cathodically generated Ni(0) complexes were found to react with organic halides to give nickel organyl-σ-complexes, which are involved in the functionalisation of white phosphorus. The reaction of organonickel compound, RNi<sup>II</sup>XL<sub>*m*</sub> with white phosphorus is the key step of the process.



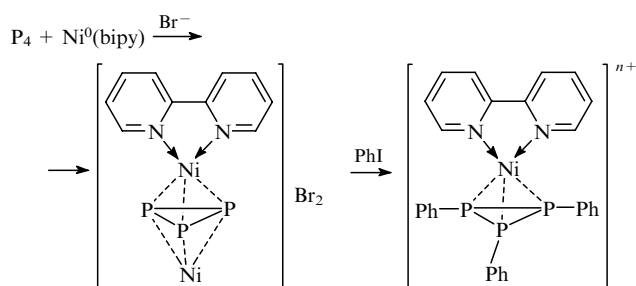
The reaction route and the yields of the final products of the electrochemical phosphorylation of organic halides with white phosphorus are considerably affected by the sacrificial anode material. The use of a zinc anode results in the synthesis of three-coordinate phosphorus compounds, triorganylphosphines, an aluminium anode stipulates the formation of triorganylphosphine oxides, and the presence of Mg(II) ions in the reaction mixture ensures the transformation of P<sub>4</sub> into cyclic polyphosphines (PhP)<sub>5</sub>.



To elucidate the pathways leading to the formation of P—C bonds, an attempt has been made to cleave the white phosphorus molecule directly using Ni(II) and Ni(0) complexes.<sup>246–248</sup> Metal-coordinated white phosphorus becomes a stronger electron acceptor and is more readily reduced on treatment with Ni(0) complexes. A voltammetric study of the behaviour of Ni(II) complexes with bipyridine in the presence of white phosphorus has shown that the latter forms a more stable complex with Ni(0) than with Ni(II). The process irreversibility and the shift of the potential from the equilibrium value to less negative values are due to the subsequent fast chemical reduction of the P<sub>4</sub> molecule with the Ni<sup>0</sup> complex.

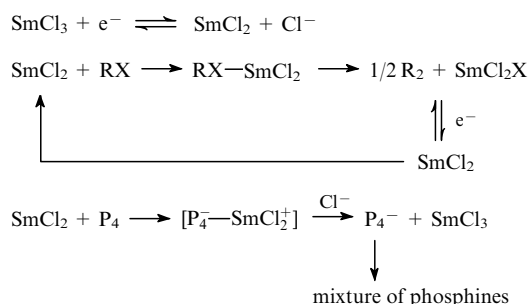


It was found that Ni<sup>0</sup>(bipy) reacts with white phosphorus to give a binuclear complex with a cyclo-P<sub>3</sub> fragment. The arylation of the phosphorus fragment with aromatic halides results in a mononuclear complex with Ph<sub>3</sub>P<sub>3</sub> ligand.



Among the numerous catalysts of OPC electrosynthesis, primary attention is attracted by samarium(II) derivatives, which possess strong reducing properties.<sup>243</sup> Electrochemical generation of these compounds from stable samarium(III) salts, in the presence of an emulsion containing a mixture of white phosphorus and iodobenzene, gives rise to products containing phosphorus—carbon bonds. If the hydrate SmCl<sub>3</sub> · 5 H<sub>2</sub>O is used, a mixture of phosphines, PhPH<sub>2</sub>, Ph<sub>2</sub>PH and Ph<sub>3</sub>P, is formed predominantly, together with the phosphonium salt Ph<sub>4</sub>PI. The anhydrous salt SmCl<sub>3</sub> catalyses the predominant formation of PhPI<sub>2</sub>; some Ph<sub>4</sub>PI

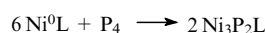
was also isolated as a minor product.<sup>244</sup> The following scheme for the catalytic process was proposed:



Different routes for the activation of white phosphorus in the coordination sphere of nickel complexes, depending on the nature of the ligands, have been considered.<sup>250</sup> The first route is based on coordination of the P<sub>4</sub> molecule to the metal, resulting in a deformation of the tetrahedron without its destruction. This is the case with the NiX<sub>2</sub>L complexes [where X = BF<sub>4</sub>, Br, Cl; L = bipy (the solvents are DMF, MeCN, acetone); L = 2,9-dimethyl-1,10-phenanthroline (phen) or PPh<sub>3</sub> (the solvents are DMF or acetone)], which are reduced at the most negative potentials, |E<sub>red</sub>| > -0.9 V. To cleave the P—P bonds in the complex formed, its electrochemical reduction is required.

The second route is oxidation of white phosphorus in the coordination sphere of a Ni(II) complex. This method is used when the NiX<sub>2</sub>L complex exhibits relatively strong oxidative properties and is reduced readily (|E<sub>red</sub>| < -0.9 V). When X = BF<sub>4</sub> and L = triphos, the reaction is carried out in acetone; for L = 1,1',5,5'-bis[methylenedi(*p*-phenylene)]di(3,7-diphenyl-1,5-diaza-3,7-diphosphacyclooctane) (n<sup>2</sup>p<sup>2</sup>), the reaction is carried out in DMF; for L = phen or PPh<sub>3</sub>, the process is conducted in MeCN. In these cases, cleavage of the P<sub>4</sub> molecule affords a new Ni(I) complex, containing a P<sub>3</sub> fragment, for example, [(triphos)-Ni(P<sub>3</sub>)Ni(triphos)](BF<sub>4</sub>)<sub>2</sub>.

The reduction of white phosphorus in the coordination sphere of the electrochemically produced nickel(0) complex with a σ-donor ligand results in previously unknown nickel phosphides.



L = bipy, phen.

A relatively high reactivity of these complexes, compared to the known nickel phosphides, has been demonstrated.<sup>251</sup>

To conclude this Section, it should be noted that electrochemical methods can be successfully used to synthesise a wide range of compounds containing P—O, P—N, P—C and P—S bonds from white phosphorus. These reactions usually proceed under mild conditions, at high rates and with high selectivities, providing a good base for consideration at an industrial level.

\* \* \*

The information on the chemical properties of elemental phosphorus considered in this review is indicative of the keen attention given by researchers to this line of investigation, situated at the junction of different fields of chemistry. This is reflected in numerous publications on the subject. An important reason for this interest is the demand for new highly effective industrial processes for the production, direct from white phosphorus, of organophosphorus compounds which possess diverse useful properties. These compounds have found extensive use in various fields of human activity. Study of the chemical behaviour of white phosphorus with respect to transition metal complexes is the most convenient technique for investigation of the mechanisms of cleavage of the P<sub>4</sub> molecule and the stabilisation of the phosphorus-containing intermediates thus formed.

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# Metal complex catalysis in the synthesis of organomagnesium compounds

U M Dzhemilev, A G Ibragimov

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**Abstract.** The published data on the synthesis of organomagnesium compounds assisted by metal complex catalysts are generalised and described systematically for the first time. Hydro-, carbo- and cyclomagnesiation reactions of unsaturated compounds with  $R^1MgR^2$  ( $R^1 = \text{Alk, Ar; } R^2 = \text{H, Hal; } R^1 = R^2 = \text{Alk}$ ) catalysed by Ti, Zr and other transition metal salts and complexes are considered. Selected examples of applications of organomagnesium reagents to organic synthesis are given. The bibliography includes 206 references.

## I. Introduction

The first organomagnesium compounds (hereinafter, OMC) were synthesised by Grignard<sup>1</sup> in 1900 by a reaction of organic halides with metallic magnesium. This simple and efficient method for the synthesis of OMC is still widely employed in synthetic practice. The Grignard reagents are used to create new C–C bonds for the syntheses of various classes of organic compounds. The preparation of OMC by this method and their applications have been subjects of numerous publications. The results reported have been summarised in a number of monographs.<sup>2–10</sup> It is evident that further progress regarding this classical method for the synthesis of OMC should primarily rely on the involvement of more complex halide-containing systems in the reaction with metallic magnesium.

The elaboration of a novel non-traditional approach to the synthesis of organomagnesium reagents from unsaturated compounds and ordinary Grignard reagents under conditions of metal complex catalysis is a sound achievement of modern organometallic chemistry. These include catalytic hydro-, carbo- and cyclomagnesiation with  $R^1MgR^2$  ( $R^1 = \text{Alk, Ar; } R^2 = \text{H, Hal; } R^1 = R^2 = \text{Alk}$ ). Owing to the high reactivity and availability of

starting magnesium-containing reagents, the applicability to the synthesis of organomagnesium compounds with diverse structures and the mild conditions of these catalytic reactions, they hold much promise in organic and organometallic synthesis.

Presently, a large body of information on the formation of OMC in the presence of metal complex catalysts and various types of promoters has been collected (for instance, see reviews<sup>11–15</sup>). The authors of the present review have also contributed to the emergence and maturation of the chemistry of organometallic compounds. The aim of the present review is to summarise the published results concerning catalytic synthesis of OMC and analyse the most promising avenues in the further development of this field of research. Applications of OMC to organic synthesis are illustrated with selected examples only. Furthermore, numerous publications on the use of organomagnesium derivatives as co-catalysts in the oligo- and polymerisation of unsaturated compounds are also beyond the scope of the review.

## II. Hydromagnesiation of $\alpha$ -alkenes

The interaction of magnesium hydrides or alkylmagnesium halides with unsaturated compounds (alkenes, dienes or alkynes) catalysed by Ti, Zr and other transition metal salts and complexes is a convenient synthetic route to diverse OMC. The diversity of unsaturated compounds and the availability of starting reagents make it possible to prepare various uncommon OMC, which can be hard to synthesise by the traditional Grignard method.

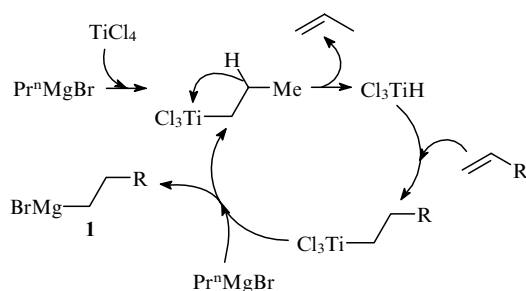
Catalytic hydromagnesiation of  $\alpha$ -alkenes with  $Pr^nMgBr$  in the presence of titanium compounds was first reported by Finkbeiner and Cooper in 1961.<sup>16</sup> They found that different terminal alkenes could be converted into the respective organomagnesium derivatives **1** in the presence of 3 mol.%  $TiCl_4$  in yields of 20%–50% with evolution of an equimolar amount of propylene. The latter is indirect evidence of the generation, under the reaction conditions, of titanium hydrides, which are responsible for the subsequent hydrometallation of the starting alkenes.

U M Dzhemilev, A G Ibragimov Institute of Petrochemistry and Catalysis, Russian Academy of Sciences, prosp. Oktyabrya 141, 450075 Ufa, Russian Federation. Fax/tel. (7-3472) 31 27 50, e-mail: ink@anrb.ru

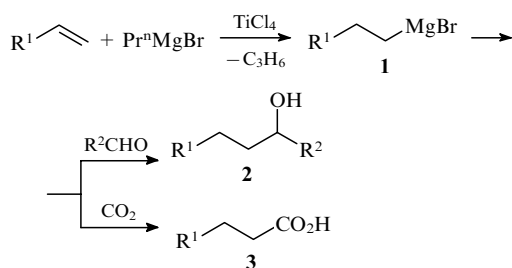
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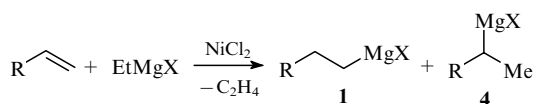


The thus prepared organomagnesium compounds **1** react with aldehydes or carbon dioxide to yield the respective alcohols **2** or carboxylic acids **3**.



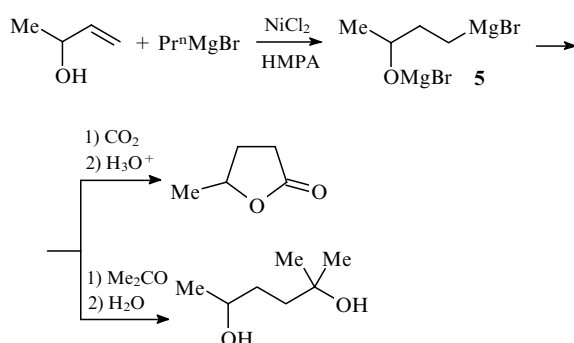
$R^1 = \text{Alk, cyclo-C}_6\text{H}_{11} \text{ (Cy), Bn; } R^2 = \text{H, Me.}$

In addition to  $TiCl_4$ , such compounds as  $Ti(OPr^i)_4$ ,  $Cp_2TiCl_2$  ( $Cp$  is cyclopentadienyl),  $ZrCl_4$ ,  $VCl_4$  (see Refs 17, 18) can also be used as catalysts for this reaction. In contrast to Ti-containing catalytic systems, nickel complexes are less selective in the reaction of  $\alpha$ -alkenes with  $RMgX$ . In particular, both primary (compounds **1**) and secondary (compounds **4**) OMC are formed in the presence of a catalytic amount of  $NiCl_2$ , their ratio being dependent on the structures of the starting alkenes and the nature of the hydrometallation agents.<sup>19, 20</sup>

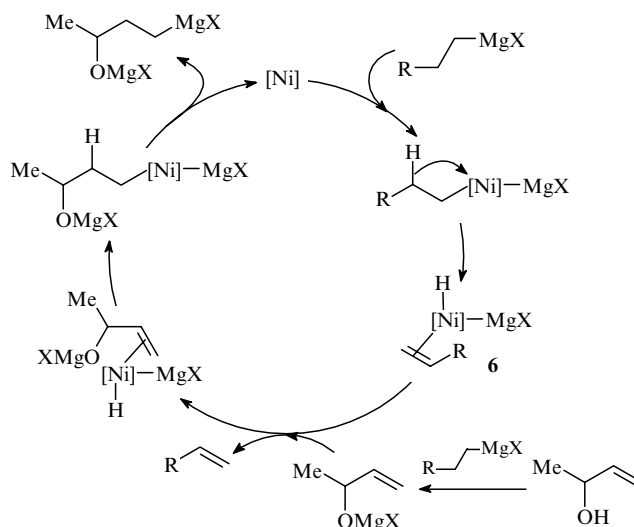


$R = \text{Alk; } X = \text{Br, Cl.}$

Meanwhile,  $NiCl_2$ -catalysed hydromagnesiation of allylic alcohols with *n*-propylmagnesium bromide yields the primary products selectively. An organomagnesium compound **5** prepared by this method further reacted with  $CO_2$  and acetone.<sup>21</sup>

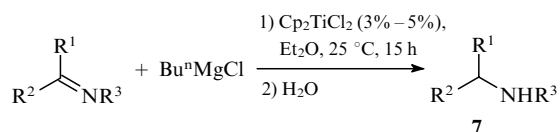


Presumably, the generation of nickel hydride complexes **6**, responsible for the hydrometallation of the starting allylic alcohols, is the key step in the synthesis of the OMC **5**. The catalytic cycle can be represented as follows.



$Cp_2TiCl_2$ -catalysed hydromagnesiation reactions of  $\alpha$ -alkenes were studied<sup>22</sup> using a variety of organomagnesium reagents ( $EtMgCl$ ,  $EtMgBr$ ,  $Pr^nMgCl$ ,  $Pr^iMgBr$ ,  $Bu^nMgCl$ ,  $Bu^iMgCl$ ,  $Bu^iMgBr$ ,  $Bu^iMgI$ ,  $Et_2Mg$ ,  $Pr_2^iMg$ ,  $Pr_2^iMg$ ,  $Bu_2^iMg$ ,  $Bu_2^iMg$ ,  $Bu_2^iMg$ ). Higher homologues of the OMC were obtained in satisfactory yields.

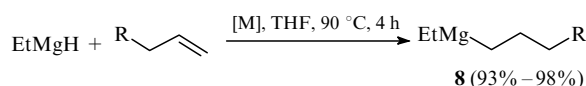
In addition to alkenes,<sup>22</sup> hydrometallation of imines was accomplished under the action of  $Bu^nMgCl$  (1.2 equiv.) and a catalytic amount of  $Cp_2TiCl_2$  under mild conditions ( $Et_2O$ ,  $25^\circ C$ , 15 h). Magnesium amides are formed in this reaction, and their subsequent hydrolysis yielded the corresponding secondary amines **7**.<sup>23</sup>



$R^1 = \text{H, Me, Et, Pr}^i; R^2 = \text{Et, Pr}^i, \text{Ph; } R^3 = \text{Pr}^n, \text{Pr}^i, \text{Bu}^i, \text{Bn.}$

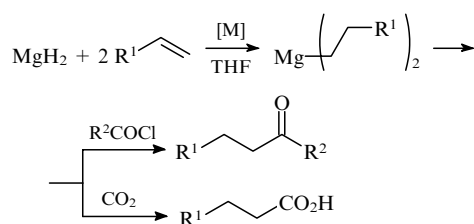
An efficient method for the hydrogenation of alkenes with hydrogen ( $p = 1 \text{ atm}$ ) using a two-component catalyst  $Cp_2TiCl_2-Pr^iMgBr$  ( $[Ti]:[Mg]:[alkene] = 1:6:50$ ,  $20^\circ C$ , 5 h), which afforded the corresponding alkanes in a nearly quantitative yield, was proposed.<sup>24</sup>

Organomagnesium hydrides  $RMgH$  ( $R = \text{H, Hal, Alk}$ ) are employed in the hydromagnesiation of alkenes. Magnesium hydride generated *in situ* from  $Mg$  and  $H_2$  adds to ethylene, isobutylene and oct-1-ene to afford the corresponding dialkylmagnesium compounds in yields 4%–13%. Meanwhile, the reaction of terminal and 1,1(or 1,2)-disubstituted alkenes with  $MgH_2$  in the presence of a catalytic amount of  $Cp_2TiCl_2$  in THF at a molar ratio alkene: $MgH_2$ : $[Ti]$  of 2:1:0.05 under mild conditions (from 20 to  $60^\circ C$ ) affords the alkylmagnesium derivatives in high yields.<sup>25</sup> A system  $CrCl_3-[Mg-\text{anthracene}]$  (1:1) in THF has been recommended as a promoter for the synthesis of magnesium hydride complexes ( $HMgCl \cdot MgH_2$  or  $2HMgCl \cdot MgH_2$ ).<sup>26, 27</sup> Organomagnesium compounds **8** are prepared in nearly quantitative yield upon hydromagnesiation of  $\alpha$ -alkenes with  $EtMgH$  in the presence of Ni- or Zr-containing catalysts.<sup>28</sup>



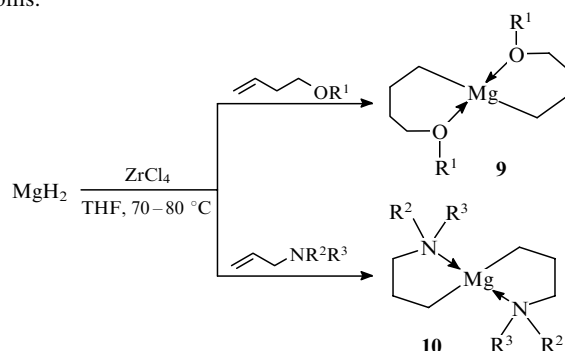
$R = \text{Alk; } [M] = NiCl_2, Cp_2ZrCl_2.$

Bogdanović *et al.*<sup>29–31</sup> have employed catalysts based on Zr, Ti, Hf, Cr and Fe halides for the hydromagnesiation of alkenes with magnesium hydride. The OMC obtained were further converted into the corresponding ketones and carboxylic acids.



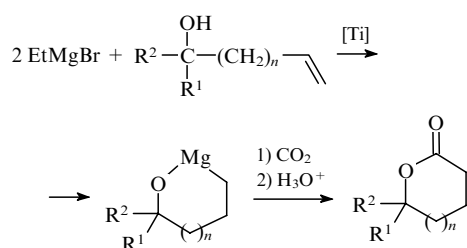
R<sup>1</sup> = H, Alk, cyclo-Alkenyl; [M] = ZrI<sub>4</sub>, ZrCl<sub>4</sub>, ZrBr<sub>4</sub>, TiCl<sub>4</sub>, Cp<sub>2</sub>TiCl<sub>2</sub>, HfCl<sub>4</sub>, CrCl<sub>3</sub>, FeCl<sub>2</sub>; R<sup>2</sup> = Alk.

Hydromagnesiation of ω-N(or O)-substituted α-alkenes with MgH<sub>2</sub> in the presence of ZrCl<sub>4</sub> yields magnesium-containing compounds **9** and **10** stabilised by intramolecular coordination of the nitrogen or oxygen atoms to the central magnesium atoms.<sup>32</sup>

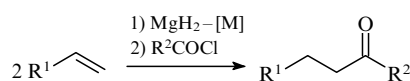
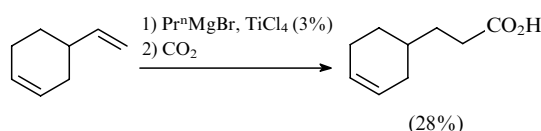


R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> = Alk.

Catalytic hydromagnesiation of α-alkenes followed by functionalisation of the resulting OMC involving the reactive Mg–C bond has been successfully used in the synthesis of steroids,<sup>33</sup> alcohols,<sup>16, 18, 21</sup> γ- and δ-lactones,<sup>34</sup> ketones, carboxylic acids<sup>16, 31</sup> and other classes of organic compounds. Selected examples of these reactions are given below.



R<sup>1</sup>, R<sup>2</sup> = Alk; R<sup>1</sup>–R<sup>2</sup> = cyclo-Alk; n = 1, 2; [Ti] = Cp<sub>2</sub>TiCl<sub>2</sub>.

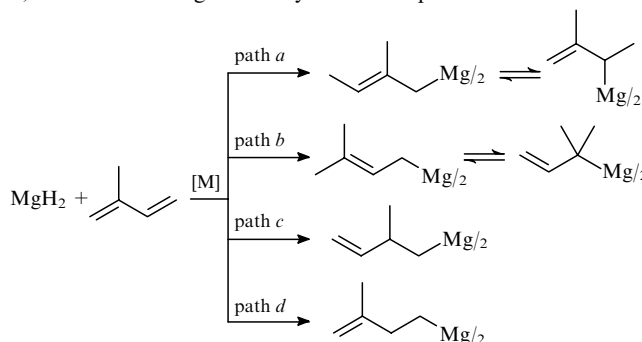


R<sup>1</sup> = H, Alk, Alkenyl; R<sup>2</sup> = Alk; [M] = TiCl<sub>4</sub>, ZrCl<sub>4</sub>, ZrI<sub>4</sub>.

### III. Hydromagnesiation of 1,3-dienes

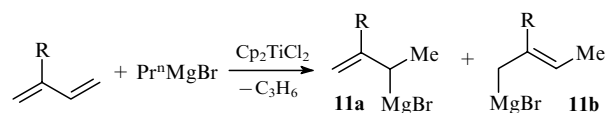
Hydromagnesiation of 1,3-dienes with magnesium hydrides is an efficient method for the synthesis of unsaturated OMC.<sup>35, 36</sup> As in the case of alkenes, Ti-containing catalysts, *viz.*, Cp<sub>2</sub>TiCl<sub>2</sub> and TiCl<sub>4</sub>, demonstrated the highest catalytic activities in this reac-

tion. With these catalysts, the conversion of the starting dienes is typically ~75%. On the other hand, the conversion of the diene did not exceed 30% and the process proceeded non-selectively with Cp<sub>2</sub>ZrCl<sub>2</sub>, ZrCl<sub>4</sub>, HfCl<sub>4</sub> and CrCl<sub>3</sub> as catalysts. This can be illustrated by catalytic reactions of isoprene with magnesium hydride, which can follow four alternative reaction pathways: 1,4-addition to form either the Mg–C(1) (path *a*) or Mg–C(4) (path *b*) bond, 1,2-addition to form either the Mg–C(1) (path *c*) or Mg–C(4) (path *d*) bond. The hydromagnesiation in the presence of Cp<sub>2</sub>TiCl<sub>2</sub>, Cp<sub>2</sub>ZrCl<sub>2</sub>, TiCl<sub>4</sub> or ZrCl<sub>4</sub> proceeds as the 1,4-addition of magnesium hydride to isoprene.<sup>35</sup>



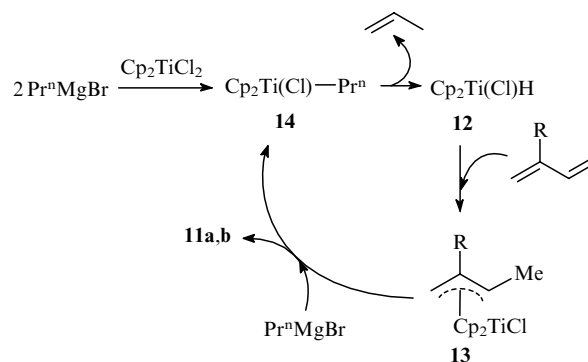
[M] = Cp<sub>2</sub>TiCl<sub>2</sub>, Cp<sub>2</sub>ZrCl<sub>2</sub>, TiCl<sub>4</sub>, ZrCl<sub>4</sub>.

Hydromagnesiation of 1,3-dienes (butadiene, isoprene or myrcene) or styrene with Pr<sup>n</sup>MgBr in the presence of a catalytic amount of Cp<sub>2</sub>TiCl<sub>2</sub> is the simplest and the most convenient method for the synthesis of unsaturated OMC.<sup>37</sup> These studies were preceded by investigations into the hydromagnesiation of α-alkenes with propylmagnesium bromide in the presence of TiCl<sub>4</sub>.<sup>16–18</sup> The attempted use of TiCl<sub>4</sub> as a catalyst for the hydromagnesiation of 1,3-dienes failed, whereas, in the presence of Cp<sub>2</sub>TiCl<sub>2</sub>, regioisomeric allylic OMC **11a,b** were successfully prepared from 2-substituted 1,3-dienes.<sup>37</sup> It is of note that such a reaction is unknown for 1-substituted 1,3-dienes.



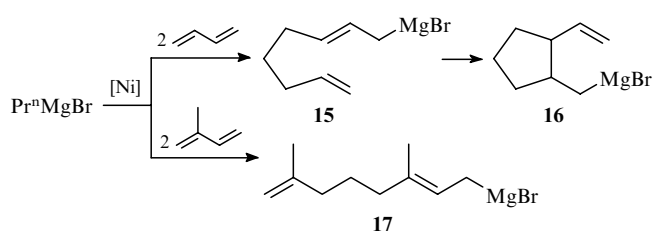
R = H, Me, (CH<sub>2</sub>)<sub>2</sub>CH = CMe<sub>2</sub>.

Sato *et al.* proposed<sup>37</sup> a mechanism of catalytic hydromagnesiation of 1,3-dienes, which implies that it is titanium organic hydrides **12** generated as a result of the reaction of Cp<sub>2</sub>TiCl<sub>2</sub> with Pr<sup>n</sup>MgBr that act as active hydrometallation intermediates in these reactions. They add to 1,3-dienes giving rise to allylic bis(cyclopentadienyl)titanium complexes **13**.<sup>38</sup> The latter undergo transmetalation by an excess of Pr<sup>n</sup>MgBr and are converted into regioisomeric allylmagnesium bromides **11a,b** with regeneration of catalytically active n-propyltitanium complexes **14**.



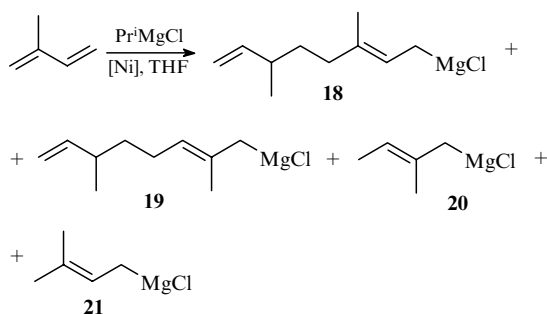
The hydromagnesiation pathway depends on both the nature of the catalyst and the structure of the starting 1,3-dienes. For instance, butadiene reacts with Pr<sup>n</sup>MgBr in the presence of a catalytic amount of Ni(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> to form octa-2,7-dienylmagne-

sium bromide (**15**), which undergoes intramolecular cyclisation into an organomagnesium compound **16**.<sup>39</sup> Isoprene reacts with  $\text{Pr}^n\text{MgBr}$  (an ethereal solution) to yield 3,7-dimethylocta-2,7-dienylmagnesium bromide (**17**).<sup>40</sup>



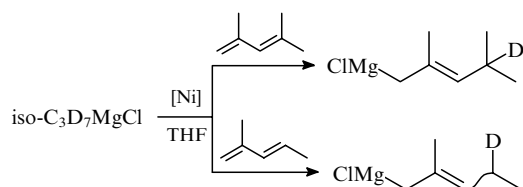
$[\text{Ni}] = \text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ .

Hydromagnesiation of 2-alkyl-1,3-dienes (isoprene, myrcene, 2-isopropylbuta-1,3-diene, 2-*tert*-butylbuta-1,3-diene) with  $\text{RMgX}$  ( $\text{R} = \text{Et}, \text{Pr}^n, \text{Pr}^i, \text{Bu}^i, \text{Bu}^s$ ;  $\text{X} = \text{Cl}, \text{Br}, \text{I}$ ) in the presence of nickel catalysts with phosphine oxide or nitrogen-containing ligands is less selective.<sup>41,42</sup> In this case, allylic-type isomers of monomeric organomagnesium compounds (**20** and **21**) are formed in addition to the regioisomeric dimeric hydromagnesiation products **18** and **19**.



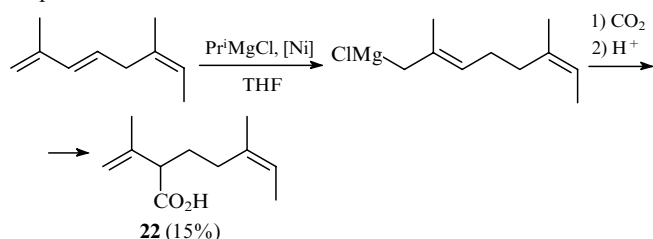
$[\text{Ni}] = \text{NiPy}_4\text{Cl}_2$ .

The use of pyridine nickel complexes as catalysts enabled the hydromagnesiation of 2-alkoxy- (see Ref. 43), 1-alkylbuta-1,3-dienes<sup>44,45</sup> and of di- and poly-alkylbuta-1,3-dienes,<sup>46</sup> which could not be effected using  $\text{Cp}_2\text{TiCl}_2$ .<sup>37</sup>



$[\text{Ni}] = \text{NiPy}_4\text{Cl}_2$ .

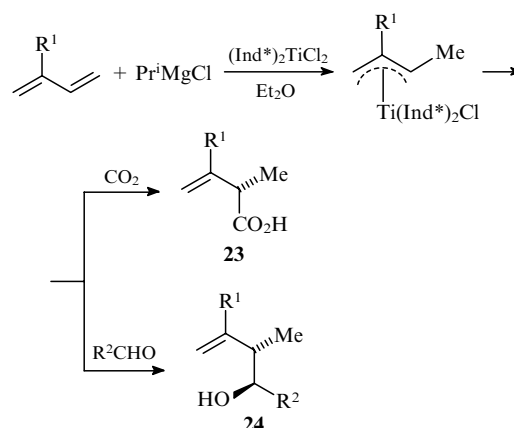
An efficient method for the synthesis of isoprenoid carboxylic acids **22** using Grignard reagents was developed.<sup>46–48</sup> It is based on the reaction of allylic OMC, generated *in situ* by the hydromagnesiation of substituted 1,3-dienes, with  $\text{CO}_2$ . If carbonyl compounds are used instead of carbon dioxide, the corresponding isoprenoid alcohols are formed.<sup>46–48</sup>



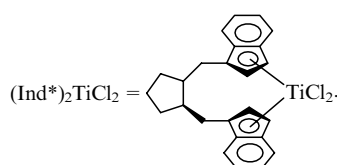
$[\text{Ni}] = \text{NiPy}_4\text{Cl}_2$ .

Hydrometallation of 2-alkylbutadienes with  $\text{Pr}^i\text{MgCl}$  catalysed by a chiral indenyl titanium complex afforded allylic

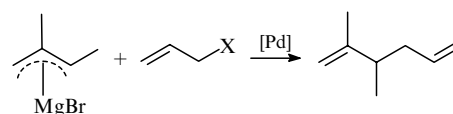
titanium complexes; their treatment with  $\text{CO}_2$  or aldehydes represents a convenient method for the synthesis of optically active  $\beta, \gamma$ -unsaturated carboxylic acids **23** or *threo*-homoallylic alcohols **24** with high enantiomeric purity (96%).<sup>49</sup>



$\text{R}^1 = n\text{-C}_9\text{H}_{19}$ ,  $\text{Me}_2\text{C} = \text{CH}(\text{CH}_2)_3$ ;  $\text{R}^2 = \text{Et}, \text{Pr}^i, \text{Bu}^i, \text{Ph}$ ;

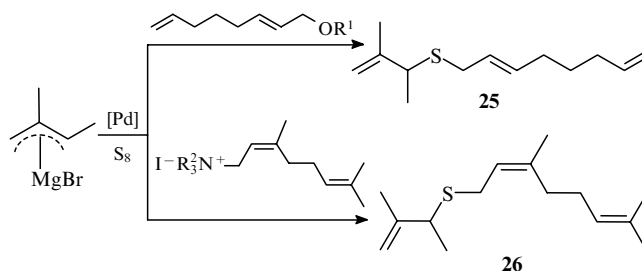


Cross-coupling of N-, O- and S-functionalised allylic compounds with dienyilmagnesium reagents catalysed by transition metal complexes results in unsaturated hydrocarbons with the isoprenoid structure in high yields.<sup>50</sup>



$\text{X} = \text{OAlk}, \text{OAr}, \text{OAc}, \text{SAlk}, \text{SO}_2\text{Alk}, \text{Alk}_3\text{N}^+\text{Hal}^-$ .

An analogous scheme was used for the synthesis of polyene sulfides **25** and **26**.<sup>51</sup> In this case, a sulfur atom (from the  $\text{S}_8$  molecule) is inserted at the  $\text{Mg}-\text{C}$  bond simultaneously with the interaction of the 'isoprenemagnesium' reagent with the allylic electrophiles.



$\text{R}^1 = \text{Me}, \text{Et}, \text{Ph}$ ;  $\text{R}^2 = \text{Me}, \text{Et}$ .

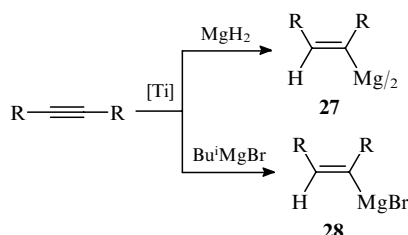
The corresponding thioesters are formed if  $\text{CS}_2$  is used in this reaction.<sup>51</sup>

Synthesis and transformations of such OMC of the non-Grignard type prepared from 1,3-dienes and highly active metallic Mg are reviewed in more detail elsewhere.<sup>13</sup>

#### IV. Hydromagnesiation of alkynes

The catalytic hydromagnesiation of alkynes with magnesium hydrides or alkylmagnesium halides in the presence of Ti complexes affords vinylic organomagnesium compounds. The direction and selectivity of this reaction depend on the nature of the

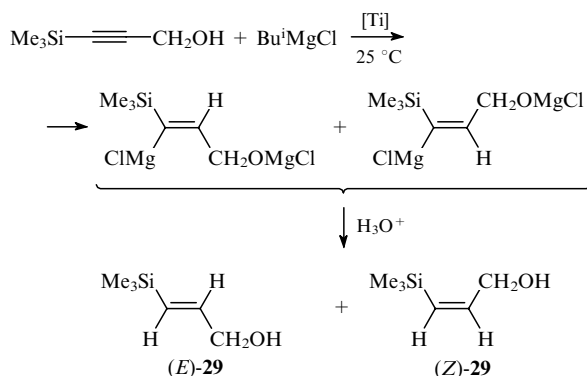
catalyst, the structure of the starting alkyne and the hydromagnesiation reagent used. Hydromagnesiation of symmetrical disubstituted acetylenes with  $\text{MgH}_2$ ,<sup>25</sup>  $\text{MgH}_2 \cdot \text{CuI}$ ,  $\text{MgH}_2 \cdot \text{CuOBu}^t$  (see Ref. 52) or  $\text{Bu}^i\text{MgHal}$  ( $\text{Hal} = \text{Cl}, \text{Br}$ )<sup>11,53</sup> in the presence of a catalytic amount of  $\text{Cp}_2\text{TiCl}_2$  yields alkenylmagnesium compounds **27** or **28** with *E*-double bonds.



$\text{R} = \text{Alk}, \text{Ph}$ ;  $[\text{Ti}] = \text{Cp}_2\text{TiCl}_2$ .

Hydromagnesiation of non-symmetrical dialkylacetylenes affords two regioisomeric alkenylmagnesium halides in nearly equal proportions. The hydromagnesiation of alkylarylacetylenes<sup>53</sup> and alkyl(trimethylsilyl)acetylenes<sup>54–59</sup> is more selective. In ether at 20 °C, the magnesium atom is preferably (>95%) attached to the carbon atom bearing the phenyl or silyl substituents.<sup>60</sup>

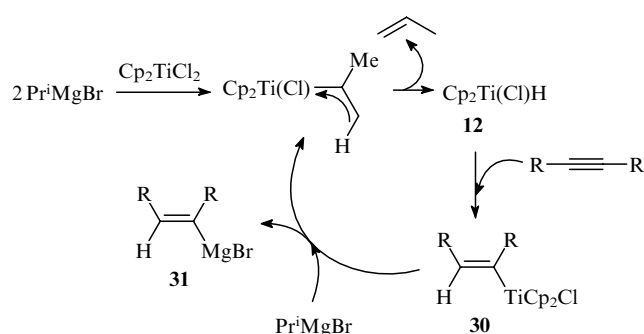
Hydromagnesiation of 3-trimethylsilylprop-2-yn-1-ol with  $\text{Bu}^i\text{MgCl}$  in the presence of  $\text{Cp}_2\text{TiCl}_2$  (the ratio  $[\text{alkyne}]:[\text{Mg}]:[\text{Ti}] = 1:2.4:0.08$ ; 25 °C, 6 h) followed by hydrolysis of the reaction mixture affords stereoisomeric alcohols **29** in a total yield of 98%, *E*:*Z* = 95:5.<sup>61</sup>



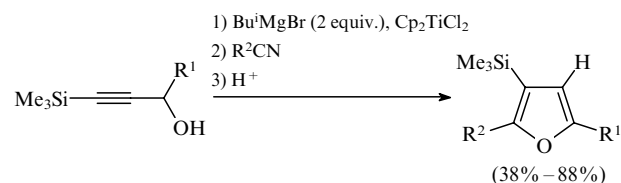
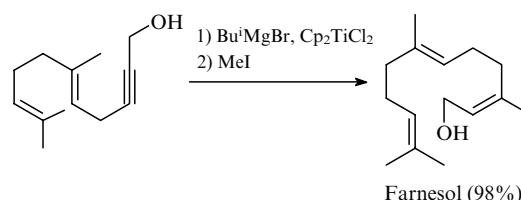
$[\text{Ti}] = \text{Cp}_2\text{TiCl}_2$ .

$\text{Cp}_2\text{TiCl}_2$ -catalysed hydromagnesiation of disubstituted acetylenes with organomagnesium compounds of the type  $\text{R}^1\text{MgR}^2$  was studied by Dzhemilev *et al.*<sup>62</sup> It was shown that reagents containing cyclic and allylic substituents are less reactive than  $\text{Alk}_2\text{Mg}$ , whereas OMC with tertiary and vinylic substituents are virtually inert in this reaction.

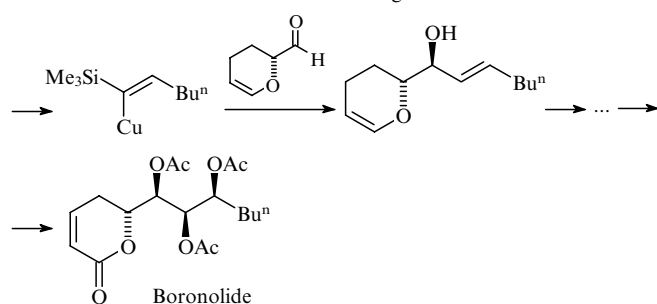
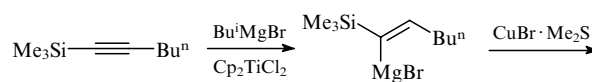
The mechanism of the hydromagnesiation of disubstituted acetylenes with Grignard reagents in the presence of Ti complexes implies the generation of reactive titanium hydrides **12** under the reaction conditions. These intermediates hydrometallate the starting alkynes to form alkenyltitanium complexes **30**. This step determines the regio- and stereoselectivities of the formation of the target products: in the case of symmetrical alkynes, the transmetalation of complexes **30** with  $\text{AlkMgX}$  yields *E*-alkenylmagnesium halides **31**.<sup>60</sup> The regioselectivity of the addition of the titanium hydride complex **12** to non-symmetrical disubstituted acetylenes is governed by the nature of substituents that determine the electron density on the carbon atoms of the  $\text{C}\equiv\text{C}$  bond.



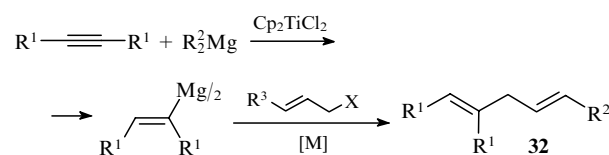
Vinylic organomagnesium compounds synthesised by the hydromagnesiation of disubstituted acetylenes are used in the selective synthesis of *Z*- (see Refs 25, 62, 63) and *E*-alkenes,<sup>64</sup> terpenoids,<sup>65</sup> *E*-allylic alcohols,<sup>66</sup> *Z*- $\alpha,\beta$ -unsaturated ketones,<sup>67</sup> substituted furans,<sup>68,69</sup> different biologically active compounds and fragrances.<sup>55,70–73</sup> Selected examples of the use of this reaction for the preparation of compounds with valuable properties are given below.



$\text{R}^1 = \text{H}, \text{Pr}^n; \text{R}^2 = \text{Me}, \text{Et}, \text{Pr}^i, \text{Ph}$ .

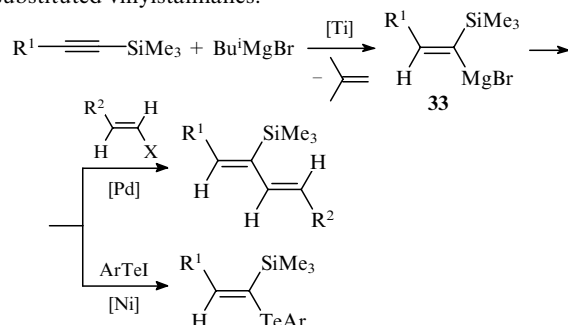


Cross-coupling of vinylic OMC with allylic ethers, sulfones, sulfides and quaternary ammonium salts catalysed by Pd, Ni and Cu complexes yields 1,4-dienes **32** with a trisubstituted double bond in the *E* configuration.<sup>74</sup>



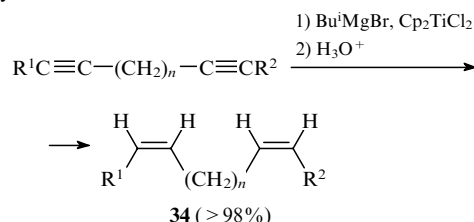
$\text{R}^1 = \text{Et}, \text{Pr}^n; \text{R}^2 = \text{Pr}^n, \text{Pr}^i, \text{Bu}^n, \text{Bu}^i; \text{R}^3 = \text{H}, (\text{CH}_2)_3\text{CH} = \text{CH}_2$ ;  
 $\text{X} = \text{OR}^4, \text{SR}^4, \text{SO}_2\text{R}^4$  ( $\text{R}^4 = \text{Et}, \text{Alk}, \text{Ph}$ ),  $\text{Et}_3\text{N}^+$ ;  $[\text{M}] = \text{Pd}, \text{Ni}, \text{Cu}$ .

Hydromagnesiation of alkynylsilanes with  $\text{Bu}^i\text{MgBr}$  catalysed by  $\text{Cp}_2\text{TiCl}_2$  (5 mol.%) followed by cross-coupling of the vinylic organomagnesium compounds **33** generated *in situ* with vinyl-, aryltellurenyl or trialkylstannyl halides represents a method for the stereoselective synthesis of 1,3-dienylsilanes,<sup>75</sup> (*E*)- $\alpha$ -aryltellurenylvinylsilanes,<sup>76</sup> (*E*)- $\alpha$ -silylvinylstannanes<sup>77</sup> and (*E*)-1,2-disubstituted vinylstannanes.<sup>78</sup>



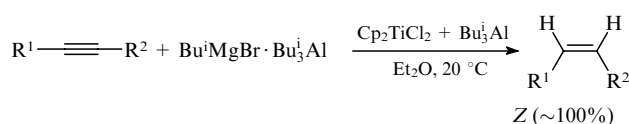
$\text{R}^1, \text{R}^2 = \text{Alk}$ ;  $\text{X} = \text{Br}, \text{I}$ ;  $\text{Ar} = \text{Ph}, 4\text{-ClC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4$ ;  
 $[\text{Ti}] = \text{Cp}_2\text{TiCl}_2$ ,  $[\text{Pd}] = \text{Pd}(\text{PPh}_3)_4$ ;  $[\text{Ni}] = \text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ .

Diynes with the triple bonds separated by hydrocarbon bridges react with  $\text{Bu}^i\text{MgBr}$  with high regio- and stereoselectivities to yield *Z*-alkenes **34**.<sup>79</sup>



$\text{R}^1, \text{R}^2 = \text{Alk}$ ;  $n = 1-4$ .

A mixed reagent  $\text{Bu}^i\text{MgBr} \cdot \text{Bu}_3^i\text{Al}$  also provides highly stereoselective hydromagnesiation of alkynes.<sup>79</sup>



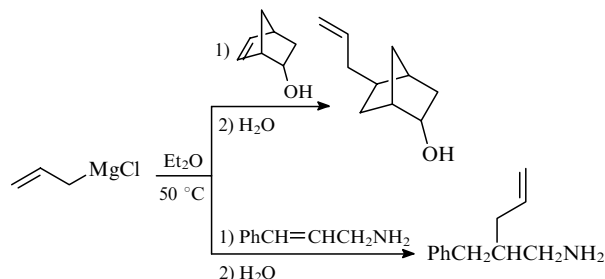
$\text{R}^1, \text{R}^2 = \text{Alk}$ .

Thus, the hydromagnesiation of disubstituted acetylenes with magnesium hydrides and alkylmagnesium halides catalysed by titanium complexes represents an efficient method for the stereoselective conversion of alkynes into *Z*-alkenes.

## V. Carbomagnesiation of alkenes

In 1978, Negishi *et al.*<sup>80</sup> suggested the term 'carbometallation' for the reaction of 1,2-addition of organometallic reagents to unsaturated compounds; later on, this term became commonly adopted.<sup>81-84</sup>

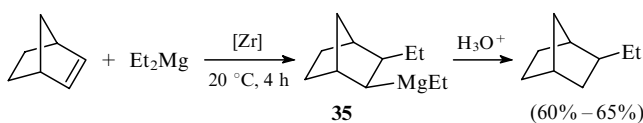
It is known<sup>81,85,86</sup> that only alkenes with activated double bonds, such as bicyclo[2.2.1]hept-5-en-2-ol or (*E*)-3-phenylallylamine, can be involved in the reaction of thermal carbomagnesiation with allylmagnesium halides.



Catalysts based on titanium and other transition metal chlorides ( $\text{NiCl}_2$  or  $\text{CoCl}_2$ ) enabled catalytic carbomagnesiation of  $\alpha$ -alkenes devoid of activated double bonds with Grignard reagents.<sup>19,20,87</sup> However, due to low regio- and stereoselectivities, these catalysts have not found wide application.

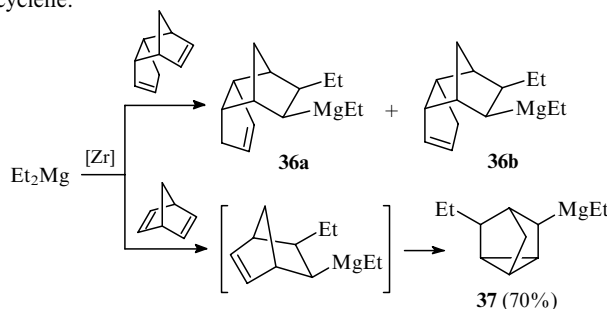
In 1983, the authors of the present review accomplished for the first time regioselective carbomagnesiation of  $\alpha$ -alkenes with non-activated double bonds. High yields of products were obtained with  $\text{Et}_2\text{Mg}$  or  $\text{EtMgBr}$  in the presence of a catalytic amount of  $\text{Cp}_2\text{ZrCl}_2$ .<sup>88</sup> This reaction, referred to as 'catalytic ethylmagnesiation', is applicable to diverse alkenes.<sup>88-91</sup>

In particular, bicyclo[2.2.1]hept-2-ene reacts with an equimolar amount of  $\text{Et}_2\text{Mg}$  in the presence of a catalytic amount of  $\text{Cp}_2\text{ZrCl}_2$  ( $\text{Et}_2\text{O}$ , 20 °C, 4 h) to form compound **35**, which was further hydrolysed to yield 2-*exo*-ethylbicyclo[2.2.1]heptane.



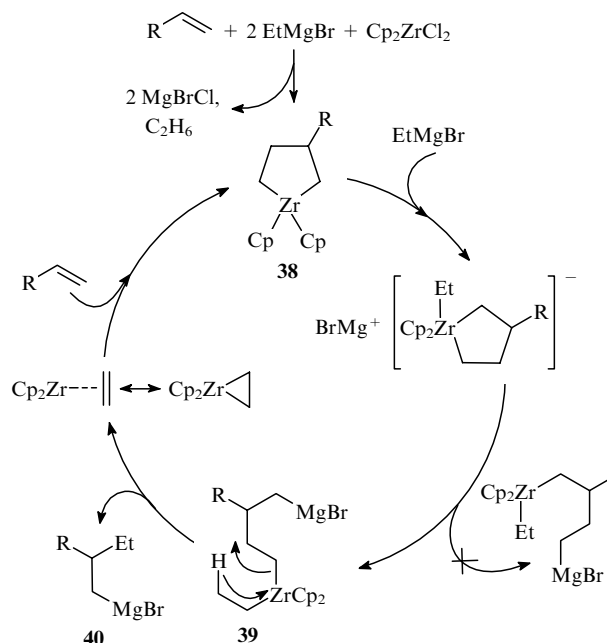
$[\text{Zr}] = \text{Cp}_2\text{ZrCl}_2$ .

The reaction of  $\text{Et}_2\text{Mg}$  with *endo*-tricyclo[5.2.1.0<sup>2,6</sup>]deca-3,8-diene ( $\text{Et}_2\text{O}$ , 20 °C,  $\text{Cp}_2\text{ZrCl}_2$  as a catalyst) affords a mixture of regioisomeric OMC **36a,b** differing in the position of the ethyl group relative to the double bond in a total yield 60%, the ratio of the isomers being ~1 : 1. Under the same conditions, the organomagnesium compound **37** is obtained from bicyclo[2.2.1]hepta-2,5-diene and  $\text{Et}_2\text{Mg}$ , and its hydrolysis resulted in 3-ethylnor-tricyclene.<sup>90</sup>



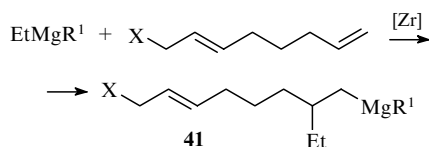
$[\text{Zr}] = \text{Cp}_2\text{ZrCl}_2$ .

A tentative mechanism of the ethylmagnesiation reaction of alkenes with  $\text{EtMgBr}$  in the presence of  $\text{Cp}_2\text{ZrCl}_2$  as a catalyst proposed by Negishi and Takahashi implies consecutive forma-



tion of a zirconacyclopentadiene intermediate **38** and a bimetallic complex **39**, which is finally converted into the target OMC **40**.<sup>92–95</sup>

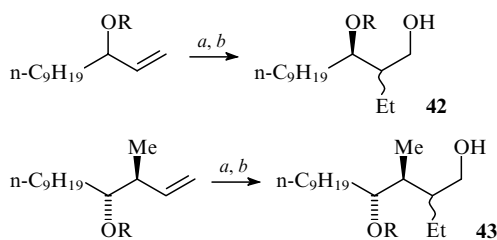
Various N-, O- and S-containing alkenes served as the substrates in the ethylmagnesiation reaction.<sup>91,96–121</sup> Ethylmagnesiation of octa-2,7-dienyl ethers and octa-2,7-dienylamines with EtMgR (R = Br, Et) catalysed by Cp<sub>2</sub>ZrCl<sub>2</sub> involves the terminal double bond to yield the corresponding O- and N-functionalised OMC **41**.



R<sup>1</sup> = Br, Et; X = OR<sup>2</sup>, SR<sup>2</sup> (R<sup>2</sup> = Me, Et, Bu<sup>n</sup>), NEt<sub>2</sub>; [Zr] = Cp<sub>2</sub>ZrCl<sub>2</sub>.

Reagents of the type EtMgOR, EtMgSR, EtMgOC(O)R, and EtMgC≡CR (R = Alk) appeared inert in ethylmagnesiation of α-alkenes catalysed by Cp<sub>2</sub>ZrCl<sub>2</sub>.<sup>91</sup>

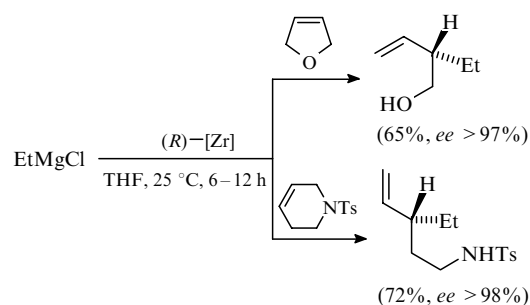
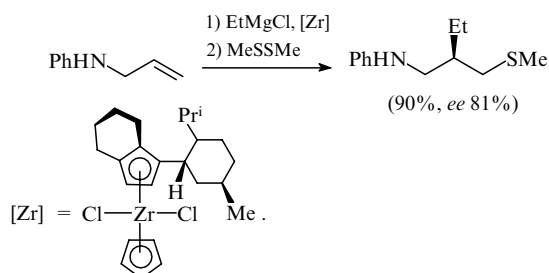
Ethylmagnesiation of allylic and homoallylic alcohols and ethers with an excess of EtMgCl in the presence of Cp<sub>2</sub>ZrCl<sub>2</sub> has been studied by Hoveyda *et al.*<sup>96–99</sup> This reaction was highly stereoselective and afforded β-ethyl-substituted organomagnesium compounds in high yields. The structures of these OMC were established by an analysis of their oxidation products, **42** and **43**. Presumably, the high stereoselectivity of ethylmagnesiation is due to the coordination of the heteroatom of the starting unsaturated compound to the central metal atom of the catalyst.



(a) EtMgCl (4 equiv.), Cp<sub>2</sub>ZrCl<sub>2</sub> (5%), Et<sub>2</sub>O, 25 °C, 12 h;  
(b) B(OMe)<sub>3</sub>, H<sub>2</sub>O<sub>2</sub>, –78 °C.

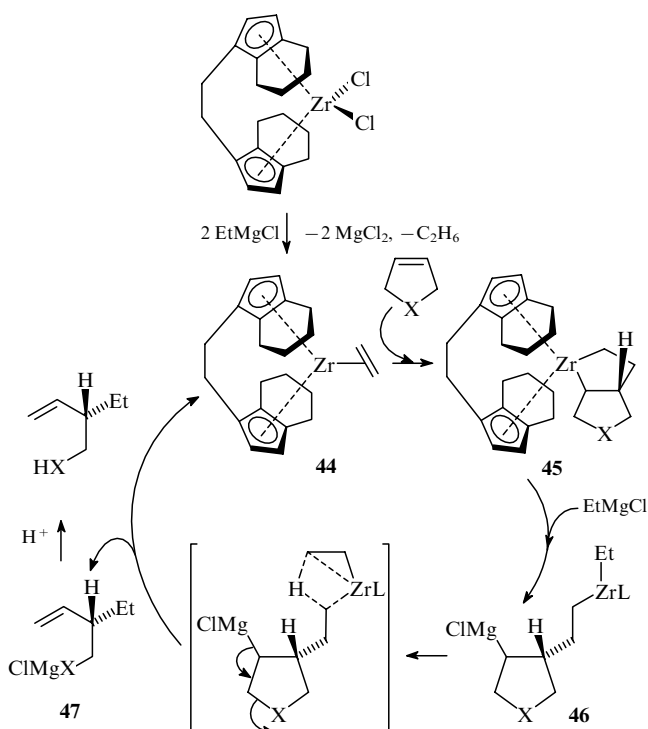
| R  | The ratio <i>anti</i> : <i>syn</i> |           | Yield (%) |           |
|----|------------------------------------|-----------|-----------|-----------|
|    | <b>42</b>                          | <b>43</b> | <b>42</b> | <b>43</b> |
| H  | 5 : 95                             | > 99 : 1  | 70        | 75        |
| Me | 89 : 11                            | 97 : 3    | 80        | 65        |

Asymmetric ethylmagnesiation of α-alkenes, non-cyclic and cyclic allylic alcohols, ethers and amines<sup>100–117</sup> in the presence of Zr-containing catalysts is highly diastereo- and enantioselective. The enantioselective formation of C–C bonds catalysed by chiral Zr and Ti complexes has been reviewed elsewhere.<sup>110–113</sup> Selected representative examples of such asymmetric syntheses are given below.



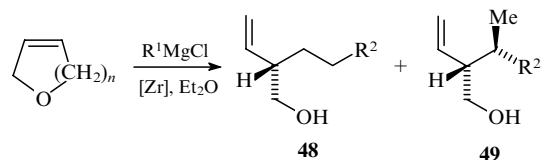
[Zr] is ethylene-1,2-bis(η<sup>5</sup>-4,5,6,7-tetrahydro-1-indenyl)zirconium dichloride.

A tentative mechanism of the catalytic reaction of EtMgCl with cyclic allylic ethers and amines involves the enantioselective addition of the starting unsaturated compound to the complex **44** to form a zirconacyclopentadiene intermediate **45**.<sup>104</sup> The regio-controlled opening of the zirconacyclopentadiene fragment with EtMgCl results in a sterically less hindered complex **46**, intramolecular rearrangement of which results in a γ-ethyl-substituted α-alkene **47**.



X = O, NC<sub>9</sub>H<sub>19–n</sub>; L is 1,2-bis(η<sup>5</sup>-4,5,6,7-tetrahydro-1-indenyl)ethylene.

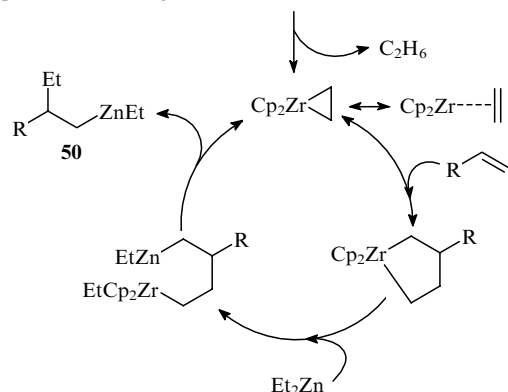
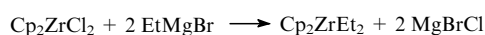
The enantioselective alkylation of cyclic allylic ethers or acyclic homoallylic alcohols (or ethers) with Pr<sup>n</sup>MgCl or Bu<sup>n</sup>MgCl in the presence of a catalytic amount of Cp<sub>2</sub>ZrCl<sub>2</sub> affords γ-substituted terminal alkenes as isomers with primary (compounds **48**) and secondary (compounds **49**) alkyl groups. The regioselectivity of the reaction depends on the structure of the starting reagents and temperature.<sup>121,122</sup> Typically, ether is used as a solvent, since tetrahydrofuran provides lower selectivities and yields of the products.



[Zr] = Cp<sub>2</sub>ZrCl<sub>2</sub>.

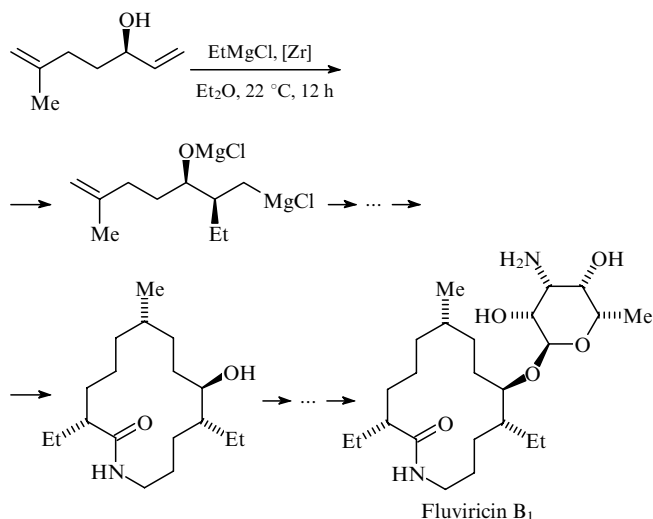
| <i>n</i> | R <sup>1</sup>  | R <sup>2</sup> | Temperature / °C | Ratio<br><b>49:48</b> | <i>ee</i> (%) |
|----------|-----------------|----------------|------------------|-----------------------|---------------|
| 1        | Pr <sup>n</sup> | Me             | 22               | 2:1                   | 99            |
| 1        | Bu <sup>n</sup> | Et             | 20               | 2:1                   | > 99          |
|          |                 |                | 70               | 15:1                  | > 90          |
| 2        | Pr <sup>n</sup> | Me             | 22               | > 25:1                | 98            |

In analogy with ethylmagnesiation,<sup>88</sup>  $\alpha$ -alkenes were successfully ethylzincated<sup>123</sup> with Et<sub>2</sub>Zn catalysed by Et<sub>2</sub>ZrCp<sub>2</sub>. The latter was generated from Cp<sub>2</sub>ZrCl<sub>2</sub> and EtMgBr. As a result, a series of organozinc compounds **50** have been obtained.



R = Alk.

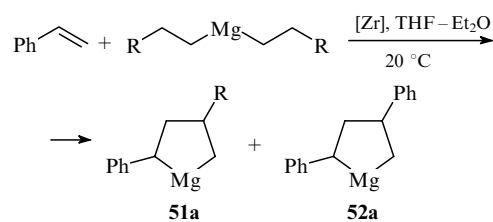
Ethylmagnesiation reaction of alkenes catalysed by Zr complexes is widely applied in the synthesis of biologically active compounds,<sup>109, 118–120, 124</sup> such as the natural antibiotic fluviricin B<sub>1</sub> (see Ref. 118).



## VI. Cyclomagnesiation of alkenes and allenes

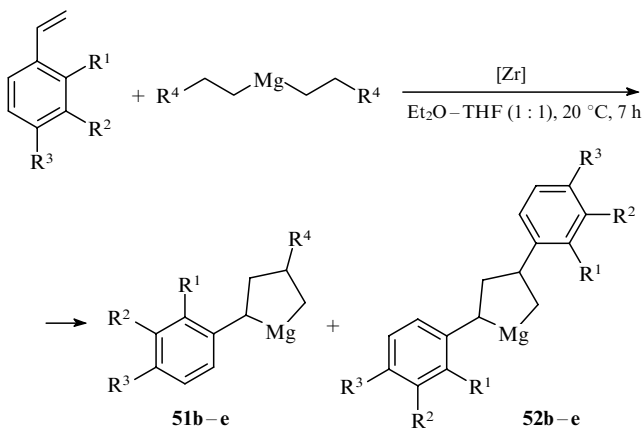
Based on the results of investigations<sup>125, 126</sup> into the catalytic cycloaluminum of alkenes with trialkyl- or alkylhaloalanes to give aluminacyclopentanes, the first cyclomagnesiation of alkenes with R<sub>2</sub>Mg and Cp<sub>2</sub>ZrCl<sub>2</sub> as a catalyst was accomplished in 1989.<sup>127</sup> It was found that the reaction of styrene with Alk<sub>2</sub>Mg (Alk = Pr<sup>n</sup>, Bu<sup>n</sup>, n-C<sub>6</sub>H<sub>13</sub>) in the presence of a catalytic amount of Cp<sub>2</sub>ZrCl<sub>2</sub> in a mixture THF–Et<sub>2</sub>O afforded a mixture of 2,4-disubstituted magnesacyclopentanes **51a** and **52a** in a ratio ~ 1:3 (the total yield is ~ 80%<sup>†</sup>).<sup>127, 128</sup>

<sup>†</sup> Hereinafter, the yields of OMC are calculated based on the hydrolysis products of the reaction mixture.



R = Me, Et, Bu<sup>n</sup>; [Zr] = Cp<sub>2</sub>ZrCl<sub>2</sub>.

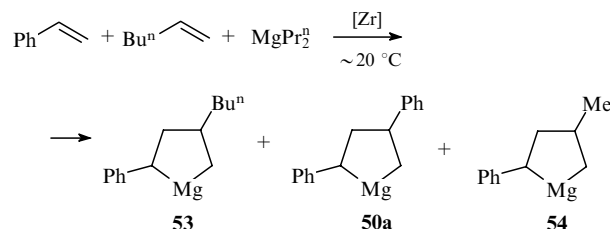
Ring-substituted styrenes (2-, 3- and 4-methyl-, 3-*tert*-butyl-) can also be cyclomagnesiated with R<sub>2</sub>Mg catalysed by Cp<sub>2</sub>ZrCl<sub>2</sub> to magnesacyclopentanes **51b–e** and **52b–e** (in a ratio of ~ 1:1) in yields of > 70%.<sup>129–131</sup>



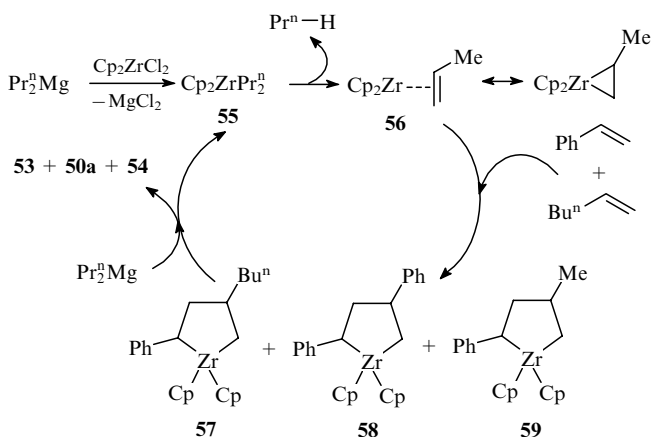
R<sup>1</sup> = Me, R<sup>2</sup> = R<sup>3</sup> = H (**b**); R<sup>2</sup> = Me, R<sup>1</sup> = R<sup>3</sup> = H (**c**);

R<sup>3</sup> = Me, R<sup>1</sup> = R<sup>2</sup> = H (**d**); R<sup>3</sup> = Bu<sup>t</sup>, R<sup>1</sup> = R<sup>2</sup> = H (**e**); R<sup>4</sup> = Me, Et.

Cyclomagnesiation of a mixture of styrene and hex-1-ene with Pr<sub>2</sub><sup>n</sup>Mg in the presence of Cp<sub>2</sub>ZrCl<sub>2</sub> as a catalyst in a mixture THF–Et<sub>2</sub>O resulted in 2,4-disubstituted magnesacyclopentanes **53:50a:54** in a ratio of ~ 35:35:30 in a total yield of 85%.<sup>132</sup>

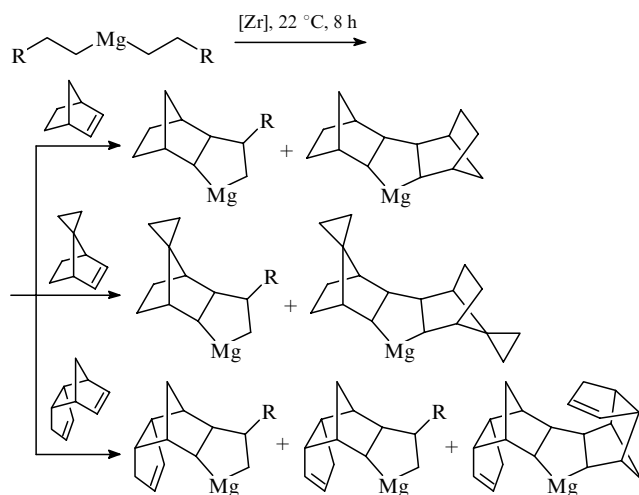


Based on the results obtained, a tentative mechanism of cyclomagnesiation of alkenes with di(n-propyl)magnesium catalysed by Cp<sub>2</sub>ZrCl<sub>2</sub> has been proposed.<sup>131</sup> It involved alkylation of Cp<sub>2</sub>ZrCl<sub>2</sub> to di(n-propyl)zirconocene **55**, intramolecular  $\beta$ -hydride transfer<sup>133</sup> with elimination of propane and formation



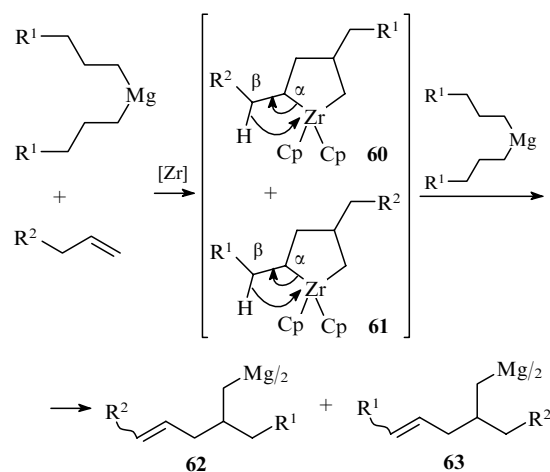
of a propylene–zirconocene intermediate **56**. The latter reacts with a mixture of alkenes affording 2,4-disubstituted zirconacyclopentanes **57–59**,<sup>134</sup> which react with the starting reagent ( $\text{Pr}_2^{\text{n}}\text{Mg}$ ) to give the corresponding 2,4-disubstituted magnesacyclopentanes **50a**, **53** and **54**.

Cyclomagnesiation of norbornenes with  $\text{Pr}_2^{\text{n}}\text{Mg}$  or  $\text{Bu}_2^{\text{n}}\text{Mg}$  catalysed by  $\text{Cp}_2\text{ZrCl}_2$  (3 mol.%) in THF– $\text{Et}_2\text{O}$  resulted in mixtures of polycyclic OMC in yields of 80%–95%.<sup>135</sup>



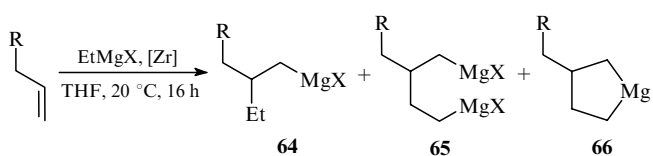
R = Me, Et.

Aliphatic  $\alpha$ -alkenes react with  $\text{Alk}_2\text{Mg}$  (Alk =  $\text{Pr}^{\text{n}}$ ,  $\text{n-C}_6\text{H}_{13}$ ,  $\text{n-C}_8\text{H}_{17}$ ) in the presence of  $\text{Cp}_2\text{ZrCl}_2$  to give predominantly acyclic unsaturated organomagnesium compounds.<sup>131, 136</sup> Presumably, intermediate 2,4-dialkyl-substituted zirconacyclopentanes **60** and **61** are formed under the reaction conditions, which undergo intramolecular  $\beta$ -hydride transfer under the action of the starting magnesium reagent and are converted into the isomeric acyclic unsaturated OMC **62** and **63**. It is of note that 2-arylzirconacyclopentanes **57–59** have no hydrogen atoms at the  $\beta$ -carbon atom and thus no transformations of this type with opening of the metallacycle take place.

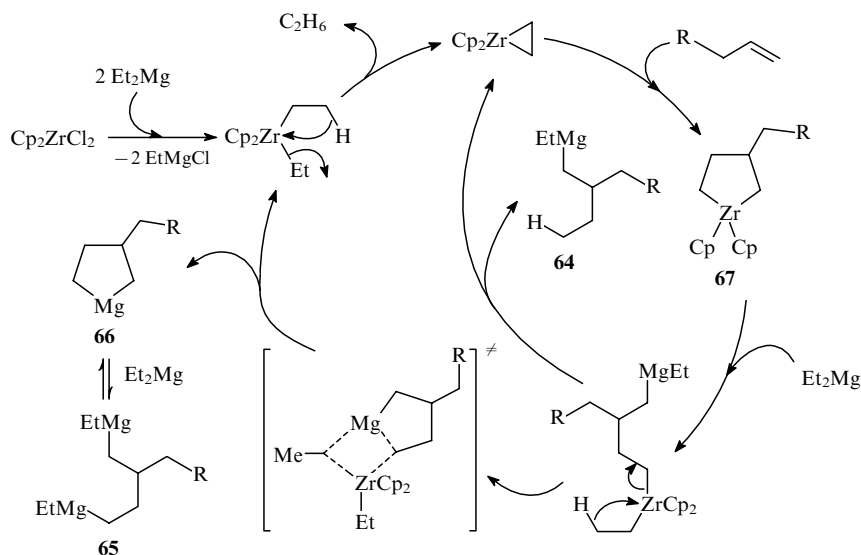


$\text{R}^1 = \text{H}, \text{Pr}^{\text{n}}, \text{n-C}_5\text{H}_{11}$ ;  $\text{R}^2 = \text{Alk}$ .

Unlike  $\text{Alk}_2\text{Mg}$  (Alk =  $\text{Pr}^{\text{n}}$ ,  $\text{Bu}^{\text{n}}$ ,  $\text{n-C}_6\text{H}_{13}$  or  $\text{n-C}_8\text{H}_{17}$ ), such magnesium reagents as  $\text{EtMgX}$  (X = Cl, Br) or  $\text{Et}_2\text{Mg}$  react with  $\alpha$ -alkenes in the presence of a catalytic amount of  $\text{Cp}_2\text{ZrCl}_2$  to yield ethylmagnesiation (**64**) or cyclomagnesiation products **65** and/or **66**, respectively (Scheme 1). The reaction pathway depends on the reaction conditions, *viz.*, the nature of the solvent, the temperature and the ratio of the starting reagents. For instance, ethylmagnesiation products are formed with high selectivity [the ratio **64**:(**65** + **66**) is 95:5] in THF (2 equiv. of  $\text{EtMgHal}$ ,  $\sim 20^\circ\text{C}$ , 16 h), whereas 1,4-dimagnesium compounds are predominantly formed [the ratio **64**:(**65** + **66**) is 15:85] in  $\text{Et}_2\text{O}$  with 4 equiv. of  $\text{Et}_2\text{Mg}$  ( $0^\circ\text{C}$ , 16 h).<sup>137</sup>



R =  $\text{n-C}_5\text{H}_{11}$  (70%),  $\text{C}_5\text{H}_9\text{N}$  (65%),  $\text{C}_5\text{H}_8\text{NCH}_2$  (75%),  $\text{C}_4\text{H}_3\text{N}_2$  (65%),  $\text{C}_4\text{H}_2\text{N}_2\text{NCH}_2$  (75%), BnO (54%),  $\text{BnOCH}_2$  (56%),  $\text{BnO}(\text{CH}_2)_2$  (65%),  $\text{Bu}^{\text{t}}\text{Me}_2\text{SiO}(\text{CH}_2)_2$  (70%), PhS (80%),  $\text{Me}_3\text{Si}$  (63%); X = Cl, Et.

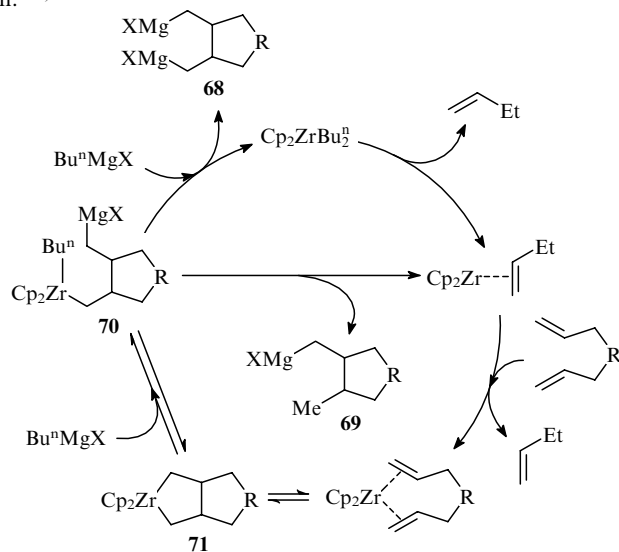


Scheme 1



A tentative mechanism was proposed in order to rationalise the experimental results, which is shown in Scheme 1. In the first step, diethylmagnesium alkylates  $\text{Cp}_2\text{ZrCl}_2$  to yield zirconacyclopentane intermediates **67**. Depending on the reaction conditions, the latter react with  $\text{Et}_2\text{Mg}$  to give either ethylmagnesium (64) or cyclomagnesium (65, 66) products.<sup>137, 138</sup>

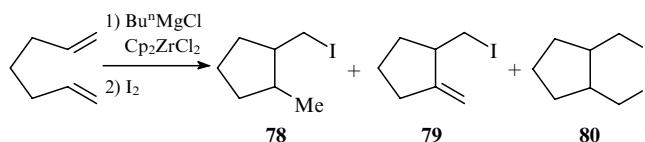
The reactions of non-conjugated  $\alpha,\omega$ -dienes with  $\text{Bu}^n\text{MgX}$  or  $\text{Bu}_2\text{Mg}$  catalysed by  $\text{Cp}_2\text{ZrCl}_2$  (1 mol.%–10 mol.%) in ether-type solvents afford 1,2-bis(magnesiomethyl)carbocycles **68** or 1-(magnesiomethyl)-2-methylcarbocycles **69**<sup>139–142</sup> via zirconacyclopentane intermediates that are formed under these conditions.<sup>143, 144</sup> The rates of formation and yields of the target products, the selectivity and stereochemistry of the process depend on the structure of the starting  $\alpha,\omega$ -diene (this can be hepta-1,6-diene, octa-1,7-diene or 9,9-diallylfluorene), the organomagnesium compound used (e.g.,  $\text{Bu}^n\text{MgHal}$  or  $\text{Bu}_2\text{Mg}$ ), reaction temperature (from 0 to 120 °C), solvent ( $\text{Et}_2\text{O}$ , THF,  $\text{Pr}_2\text{O}$ ,  $\text{Bu}_2\text{O}$ ) and the ratio of the reagents. For instance, with  $\text{Bu}_2\text{Mg}$  in  $\text{Et}_2\text{O}$  at 20 °C, 1,2-bis(n-butylmagnesiomethyl)cycloalkanes **68** are predominantly formed. In contrast, the reaction of  $\alpha,\omega$ -dialkenes with  $\text{Bu}^n\text{MgHal}$  in THF yields mainly 1-(halomagnesiomethyl)-2-methylcarbocycles **69**. It is of note that the total yield of organomagnesium compounds **68** and **69** in  $\text{Et}_2\text{O}$  is higher than that in THF. The ratio between *trans* and *cis* isomers in the products **68** and **69** increases with an increase in temperature. The transmetalation of bimetallic complexes **70** with the starting organomagnesium reagents is the key step of the catalytic cycle, which determines the overall chemoselectivity of the reaction.<sup>141, 142</sup>



Negishi *et al.*<sup>145</sup> investigated the reactions of  $\text{Bu}^n\text{MgCl}$  and  $\text{Bu}_2\text{Mg}$  with 3-bis( $\eta^5$ -cyclopentadienyl)zirconabicyclo[3.3.0]octane **71** (R =  $\text{CH}_2$ ) in two solvents, *viz.*, THF and  $\text{Et}_2\text{O}$  (Scheme 2) to get an insight into the mechanism of the above transformations. The complex **71** (R =  $\text{CH}_2$ ) is a possible intermediate in the reaction of hepta-1,6-diene with  $\text{Bu}^n\text{MgX}$  (X = Cl,  $\text{Bu}^n$ ) catalysed by  $\text{Cp}_2\text{ZrCl}_2$ .

It was found that the monomagnesium derivative **72** is formed only in the case of  $\text{Bu}^n\text{MgCl}$  in THF. In all other cases ( $\text{Bu}^n\text{MgCl}$  in  $\text{Et}_2\text{O}$  and  $\text{Bu}_2\text{Mg}$  in any of the two solvents), the 1,4-dimagnesium derivative **73** was the major product. This fact can be explained as follows. It is known that the Grignard reagents  $\text{AlkMgHal}$  exist as monomers in tetrahydrofuran and as dimers in diethyl ether.<sup>146</sup> In the case of dimeric structures ( $\text{Bu}^n\text{MgCl}$  in  $\text{Et}_2\text{O}$  or  $\text{Bu}_2\text{Mg}$ ), an intramolecular transfer of the butyl group from the magnesium to the zirconium atom occurs in the complexes **74** and **75** resulting in the 1,4-dimagnesium compound **73**. No similar process is possible for monomeric structures ( $\text{Bu}^n\text{MgCl}$  in THF) or at a molar ratio complex **71**: $\text{Bu}_2\text{Mg}$  other than 1:1 or 1:2. If the reaction is performed with  $\text{Bu}_2\text{Mg}$ , the magnesium-containing bicyclic compound **76** is formed in addition to **73** in both solvents.

Unsaturated monomagnesium compounds **77** are obtained only in the reaction of  $\text{Bu}^n\text{MgCl}$  with hepta-1,6-diene in THF or  $\text{Et}_2\text{O}$  in the presence of a catalytic amount of  $\text{Cp}_2\text{ZrCl}_2$  in a yield of ~10%. This conclusion was drawn from the analysis of subsequent iodination products, **78–80**.

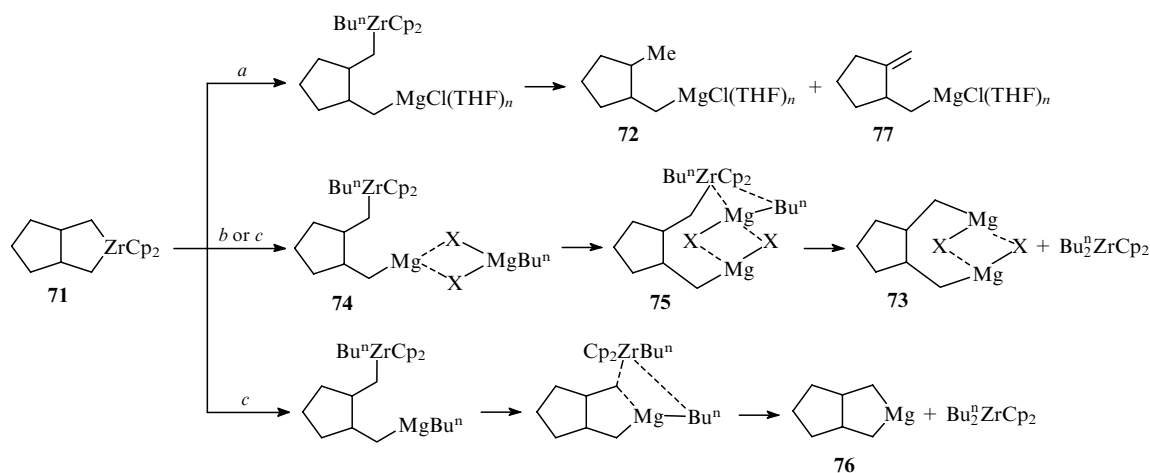


| Solvent               | Yield (%) |    |        |
|-----------------------|-----------|----|--------|
|                       | 78        | 79 | 80     |
| THF                   | 45        | 10 | traces |
| $\text{Et}_2\text{O}$ | 10        | 10 | 40     |

The stereochemistry of the carbomagnesium and cyclo-magnesium of  $\alpha$ -alkenes or non-conjugated dienes with  $\text{Alk}_2\text{Mg}$  or  $\text{AlkMgHal}$  catalysed by chiral zirconium complexes was discussed elsewhere.<sup>147–149</sup> Under the reaction conditions, intermediate *cis*- (**81**) and *trans*-zirconacyclopentanes **82** are selectively formed, which are further converted into the corresponding *cis*- and *trans*-dimagnesium compounds **83** and **84** (Scheme 3).<sup>149</sup>

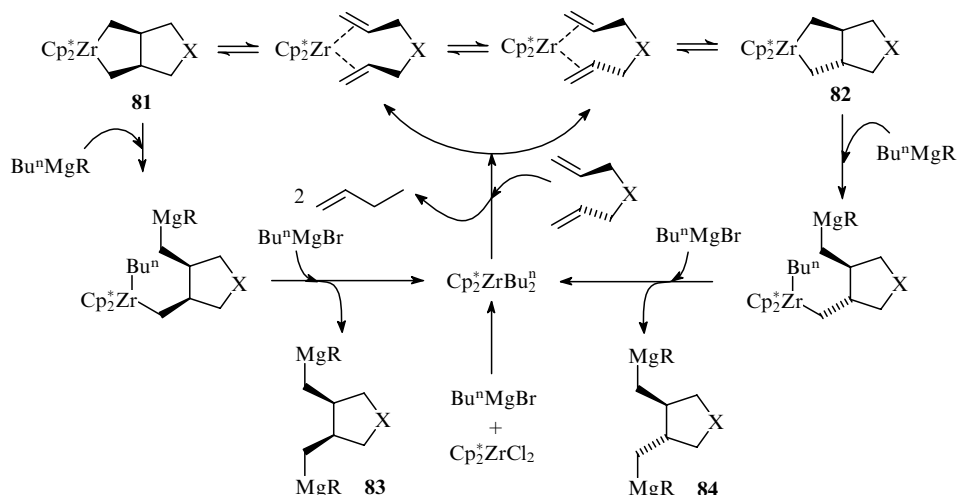
Carbocyclisation of unsaturated compounds using OMC and Zr-containing catalysts is applied to the synthesis of hydrogenated indane derivatives, including optically active ones.<sup>150–160</sup> The

Scheme 2



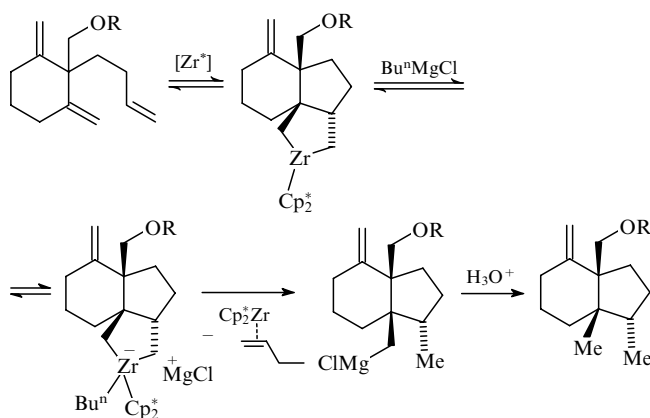
(a)  $\text{Bu}^n\text{MgCl}$ , THF; (b)  $\text{Bu}^n\text{MgCl}$ ,  $\text{Et}_2\text{O}$ ; (c)  $\text{Bu}_2\text{Mg}$ ,  $\text{Et}_2\text{O}$  (THF);  $n = 1$  or  $2$ ; X = Cl (for b) and  $\text{Bu}^n$  (for c).

Scheme 3

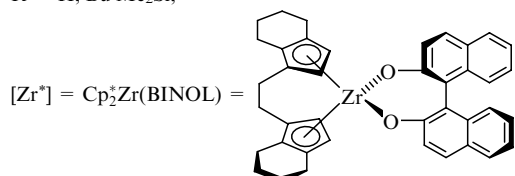


$\text{X} = (\text{CH}_2)_n$  ( $n = 1, 2$ ),  $\text{NBu}^t$ ,  $\text{SiMe}_2$ ;  $\text{R} = \text{Bu}^n$ ,  $\text{Cl}$ ;  $\text{Cp}_2^*\text{ZrCl}_2$  is 2,2'-biphenyl-bis(3,4-dimethylcyclopentadienyl)zirconium dichloride.

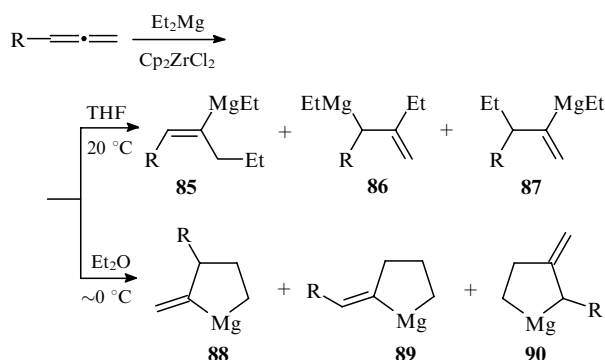
multistep synthesis shown below has been accomplished by Mori *et al.*<sup>153</sup>



$\text{R} = \text{H}$ ,  $\text{Bu}^t\text{Me}_2\text{Si}$ ;

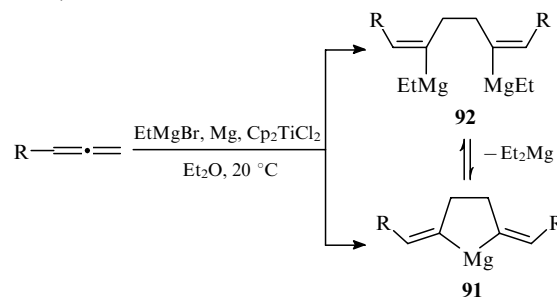


Allenes react with  $\text{Et}_2\text{Mg}$  in the presence of  $\text{Cp}_2\text{ZrCl}_2$ . Depending on the conditions, either carbomagnesiation (**85**–**87**) or cyclomagnesiation products **88**–**90** can be obtained.<sup>161</sup>



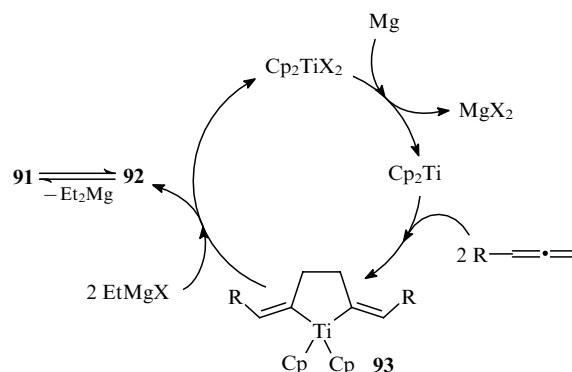
$\text{R} = n\text{-C}_5\text{H}_{11}$ ,  $n\text{-C}_7\text{H}_{15}$ ,  $\text{Bn}$ .

2,5-Dialkylidenemagnesacyclopentanes **91** and 1,4-dimagnesium compounds **92** (in a ratio of  $\sim 1:1$ ) were obtained<sup>161</sup> by  $\text{Cp}_2\text{TiCl}_2$ -catalysed cyclomagnesiation of substituted allenes with  $\text{EtMgX}$  ( $\text{X} = \text{Cl}$ ,  $\text{Br}$ ) and activated magnesium (see also Ref. 162).



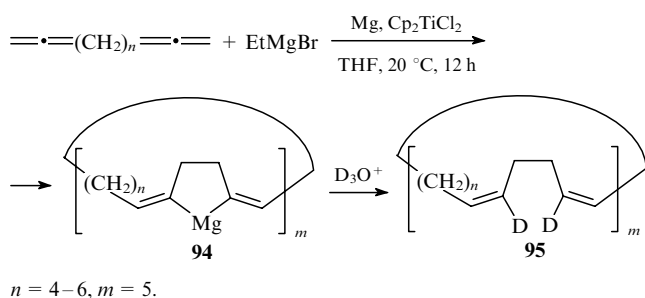
$\text{R} = n\text{-C}_5\text{H}_{11}$ ,  $n\text{-C}_7\text{H}_{15}$ ,  $\text{Bn}$ .

The formal reduction of  $\text{Cp}_2\text{TiCl}_2$  to ' $\text{Cp}_2\text{Ti}$ ', selective formation of intermediate 2,5-dialkylidenetitanacyclopentanes **93** followed by their transmetalation with  $\text{EtMgX}$  are the most probable intermediate steps, which explain the formation of the unsaturated OMC **91** and **92**.



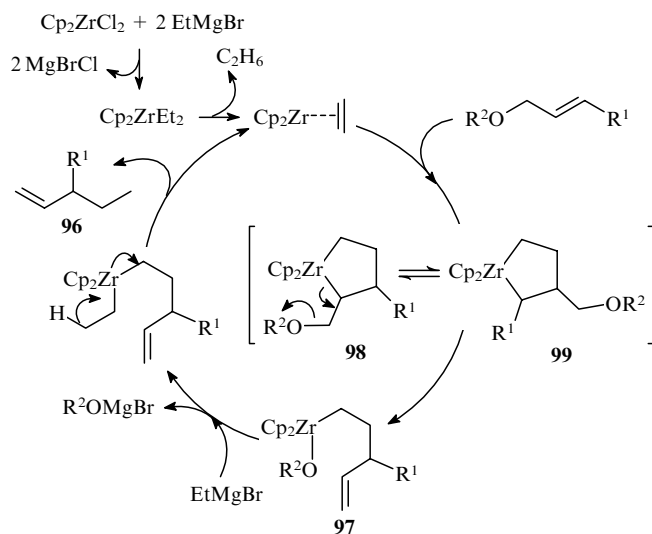
$\text{X} = \text{Cl}$ ,  $\text{Br}$ .

Intermolecular cyclomagnesiation of  $\alpha,\omega$ -diallenes with  $\text{EtMgX}$  and activated magnesium catalysed by  $\text{Cp}_2\text{TiCl}_2$  (10 mol.%) has led to  $\text{Mg}$ -containing macrocycles **94** under mild conditions and in high yields ( $> 90\%$ ).<sup>161</sup> Subsequent treatment of the OMC **94** with a deuterated acid affords macrocyclic compound **95** with alternating *cis*-double bonds.



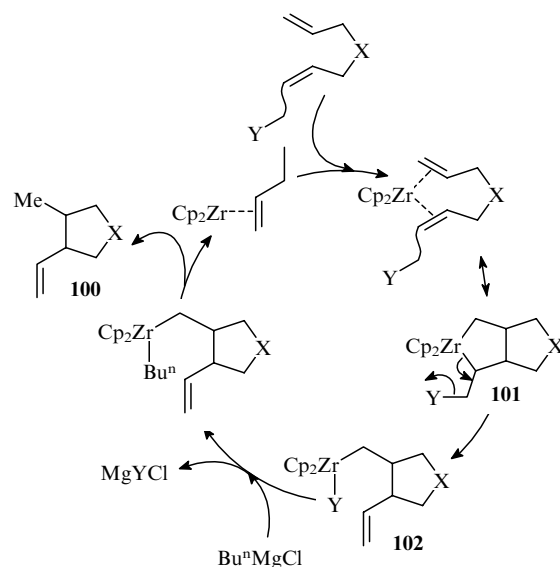
The idea of generation of zirconacyclopentane intermediates in the reaction of allylic ethers with EtMgBr in the presence of a catalytic amount of  $\text{Cp}_2\text{ZrCl}_2$  is exploited in an efficient method for the formation of C–C bonds. In contrast to the cyclo- and carbomagnesiation reactions (see Section V), it is unsaturated compounds rather than organomagnesium compounds that are the target products of these reactions. In particular, the reaction of allylic ethers containing a disubstituted double bond with EtMgBr catalysed by  $\text{Cp}_2\text{ZrCl}_2$  (THF, 20  $^\circ\text{C}$ , 6 h) results in the regioselective formation of a C–C bond involving the  $\gamma$ -carbon atom of the allylic ether, *i.e.*, affords an unsaturated compound **96**.<sup>163</sup> The high regioselectivity of the reaction is due to the formation of zirconium alkoxide **97** from regioisomeric<sup>164</sup> zirconacyclopentane intermediates **98** and **99**.

In addition to  $\text{Cp}_2\text{ZrCl}_2$ ,  $\text{Cp}_2\text{HfCl}_2$  can be used as a catalyst for these reactions. However, in this case, a satisfactory yield can be obtained only for a longer reaction time (65 h). No target products **96** are formed if MeMgBr devoid of the  $\beta$ -hydrogen atoms is used instead of EtMgBr.



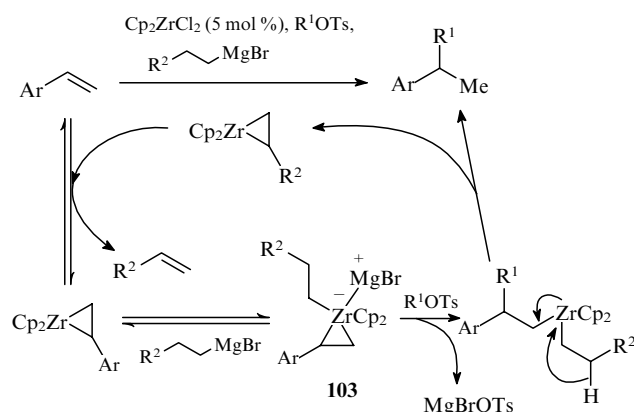
$\text{R}^1 = \text{Pr}^n; \text{R}^2 = \text{Me, Bn, Ph}.$

2-Bromo- $\alpha,\omega$ -diene,<sup>165</sup> dienic ethers and amines with allylic double bonds<sup>166,167</sup> cyclised into unsaturated carbo- and heterocyclic compounds **100** with high selectivities using  $\text{Bu}^n\text{MgCl}$  and  $\text{Cp}_2\text{ZrCl}_2$  as a catalyst. The formation of zirconacyclopentane intermediates **101** is the key step of this reaction. Subsequent intramolecular rearrangement proceeds through zirconium alkoxide complexes **102**, which are further transmetalated with the starting reagent  $\text{Bu}^n\text{MgCl}$ . The catalytic cycle is closed by elimination of the unsaturated cyclic product **100**.



$\text{X} = \text{CH}_2, \text{NPr}^n, \text{NPh}; \text{Y} = \text{OMe, OPh}.$

Electrophilic alkylation of alkenes, indenes and chromenes with alkyl *p*-toluenesulfonates, sulfates or bromides has been realised<sup>168–170</sup> *via* intermediate zirconamagnesium complexes of the type **103** (see Ref. 168).

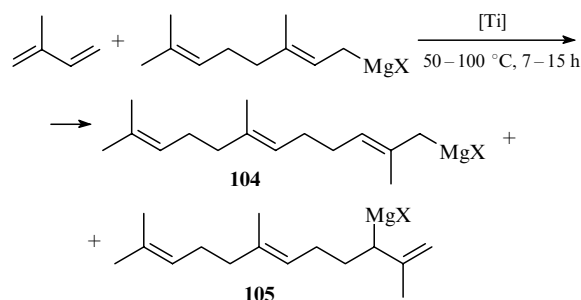


$\text{R}^1, \text{R}^2 = \text{Alk}.$

## VII. Carbomagnesiation of 1,3-dienes

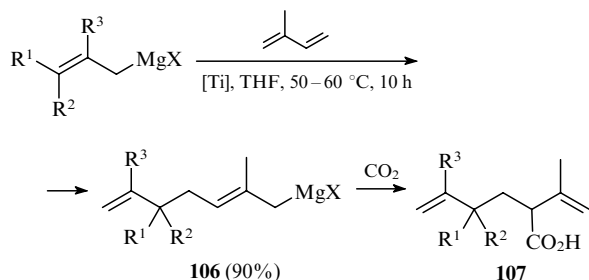
Thermal carbomagnesiation of conjugated dienes can only be performed with allylic OMC.<sup>171,172</sup> Alkyl- and arylmagnesium halides do not react with 1,3-dienes under these conditions.

It was demonstrated<sup>173</sup> that isoprene undergoes carbomagnesiation with geranylmagnesium halides under relatively mild conditions in the presence of Ti-containing catalysts. The OMC **104** and **105** synthesised in this way were further converted into the corresponding isoprenoid alcohols.



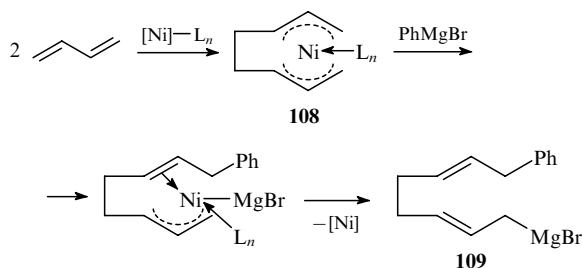
$[\text{Ti}] = \text{Ph}_2\text{TiCl}_2, (\text{RO})_2\text{TiCl}_2 (\text{R} = \text{Alk, Ar}).$

Carbomagnesiation of isoprene with allylic OMC catalysed by  $\text{Cp}_2\text{TiCl}_2$  proceeds in THF with heating.<sup>174, 175</sup> The OMC **106** formed can be converted into the corresponding alcohols or carboxylic acids **107** by oxidation or reaction with  $\text{CO}_2$ .



$\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{R}^3 = \text{H}$  (25%);  $\text{R}^1 = \text{R}^2 = \text{Me}$ ,  $\text{R}^3 = \text{H}$  (20%);  
 $[\text{Ti}] = \text{Cp}_2\text{TiCl}_2$

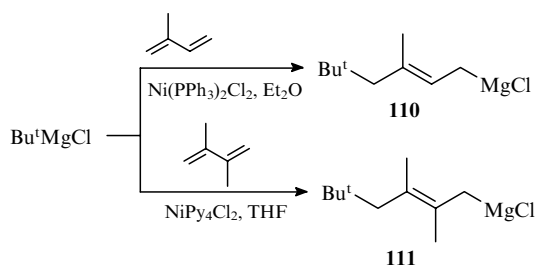
The addition of  $\text{PhMgBr}$  to butadiene in the presence of low-valent nickel complexes activated by  $\text{P}(\text{O}Ph)_3$ <sup>176</sup> is the earliest example of carbomagnesiation of dienes with arylmagnesium halides. The formation of intermediate bis- $\pi$ -allyl nickel complexes **108** is the key step of this reaction. This is followed by the oxidative addition of  $\text{PhMgBr}$  to this intermediate and reductive elimination of  $\text{Ni}^0$ , which yields (*E,E*)-octa-2,7-dienylmagnesium bromide **109** selectively.



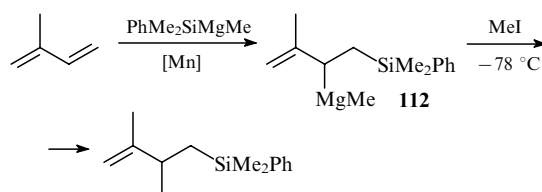
$\text{L}_n = \text{P}(\text{O}Ph)_3$ .

Phosphines and acetylacetonate can be used as ligands in the nickel complexes. The activity of the Ni-containing catalysts in the reaction of arylmagnesium halides with butadiene decreases in the series:  $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2 > \text{Ni}(\text{Ph}_2\text{PCH}_2\text{CH}_2\text{PPh}_2)\text{Cl}_2 > \text{Ni}(\text{Ph}_2\text{PCH}_2\text{CH}_2\text{PPh}_2)(\text{acac})_2 > \text{Ni}(\text{acac})_2$ .<sup>177</sup> In the case of phenylmagnesium bromide, a number of salts and complexes of various transition metals, including Pd, Cu, Rh, Ni, Co, Cr and Fe, in different oxidation states with different types of metal atom coordination, ligands and counterions were assayed as catalysts. In the presence of Fe(III) salts and complexes, the reactions of alka-1,3-dienes with arylmagnesium halides yield 1-aryllalka-1,3-dienes. This reaction catalysed by phosphine Ni(II) complexes affords telomeric 1-aryllalka-2,7- and 1-aryllalka-2,6-dienes.<sup>178, 179</sup>

In contrast to arylmagnesium halides,  $\text{Bu}^t\text{MgCl}$  reacts with 1,3-dienes in the presence of nickel complexes yielding 1,4-addition products **110** and **111**.<sup>40, 46</sup>



By analogy with the carbomagnesiation reaction, silylmagnesiation of 1,3-dienes leading to unsaturated Si-containing OMC **112** in the presence of manganese catalysts was carried out.<sup>180</sup>

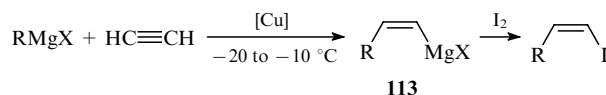


Carbomagnesiation of 1,3-dienes with alkyl-, aryl- and allyl-type OMC catalysed by metal complexes affords unsaturated organomagnesium reagents that are difficult to obtain by conventional methods.

## VIII. Carbomagnesiation of alkynes

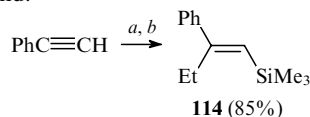
Regio- and stereoselective carbomagnesiation of alkynes is used in synthetic practice for the preparation of substituted alkenes with *Z*-configuration of the double bond.<sup>181</sup>

As a rule, non-catalytic carbomagnesiation of alkynes requires drastic conditions and long reaction time.<sup>182</sup> The use of metal complex catalysts makes it possible to decrease the temperature, reduce the duration and increase the yields of the target products. For instance, carbomagnesiation of acetylene with Grignard reagents in the presence of Cu(I) compounds takes 1–2 h at low temperature to give organomagnesium compounds **113** containing *Z*-double bonds.<sup>183</sup>



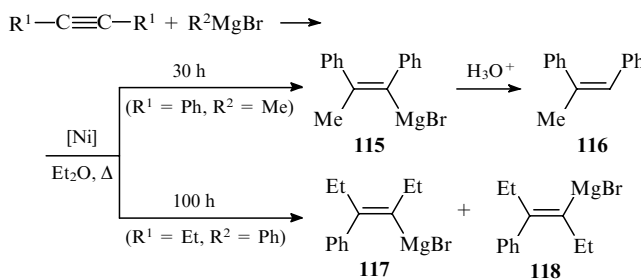
$\text{R} = \text{Alk}$ ;  $\text{X} = \text{Cl}, \text{Br}$ ;  $[\text{Cu}] = \text{CuBr}, \text{CuCN}, \text{PhSCu}, \text{Bu}^t\text{OCu}, \text{MeCu}$ .

Carbomagnesiation of monosubstituted alkynes in the presence of copper salts involves the addition of the magnesium atom to the non-substituted  $\alpha$ -carbon atom of the original alkyne. Subsequent functionalisation of the OMC formed with chlorosilanes is of interest as a method for the synthesis of unsaturated silanes of the type **114** with a *Z*(or *E*)-trisubstituted double bond.<sup>184</sup>



(a)  $\text{EtMgCl}$ ,  $\text{CuI}$ ,  $\text{LiBr}$ , THF,  $-60^\circ\text{C}$ , 14 h;  
 (b)  $\text{Me}_3\text{SiCl}$ , HMPA,  $-60$  to  $20^\circ\text{C}$ , 5 h.

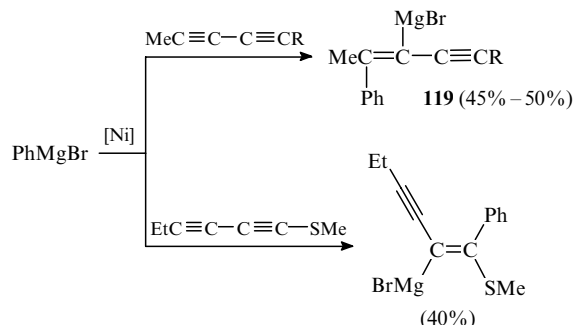
Carbomagnesiation of disubstituted acetylenes results in OMC containing *E*- and *Z*-double bonds. In particular, prolonged boiling of diphenylacetylene in ether with a twofold excess of  $\text{MeMgBr}$  in the presence of  $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$  (10 mol.%) yields the unsaturated OMC **115**, which is hydrolysed to the individual trisubstituted alkene **116** with *cis*-arrangement of the phenyl substituents.<sup>185</sup> The reaction of hex-3-yne with  $\text{PhMgBr}$  under similar conditions affords *cis*- (**117**) and *trans*-isomers (**118**) in a ratio of 9:1. Duboudin *et al.*<sup>185</sup> proposed that the *cis*–*trans*-isomerisation of organomagnesium compounds in the latter case



$[\text{Ni}] = \text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ .

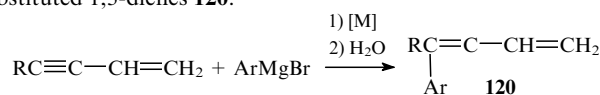
is due to the formation of intermediate  $\pi$ -allyl nickel complexes.<sup>186, 187</sup>

Diacetylenes undergo carbomagnesiation in the presence of  $\text{NiCl}_2$ , which results in OMC **119** with an enyne fragment.<sup>188</sup> Functionalised alkadiynes, such as alkyl(alkylthio)diacetylenes, have also been carbomagnesiated in the presence of Ni-containing catalysts.<sup>189</sup>



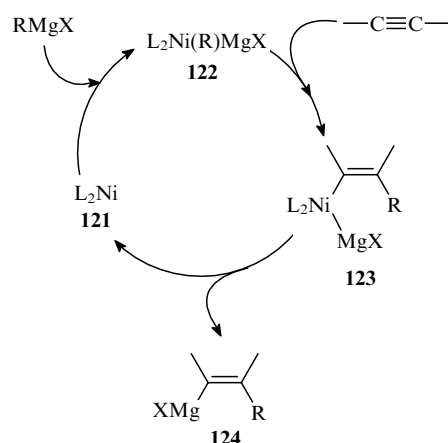
R = Me, Bu<sup>t</sup>.

Carbomagnesiation of conjugated enynes yields alkadienylmagnesium halides, and their hydrolysis offers a convenient route to 1,3-dienic hydrocarbons.<sup>190</sup> Pd, Fe, Ni and Co complexes can be used as catalysts in the carbomagnesiation of 1-en-4-yne with arylmagnesium bromides to a mixture of *Z*- and *E*-isomers of aryl-substituted 1,3-dienes **120**.<sup>191</sup>



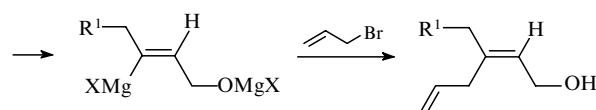
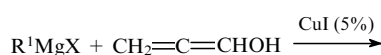
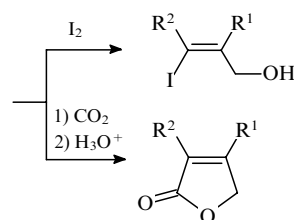
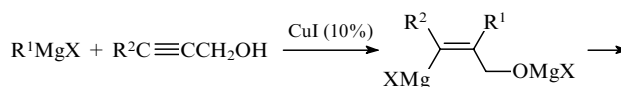
R = Me, Et; Ar = Ph, 2-MeC<sub>6</sub>H<sub>4</sub>, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>, 4-Me<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>; [M] = Pd, Fe, Ni, Co.

A proposed mechanism of carbomagnesiation of alkynes with the Grignard reagents in the presence of Ni-containing catalysts involves the oxidative addition of  $\text{RMgHal}$  to the low-valent nickel complex **121** to form the alkenylmagnesium complex **122**, which induces carbomagnesiation of the original alkyne to give the alkenylmagnesium complex **123**.<sup>192</sup> Subsequent reductive elimination of a low-valent Ni complex yields the target alkenyl OMC **124**.



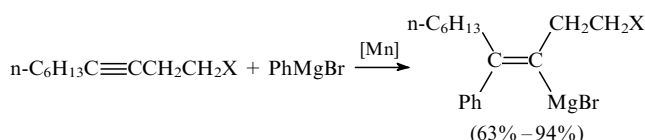
Carbomagnesiation of silylacetylenes with a fourfold excess of  $\text{MeMgBr}$  in the presence of a two-component catalyst  $\text{Ni}(\text{acac})_2-\text{Me}_3\text{Al}$  (1:1) is rather highly regioselective. The Grignard reagent adds predominantly (~90%) to the carbon atom bearing the silyl group.<sup>193</sup> The use of  $\text{EtMgBr}$  and a system  $\text{Ni}(\text{acac})_2-\text{Bu}_3\text{AlH}$  as a catalyst affords alkenyl- (~50%) and alkadienylmagnesium bromides (~30%). The latter are formed upon carbomagnesiation of the original alkyne with alkenylmagnesium halide generated *in situ*.<sup>194</sup>

Cu(I) salts are more active catalysts in the carbomagnesiation of propargylic and allenic alcohols in contrast to the corresponding reactions with alkyl-, aryl- and silylacetylenes.<sup>195–197</sup>



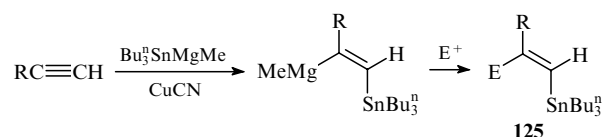
R<sup>1</sup> = Me, Et, Pr<sup>i</sup>, Bu<sup>t</sup>, All, Bn, Ph; R<sup>2</sup> = H, Me, Ph, Bu<sup>n</sup>, Me<sub>3</sub>Si; X = Cl, Br.

Propargylic ethers readily react with Grignard reagents (~20 °C, ether, 10 mol.% of CuBr) to afford carbomagnesiation products in 70%–80% yields.<sup>198</sup> In the presence of  $\text{MnCl}_2$  as a catalyst, carbomagnesiation<sup>199</sup> as well as silylmagnesiation<sup>180</sup> of disubstituted acetylenes, including those containing functional groups, can successfully be carried out.



X = OH, OMe, OBn, NEt<sub>2</sub>.

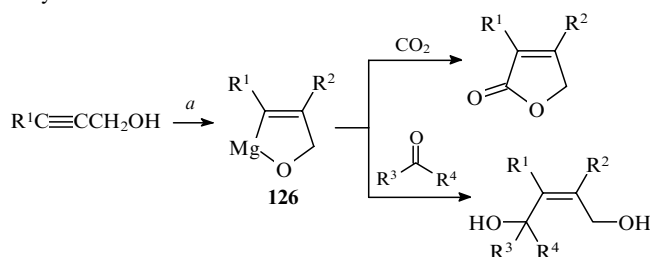
Stannylmagnesiation of terminal alkynes, like carbomagnesiation, is performed in the presence of CuCN. This reaction with various electrophilic reagents yields vinylstannanes **125** with high regio- and stereoselectivities.<sup>200</sup>



R = Alk, cyclo-Alk, Ph, BnO(CH<sub>2</sub>)<sub>2</sub>; E = H, D, Me, Et, All, PhCH(OH).

Carbomagnesiation of alkynes with the Grignard reagents is widely applied to the synthesis of unsaturated halides,<sup>201</sup>  $\Delta^{\alpha,\beta}$ -butenolides, alk-2-ene-1,4-diols,<sup>202</sup> cyclopentenones,<sup>203</sup> vinyl sulfones<sup>204</sup> and various biologically active compounds.<sup>205</sup> Furthermore, it is useful in the cross-coupling reactions.<sup>206</sup>

In particular, Duboudin and Jousseau<sup>202</sup> reported the synthesis of a number of unsaturated diols and lactones exploiting organomagnesium compounds **126** prepared from the respective alkyne.



(a) R<sup>2</sup>MgBr, CuI (10%); R<sup>1</sup>, R<sup>2</sup> = H, Me, Et, Ph, Bz, All; R<sup>3</sup>C(O)R<sup>4</sup> = EtCH(O), Me<sub>2</sub>C(O), PhC(O)Me, (CH<sub>2</sub>)<sub>5</sub>C(O).

The above results demonstrate that the carbomagnesiation of alkynes with Grignard reagents in the presence of transition metal-based catalysts represents a convenient method for the synthesis of alkenylic, alkadienylic and enynic organomagnesium compounds. Functionalisation of such derivatives offers new potential in synthetic practice.

## IX. Conclusion

The application of metal complex catalysis to the chemistry of OMC has led to the discovery of new reactions, development of efficient methods of synthesis of various types of compounds and development of novel highly reactive reagents to meet the needs of modern organic and organometallic chemistry. Non-traditional 'non-Grignard' organomagnesium compounds with different structures that became available due to advances in the metal complex catalysis, have solidly taken their places in the arsenal of common reagents. Investigations into hydro- and carbomagnesiation of alkenes, dienes and alkynes with magnesium hydride and alkylmagnesium compounds in the presence of transition metal-based catalysts are currently in progress, which unveils new avenues in the preparation of non-trivial magnesium-containing systems. Catalytic cyclomagnesiation of unsaturated compounds with  $\text{AlkMgHal}$  (or  $\text{Alk}_2\text{Mg}$ ) has led to new classes of cyclic OMC.

According to the above analysis of the published data, one can expect, in the very near future, further progress in several promising directions, in particular, selective functionalisation of unsaturated compounds through the intermediate formation of  $\text{Mg}-\text{C}$  bonds; chiral synthesis of organomagnesium reagents and their conversion into optically active compounds. Hopefully, the catalytic hydro-, carbo- and cyclomagnesiation of  $\alpha,\omega$ -dialkenes, diallenes or dialkynes will be demanded by chemists for the synthesis of metal-containing and polyfunctional macrocycles required for the preparation of new reagents and materials.

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<sup>b</sup> — *Russ. J. Gen. Chem. (Engl. Transl.)*

<sup>c</sup> — *Russ. J. Org. Chem. (Engl. Transl.)*

<sup>d</sup> — *Chem. Nat. Compd. (Engl. Transl.)*



# Estimation of the bond dissociation energies from the kinetic characteristics of liquid-phase radical reactions

E T Denisov, V E Tumanov

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**Abstract.** Three methods used in the kinetics of liquid-phase radical reactions for estimating the dissociation energies of individual bonds in polyatomic molecules are described. The first approach is based on the study of the equilibrium in radical abstraction reactions involving stable radicals and measurements of the equilibrium constants. The second method is based on the study of the kinetics of homolytic decomposition of molecules. Measuring the activation energy of these reactions makes it possible to estimate the dissociation energies of the weakest bonds, *e.g.*, the O–O bonds in various peroxides. The essence of the third approach developed in the framework of the model of intersecting parabolas is calculations of the bond dissociation energy from the activation energy of a radical reaction involving the molecules under consideration. This method allowed the dissociation energies of the C–H, N–H, O–H and S–H bonds in a large number of organic compounds to be estimated. The scope and the specific features of application of each method are discussed and the bond dissociation energies determined by these methods are given. The bibliography includes 78 references.

## I. Introduction

The dissociation energies of individual bonds in a molecule and the enthalpies of formation of a molecule or radical are the most important energy characteristics of such species, which are widely used in science and technology. Every year brings tens of studies presenting the results of measurements of these parameters. The first review summarising data on the bond dissociation energies in molecules was reported five decades ago.<sup>1</sup> In the USSR, collec-

tion, systematisation and publication of such data were initiated by academician V N Kondrat'ev.<sup>2,3</sup> Publication of a multivolume handbook of the thermal properties of molecules and atoms<sup>4</sup> became a great scientific event. A recently published handbook<sup>5</sup> by Luo contains a considerable body of information on the bond dissociation energies in polyatomic molecules.

A broad spectrum of physicochemical methods developed for measuring the bond dissociation energies comprises low-pressure pyrolysis, kinetic studies of gas-phase bromination and iodination of hydrocarbons, spectral methods (these are used for estimating the bond energy in diatomic molecules), electron impact mass spectrometry, photoelectron spectroscopy, electrochemical methods and recently elaborated photoacoustic calorimetry. Each method has its own field of application, specific features and limitations.<sup>6–15</sup>

The last two decades have been characterised by the widespread use of kinetic methods for studying and analysing liquid-phase radical reactions. Such methods allow one to estimate the strengths of individual bonds in polyatomic molecules and considerably extend the range of compounds with known bond strengths. They include:

(1) studies of equilibrium bimolecular reactions involving stable free radicals;

(2) investigations on the kinetics of monomolecular decomposition of compounds involving homolysis of one (the weakest) bond;

(3) measurements of the absolute or relative rate constants for radical abstraction reactions or the activation energies of such reactions followed by calculations of the dissociation energy of a particular bond involved in the rearrangement.

The aim of this review is to consider these methods and the values of the strengths of individual bonds in various organic compounds obtained using these approaches. The methods mentioned above made it possible to significantly extend the range of complex polyatomic molecules for which the bond dissociation energies were determined from experimental data.

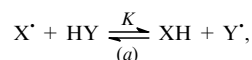
**E T Denisov, V E Tumanov** Institute of Problems of Chemical Physics, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation. Fax (7-096) 515 54 20, tel. (7-096) 522 19 14, e-mail: edenisov@icp.ac.ru (E T Denisov), tel. (7-096) 522 13 66, e-mail: tve@icp.ac.ru (V E Tumanov)

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## II. Chemical equilibrium $X^\bullet + HY \rightleftharpoons HX + Y^\bullet$

The chemical equilibrium



where  $X^\bullet$  and  $Y^\bullet$  are reactive free radicals, cannot be achieved in solution owing to very fast recombination or disproportionation of these species. Such an equilibrium can be attained only when both radicals ( $X^\bullet$  and  $Y^\bullet$ ) are stable and do not enter the recombination reaction. In this case the equilibrium concentrations of both radicals can be determined by EPR spectroscopy or spectrophotometrically. The equilibrium constant ( $K$ ) is calculated from the ratio of the equilibrium concentrations of the molecules and radicals:

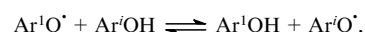
$$K = \frac{[Y^\bullet]_\infty [XH]_\infty}{[X^\bullet]_\infty [YH]_\infty}, \quad (1)$$

and the equilibrium enthalpy ( $\Delta H$ ) is calculated from the temperature dependence of  $\ln K$ . On the other hand, the equilibrium enthalpy of this reaction is equal to the difference between the dissociation energies ( $D$ ) of the bonds involved in the reaction

$$\Delta H = D_{Y-H} - D_{X-H} \quad (2)$$

provided that solvation of reactants makes an insignificant contribution to the equilibrium. This can be attained by carrying out experiments in non-polar solvents.

The approach was employed in a number of studies<sup>16–18</sup> for estimating the dissociation energies of the O–H bonds in phenols. Belyakov *et al.*<sup>16</sup> measured the equilibrium of the type



with galvinoxyl as the reference phenoxyl radical  $Ar^1O^\bullet$  and *para*-substituted 2,6-di-*tert*-butylphenols as the second reactants  $Ar^1OH$ . Changes in the galvinoxyl and phenoxyl  $Ar^1O^\bullet$  concentrations were monitored by EPR spectroscopy (benzene, 298 K). Calculations of the equilibrium constant

$$K = \frac{[Ar^1O^\bullet][Ar^1OH]}{[Ar^1O^\bullet][Ar^1OH]}, \quad (3)$$

from the reactant concentration ratio were followed by calculations of the Gibbs free energy of equilibrium ( $\Delta G$ ):

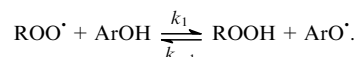
$$\Delta G = -RT \ln K. \quad (4)$$

The equilibrium enthalpy was determined using the temperature dependence of the equilibrium constant. Experience showed that in such reactions one has  $\Delta H \approx \Delta G$  within the limits of error in measurements. An analogous conclusion was also drawn by authors of other studies.<sup>17,18</sup> The dissociation energies of the O–H bonds in phenols thus measured are listed in Table 1.

It was found that this approach can also be used in studies of the systems characterised by recombination of phenoxyl radicals formed. Here, the reaction conditions are chosen in such a fashion that an equilibrium between reactants is attained and the phenols are consumed slowly, so it is possible to monitor each reactant and calculate the equilibrium constant.<sup>17,18</sup> This allowed the range of phenols with known O–H bond dissociation energies to be extended.

Having determined the equilibrium constant, it is possible to estimate the O–H bond strength difference between two phenols. To calculate the absolute value of  $D_{O-H}$ , one must know the  $D_{O-H}$  value for one phenol. For 2,4,6-tri-*tert*-butylphenol,  $D_{O-H} = 339.7 \text{ kJ mol}^{-1}$  (see Ref. 19), which is in good agreement with the  $D$  value for unsubstituted phenol ( $D_{O-H} = 369.0 \text{ kJ mol}^{-1}$ ).<sup>5,21</sup> Both these phenols were used as reference compounds for calculating the absolute values of  $D_{O-H}$  of some other phenols (see Table 1). The error in estimating  $\Delta H$  values is only  $\pm 1.1 \text{ kJ mol}^{-1}$  (see Ref. 17).

In order to evaluate the dissociation energies of O–H bonds in various phenols, Mahoney and DaRooge<sup>22</sup> measured the equilibrium constant  $K = k_1/k_{-1}$  for the reactions

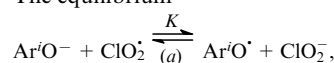


To this end, 9,10-dihydroanthracene (RH) was oxidised with oxygen in the presence of corresponding hydroperoxide (ROOH) and phenol (ArOH) in chlorobenzene at 333 K with 2,2,3,3-tetraphenylbutane as initiator. The experimental conditions were chosen in such a manner that the equilibrium (see above) was established in the system and the chain termination step was limited by the recombination of  $ArO^\bullet$  and  $ROO^\bullet$  radicals. In this case the rate, ( $v_v$ ), of the chain oxidation process is satisfactorily described by the following equation<sup>21</sup>

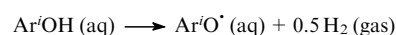
$$v_v = k_p[RH] \sqrt{\frac{k_{-1}v_i[ROOH]}{2k_1k_t[ArOH]}}, \quad (5)$$

where  $k_p$  and  $k_t$  are the rate constants for the reactions of  $ROO^\bullet$  with RH and  $ROO^\bullet$  with  $ArO^\bullet$ , respectively, and  $v_i$  is the initiation rate.<sup>21</sup> The dependence of the chain oxidation rate  $v_v = v - v_i$  ( $v$  is the overall reaction rate) on the ROOH and ArOH concentrations was used to determine the  $k_p^2/(2Kk_t)$  ratio and then the equilibrium constant  $K = k_1/k_{-1}$  was calculated using known values of  $k_p$  and  $2k_t$ . The  $\Delta H = D_{ArO-H} - D_{ROO-H}$  values were determined assuming that  $\Delta H = \Delta G = -RT \ln K$ . The  $D_{ArO-H}$  calculated relative to the O–H bond dissociation energy in PhOH ( $369.0 \text{ kJ mol}^{-1}$ ) are listed in Table 1. Analysis of the data from Table 1 shows that differences between  $D_{O-H}$  values for the same phenol, reported by different authors, are small, being on average  $1.2 \pm 0.7 \text{ kJ mol}^{-1}$ .

The equilibrium



was studied by pulse radiolysis.<sup>20</sup> Here, the equilibrium constant was used to calculate the redox potential ( $E_0$ ) of the aroxyl radical in aqueous solution. The Gibbs energy ( $\Delta G^\circ$ , in  $\text{kJ mol}^{-1}$ ) of the reaction

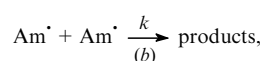
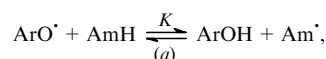


was calculated as follows

$$\Delta G^\circ = 96.5 E_0 + 5.70 pK_a \quad (6)$$

( $pK_a$  characterises acid dissociation of phenol) and used for calculating the O–H bond dissociation energy of phenol in water. This energy was estimated to be  $12 \pm 4 \text{ kJ mol}^{-1}$  higher than in the gas phase due to solvation.<sup>20</sup> Table 1 lists the O–H bond dissociation energies for monosubstituted phenols (corrected for solvation effects in water), obtained based on the  $D_{O-H} = 369.0 \text{ kJ mol}^{-1}$  value for phenol.

Reactions of aminyl radicals with phenols are extremely fast. The reverse reactions of phenoxyl radicals with amines also proceed at a high rate.<sup>23–25</sup> The interaction of a stable phenoxyl radical  $ArO^\bullet$  with amine (AmH) in the presence of phenol (ArOH) can be considered as a two-step process:<sup>23</sup>



with the total rate given by

$$v_v = k[Am^\bullet]^2 = kK^2 \left( \frac{[ArO^\bullet][AmH]}{[ArOH]} \right)^2. \quad (7)$$

The kinetics of the reactions of 2,4,6-tri-*tert*-butylphenoxyl radical with eleven amines (AmH) were studied<sup>23</sup> under the conditions

**Table 1.** Dissociation energies of O–H bonds in phenols calculated from the equilibrium constants.

| Phenol | $D_{\text{O-H}}/\text{kJ mol}^{-1}$ | Ref.           | Phenol                 | $D_{\text{O-H}}/\text{kJ mol}^{-1}$ | Ref.     |
|--------|-------------------------------------|----------------|------------------------|-------------------------------------|----------|
| PhO–H  | 369.2                               | 18             |                        | 334.5                               | 18       |
|        | 360.5<br>361.8<br>360.2             | 18<br>19<br>20 |                        | 331.2                               | 18       |
|        | 356.7<br>361.5                      | 18<br>19       |                        | 342.4                               | 18       |
|        | 355.4                               | 19             |                        | 388.7                               | 20       |
|        | 346.3<br>351.3<br>345.6             | 18<br>19<br>20 |                        | 394.1                               | 20       |
|        | 365.6                               | 20             |                        |                                     |          |
|        | 366.4                               | 20             |                        |                                     |          |
|        | 368.6                               | 20             | X = H                  | 346.2                               | 18       |
|        | 367.7                               | 20             | X = Me                 | 342.8                               | 16       |
|        | 376.1                               | 20             |                        | 337.2                               | 17       |
|        | 375.7                               | 19             | X = CH <sub>2</sub> Ph | 338.8                               | 18       |
|        |                                     |                | X = Ph                 | 335.1                               | 16       |
|        |                                     |                | X = Cl                 | 337.9                               | 16       |
|        |                                     |                | X = OMe                | 344.5                               | 16       |
|        |                                     |                |                        | 325.5                               | 16       |
|        |                                     |                |                        | 324.3                               | 17       |
|        |                                     |                | X = OBu <sup>t</sup>   | 327.5                               | 18       |
|        |                                     |                | X = Ac                 | 330.2                               | 16       |
|        |                                     |                | X = CN                 | 352.3                               | 16       |
|        |                                     |                |                        | 356.9                               | 16       |
|        | 353.3<br>355.7                      | 18<br>19       |                        | 361.6                               | 19       |
|        | 362.2<br>363.4                      | 18<br>19       |                        | 328.2<br>329.3                      | 16<br>17 |
|        |                                     |                |                        | 330.0<br>327.1                      | 17<br>18 |
|        | 350.0                               | 18             |                        |                                     |          |
|        |                                     |                | Y =                    |                                     |          |
|        | 362.6                               | 18             |                        | 327.2                               | 18       |
|        |                                     |                |                        |                                     |          |
|        | 345.9                               | 18             |                        |                                     |          |
|        |                                     |                |                        | 338.0                               | 17       |

**Note.** Hereinafter the attacked bonds are shown.

of fast establishment of the equilibrium between the (ArO $\cdot$ ) radical involved in the reaction and the forming (Am $\cdot$ ) radical. The equilibrium constants  $K$  (in CCl $_4$  at 298–340 K) were calculated from the reagent concentration ratio [see Eqn (7)]. The equilibrium enthalpies were determined from the temperature dependence of  $K$

$$\Delta H = -R \frac{d \ln K}{d(1/T)}. \quad (8)$$

As mentioned above, the entropy of equilibrium in exchange radical reactions varies only slightly and can be set to zero; in these cases, one has  $\Delta H = \Delta G$ . Then the enthalpy of reaction can be determined from the equilibrium constant [see Eqn (4)].

The  $D_{N-H}$  values were calculated using two procedures:<sup>23</sup> (1) from the equilibrium constant measured at the same temperature (298 K),

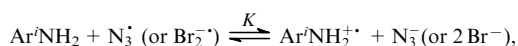
$$D_{N-H} = 339.7 - RT \ln K \text{ (kJ mol}^{-1}\text{)}; \quad (9)$$

and (2) from the equilibrium enthalpy determined using expression (8). In this case the N–H bond strength was calculated as follows:

$$D_{N-H} = 339.7 + \Delta H \text{ (kJ mol}^{-1}\text{)}. \quad (10)$$

The first term in Eqns (9) and (10) is the dissociation energy of the O–H bond in the newly forming phenol. The dissociation energies of the N–H bonds in amines thus obtained are listed in Table 2. These  $D_{N-H}$  values are in agreement with the  $D_{O-H}$  values for phenols (see Table 1).

Jonsson *et al.*<sup>26,27</sup> reported a flash radiolysis study of two equilibrium reactions involving a number of substituted anilines



each of them being followed by the equilibrium deprotonation reaction



The equilibrium constant of one reaction was used to calculate the redox potential  $E_0$  of aminyl radical in aqueous solution. The N–H bond strength (in kJ mol $^{-1}$ ) in aniline was calculated as follows:

$$D_{N-H} = 96.48 E_0 + 5.70 \text{ p}K_a + 238.5. \quad (11)$$

The  $D_{N-H}$  values thus obtained for eighteen anilines studied are listed in Table 2 along with the dissociation energies of the N–H bonds in substituted anilines determined using the recommended<sup>5</sup> value  $D_{N-H}(\text{PhNH}_2) = 375.3 \text{ kJ mol}^{-1}$ .

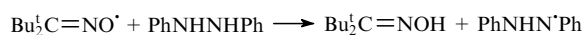
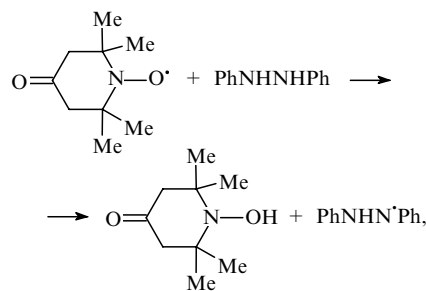
The composition of radicals produced upon photolysis of di-*tert*-butylperoxide in a benzene solution in the presence of phenol and amine was studied by EPR spectroscopy.<sup>28</sup> The radical ratio established in the system after fast exchange reaction is characteristic of the equilibrium (a).

The phenoxyl-to-aminyl radical concentration ratio was determined by EPR spectroscopy and the equilibrium constant of this reaction,

$$K = \frac{[\text{Am}^{\cdot}][\text{ArOH}]}{[\text{ArO}^{\cdot}][\text{AmH}]}. \quad (12)$$

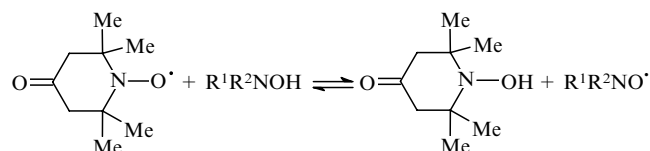
was calculated. 2,6-Di-*tert*-butyl-4-methoxyphenol was used as the reference phenol. The  $D_{N-H}$  thus obtained for ten amines are listed in Table 2.

A number of EPR studies on the equilibrium between stable iminoxyl radicals and various hydroxylamines and oximes are available.<sup>29–32</sup> A calorimetric study of the reactions of such radicals with 1,2-diphenylhydrazine<sup>29</sup>



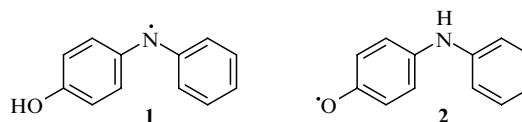
made it possible to determine their enthalpies of formation and use this parameter for calculating the O–H bond strengths in the corresponding hydroxylamines and oximes (Table 3).

The  $D_{O-H}$  value for 2,4,6-*tert*-butylphenol was determined analogously.<sup>19</sup> Thus, it was found that the equilibrium-based  $D_{O-H}$  scale for hydroxylamines is consistent with the  $D_{O-H}$  scale for phenols and  $D_{N-H}$  scale for amines (see Tables 1 and 2). The  $D_{O-H}$  for various hydroxylamines calculated from the equilibrium constants of the following reactions

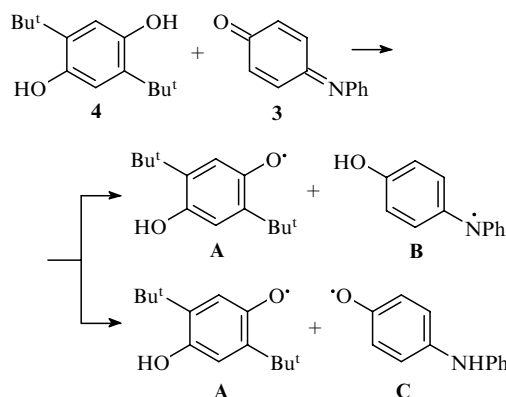


are listed in Table 3.

Determination of the dissociation energy of the attacked bond in various semiquinone radicals is a rather complicated task. For instance, a radical attack on *p*-hydroxydiphenylamine produces two radicals, namely, *p*-hydroxyphenylaminyl radical **1** and *p*-(phenylamino)phenoxyl radical **2**:



The strengths of the O–H bond in radical **1** and the N–H bond in radical **2** were estimated by Varlamov<sup>33</sup> in a recent detailed study of a reversible exchange reaction between *N*-phenyl-1,4-benzoquinoneimine (**3**) and 2,5-di-*tert*-butylhydroquinone (**4**). As was shown earlier, this reaction proceeds by a chain mechanism,<sup>34</sup> the chain initiation following two pathways:



The chain propagation step involves four very fast reactions of radicals **A–C** with quinoneimine **3** and quinone **5**.

**Table 2.** N–H bond dissociation energies in aromatic amines calculated from the equilibrium constants.

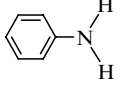
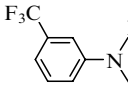
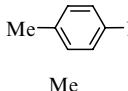
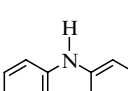
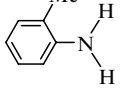
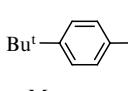
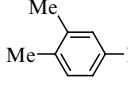
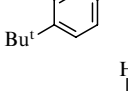
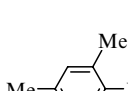
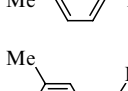
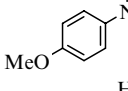
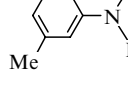
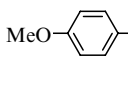
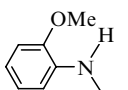
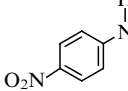
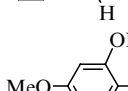
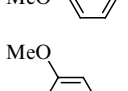
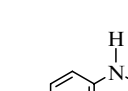
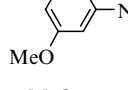
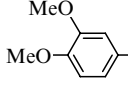
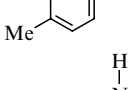
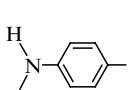
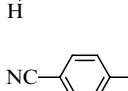
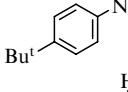
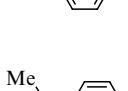
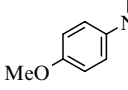
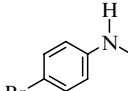
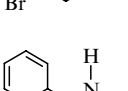
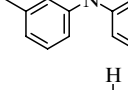
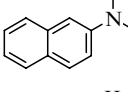
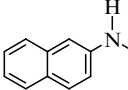
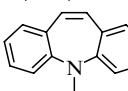
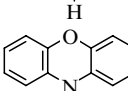
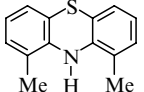
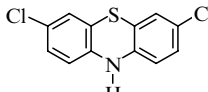
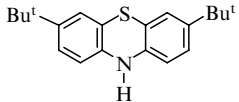
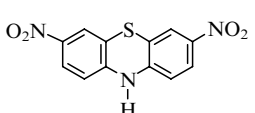
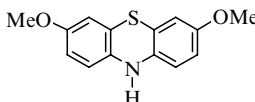
| Amine                                                                               | $D_{\text{N-H}}/\text{kJ mol}^{-1}$ | Ref. | Amine                                                                               | $D_{\text{N-H}}/\text{kJ mol}^{-1}$ | Ref. |
|-------------------------------------------------------------------------------------|-------------------------------------|------|-------------------------------------------------------------------------------------|-------------------------------------|------|
|    | 375.3                               | 26   |    | 392.3                               | 27   |
|    | 373.3                               | 26   |    | 362.5 <sup>a</sup>                  | 23   |
|    | 361.3                               | 27   |                                                                                     | 364.7 <sup>b</sup>                  | 23   |
|    | 374.3                               | 26   |                                                                                     | 359.0                               | 28   |
|    | 373.3                               | 27   |    | 361.6 <sup>a</sup>                  | 23   |
|    | 370.3                               | 27   |                                                                                     | 360.0 <sup>b</sup>                  | 23   |
|    | 380.3                               | 27   |    | 353.3 <sup>a</sup>                  | 23   |
|   | 367.3                               | 26   |                                                                                     | 355.7 <sup>b</sup>                  | 23   |
|  | 373.3                               | 27   |                                                                                     | 347.9                               | 28   |
|  | 369.3                               | 27   |    | 378.8 <sup>a</sup>                  | 23   |
|  | 385.3                               | 27   |                                                                                     | 372.6 <sup>b</sup>                  | 23   |
|  | 372.3                               | 27   |    | 357.5 <sup>a</sup>                  | 23   |
|  | 362.3                               | 26   |                                                                                     | 357.2 <sup>b</sup>                  | 23   |
|  | 386.3                               | 26   |   | 355.1 <sup>a</sup>                  | 23   |
|  | 381.3                               | 26   |                                                                                     | 358.5 <sup>b</sup>                  | 23   |
|  | 389.3                               | 27   |  | 342.5 <sup>a</sup>                  | 23   |
|  | 387.3                               | 26   |                                                                                     | 348.3 <sup>b</sup>                  | 23   |
|                                                                                     |                                     |      |  | 358.9 <sup>a</sup>                  | 23   |
|                                                                                     |                                     |      |                                                                                     | 363.9 <sup>b</sup>                  | 23   |
|                                                                                     |                                     |      |  | 352.8 <sup>a</sup>                  | 23   |
|                                                                                     |                                     |      |                                                                                     | 356.8 <sup>b</sup>                  | 23   |
|                                                                                     |                                     |      |  | 362.3 <sup>a</sup>                  | 23   |
|                                                                                     |                                     |      |                                                                                     | 362.6 <sup>b</sup>                  | 23   |
|                                                                                     |                                     |      |  | 360.5 <sup>a</sup>                  | 23   |
|                                                                                     |                                     |      |                                                                                     | 359.9 <sup>b</sup>                  | 23   |
|                                                                                     |                                     |      |  | 344.8                               | 28   |
|                                                                                     |                                     |      |  | 323.0                               | 28   |
|                                                                                     |                                     |      |  | 336.4                               | 28   |
|                                                                                     |                                     |      |  | 331.8                               | 28   |

**Table 2** (continued).

| Amine                                                                             | $D_{N-H}$ /kJ mol <sup>-1</sup> | Ref. | Amine                                                                              | $D_{N-H}$ /kJ mol <sup>-1</sup> | Ref. |
|-----------------------------------------------------------------------------------|---------------------------------|------|------------------------------------------------------------------------------------|---------------------------------|------|
|  | 325.1                           | 28   |  | 333.9                           | 28   |
|  | 326.8                           | 28   |  | 338.9                           | 28   |
|  | 318.8                           | 28   |                                                                                    |                                 |      |

<sup>a</sup>  $D_{N-H}$  value was calculated based on  $\ln K$  (at 298 K). <sup>b</sup>  $D_{N-H}$  value was calculated based on the enthalpy of equilibrium,  $\Delta H$ .

**Table 3.** O–H bond dissociation energies in hydroxylamines and oximes calculated from the equilibrium constants.

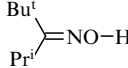
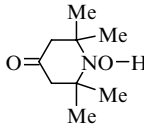
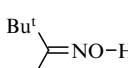
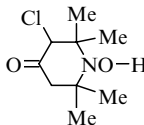
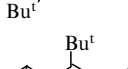
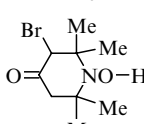
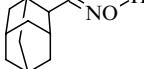
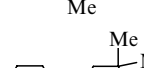
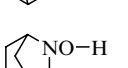
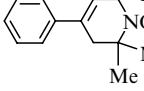
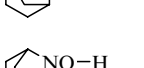
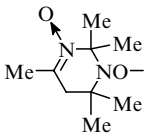
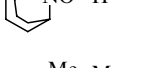
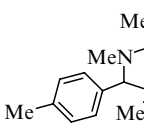
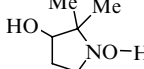
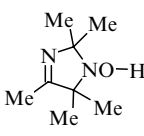
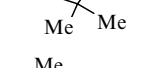
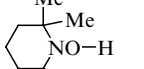
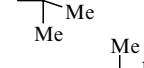
| Compound                                                                            | $D_{O-H}$ /kJ mol <sup>-1</sup> | Ref.   | Compound                                                                            | $D_{O-H}$ /kJ mol <sup>-1</sup> | Ref.   |
|-------------------------------------------------------------------------------------|---------------------------------|--------|-------------------------------------------------------------------------------------|---------------------------------|--------|
|    | 352.7                           | 29     |    | 300.4                           | 29     |
|    | 338.5                           | 29     |   | 307.9                           | 21, 31 |
|   | 334.7                           | 29     |  | 303.4                           | 21, 31 |
|  | 322.2                           | 29     |  | 295.0                           | 32     |
|  | 318.8                           | 29     |  | 308.8                           | 21, 31 |
|  | 287.3                           | 30     |  | 290.7                           | 21, 31 |
|  | 297.7                           | 29     |  | 295.2                           | 21, 31 |
|  | 292.6                           | 30     |  | 294.2                           | 21, 31 |
|  | 295.9                           | 30     |                                                                                     |                                 |        |
|  | 302.2                           | 21, 31 |                                                                                     |                                 |        |
|  | 300.3                           | 21, 31 |                                                                                     |                                 |        |

Table 3 (continued).

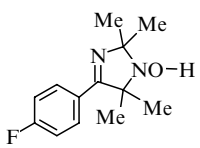
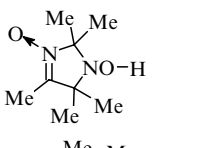
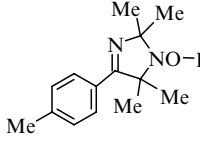
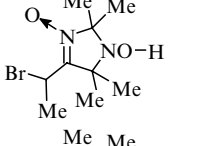
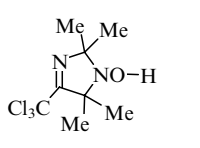
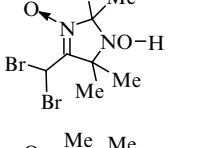
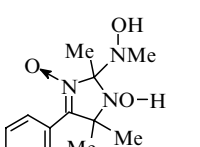
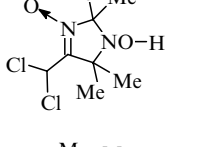
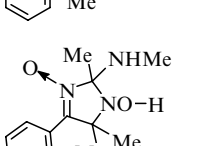
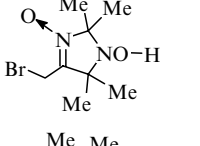
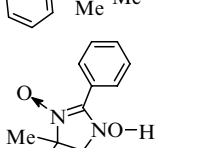
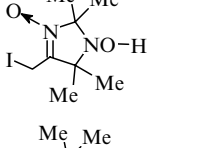
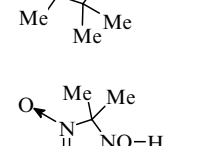
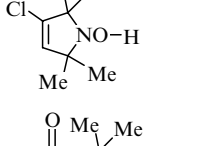
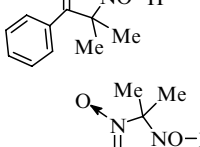
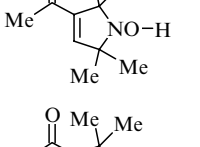
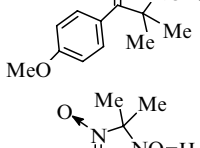
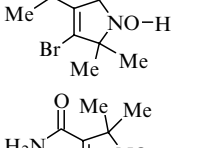
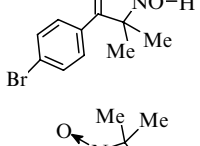
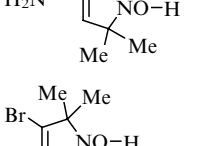
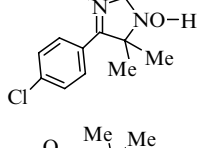
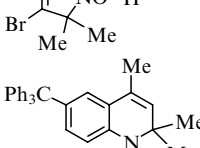
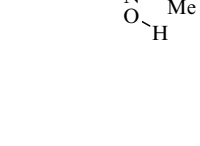
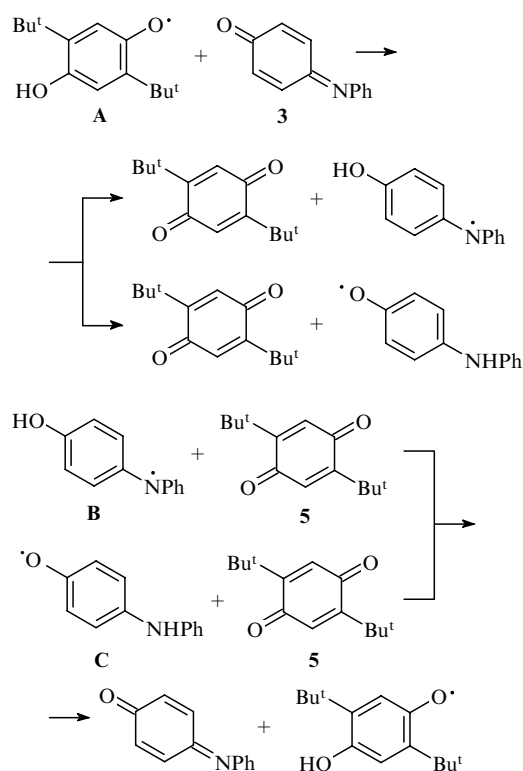
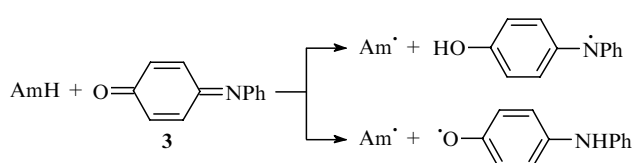
| Compound                                                                            | $D_{O-H}$ /kJ mol <sup>-1</sup> | Ref.   | Compound                                                                             | $D_{O-H}$ /kJ mol <sup>-1</sup> | Ref.     |
|-------------------------------------------------------------------------------------|---------------------------------|--------|--------------------------------------------------------------------------------------|---------------------------------|----------|
|    | 296.1                           | 31     |    | 305.8                           | 21, 31   |
|    | 296.9                           | 31     |    | 305.8                           | 21, 31   |
|    | 297.1                           | 31     |    | 311.4                           | 21, 31   |
|    | 310.0                           | 31     |    | 309.8                           | 21, 31   |
|   | 309.5                           | 21, 31 |   | 306.3                           | 31       |
|  | 297.1                           | 31     |  | 306.8                           | 21, 31   |
|  | 304.5                           | 21, 31 |  | 293.3                           | 21, 31   |
|  | 303.2                           | 31     |  | 294.3                           | 31       |
|  | 306.0                           | 31     |  | 294.5                           | 21, 31   |
|  | 306.3                           | 31     |  | 293.1                           | 31       |
|  | 305.8                           | 31     |  | 293.9                           | 31       |
|                                                                                     |                                 |        |  | 289.5<br>291.3                  | 32<br>30 |

Table 3 (continued).

| Compound | $D_{O-H}$ /kJ mol <sup>-1</sup> | Ref.         | Compound | $D_{O-H}$ /kJ mol <sup>-1</sup> | Ref.     |
|----------|---------------------------------|--------------|----------|---------------------------------|----------|
|          | 292.8                           | 32           |          | 292.6                           | 21, 31   |
|          | 295.0                           | 30, 31       |          | 282.5                           | 30       |
|          | 286.6                           | 30           |          | 312.2                           | 21, 31   |
|          | 290.8<br>288.7                  | 21, 31<br>30 |          | 296.5<br>303.7                  | 32<br>30 |
|          |                                 |              |          | 304.3                           | 21, 31   |



The chain termination step involves six disproportionation reactions of the three radicals involved in the chain reaction. In order to obtain an additional chain initiation, an amine (AmH), namely, di-*p*-tolylamine or 4-methoxyphenyl-*p*-tolylamine was introduced into the system. The amine reacted with quinoneimine, which accelerated the process.<sup>35</sup>



The overall rate of the additional initiation was measured from the dependence of the initial reaction rate of quinoneimine reduction on the initiation rate (with tetraphenylhydrazine as initiator, mixed initiation technique). Based on the kinetic data, the overall initiation rate constants were calculated for the reactions involving amines. Experiments were carried out at different temperatures. The  $D_{O-H}$  and  $D_{N-H}$  values for the radicals mentioned above were calculated using the intersecting parabolas method (see Section V). These parameters were also calculated from experimental values of the activation energies for these reactions. The O–H and N–H bond strengths in *p*-hydroxydiphenylamine were estimated using the Hammett correlation equations. Their values (in kJ mol<sup>-1</sup>) are listed below<sup>35</sup> (for comparison, we also present the  $D_{O-H}$  values in hydroquinone and in semiquinone radical<sup>21</sup>):

| Compound (radical) | $D_{O-H}$ | $D_{N-H}$ |
|--------------------|-----------|-----------|
|                    | 339.3     | 353.4     |
|                    | 259.5     | —         |
|                    | —         | 273.6     |
|                    | 352.0     | —         |
|                    | 223.0     | —         |



### III. The kinetics of homolytic decomposition of molecules

Consider decomposition of a molecule into two radicals involving cleavage of a single bond, *e.g.*, the O–O bond in a peroxide



The activation energy ( $E_a$ ) for this reaction is very similar to the dissociation energy of the bond being cleaved. In the framework of the Rice–Ramsperger–Kassel–Marcus (RRKM) theory in accord with the harmonic model the activation energy for the decomposition of a molecule differs from the dissociation energy by only  $0.5RT$ .<sup>36</sup>

$$D_{O-O} = E_a - 0.5RT. \quad (13)$$

This holds for gas-phase decomposition of substances at high pressures and, apparently, for liquid-phase decomposition (in solution) in non-polar solvents.

The rate constant for decomposition:

$$k = -\frac{d \ln[R^1OOR^2]}{dt}, \quad (14)$$

is determined from the kinetics of decomposition of the initial compound and the activation energy:

$$E_a = -\frac{R d \ln k}{d(T^{-1})}, \quad (15)$$

is found from the temperature dependence of  $k$  in a series of experiments carried out at different temperatures.

The rate constants for decomposition of various peroxides can be found in the literature;<sup>37</sup> they were used<sup>38,39</sup> for estimating the  $D_{O-O}$  values. Analysis of experimental data on the kinetics of peroxide decomposition revealed a large error in measuring the activation energies for the decomposition of these compounds.<sup>37</sup> To improve the accuracy in determining this characteristic, the following procedure was employed. Experimental data for the structurally similar group in peroxides were used to calculate the average pre-exponent  $A$

$$\ln A = \frac{1}{n} \sum_i \ln A_i$$

and then the activation energy was calculated from the rate constant for the reaction at each temperature using the Arrhenius relation:

$$E_a = RT \ln \left( \frac{A}{k} \right). \quad (16)$$

Listed below are the average  $A$  values for various peroxides:<sup>38,39</sup>

| Peroxide              | ROOR | PhR <sup>1</sup> R <sup>2</sup> COOCR <sup>1</sup> R <sup>2</sup> Ph | RC(O)OOC(O)R |
|-----------------------|------|----------------------------------------------------------------------|--------------|
| $10^{-15} A / s^{-1}$ | 2.4  | 1.4                                                                  | 0.63         |

Knowing the O–O bond dissociation energy and the enthalpy of formation of the initial ROOR molecule, it is possible to calculate the standard enthalpy of formation of RO<sup>•</sup> radical:

$$2\Delta H_f^\circ(RO^\bullet) = \Delta H_f^\circ(ROOR) - D_{O-O}. \quad (17)$$

Such calculations were performed using the experimental values of the standard enthalpies of formation of peroxides and the enthalpies of vaporisation or sublimation of these compounds (see Ref. 37). In turn, the enthalpy of formation of the RO<sup>•</sup> radical allows the dissociation energies of the RO–H, RO–Alk, RO–Acyl bonds, *etc.* to be calculated. This was done for a series of alkoxy and acyloxy radicals using the kinetic characteristics of decomposition of corresponding peroxides.<sup>38,39</sup> The results of calculations of  $D_{O-H}$  values for alcohols and organic acids are presented in Table 4.

† Hereafter R (R<sup>1</sup>, R<sup>2</sup>) denotes alkyls.

In addition to the  $D_{O-H}$  values calculated from the peroxide decomposition kinetics, Table 4 lists the published<sup>5</sup>  $D_{O-H}$  values for a number of alcohols and acids (figures in parentheses). The differences between them lie within the range of scatter for similar values. Usually, the  $D_{O-H}$  values calculated using the procedure mentioned above are smaller than those obtained by other methods.

Aliphatic acids  $C_nH_{2n+1}COOH$  are characterised by similar O–H bond strengths, the average  $D_{O-H}$  value being equal to  $441.0 \pm 3.3 \text{ kJ mol}^{-1}$ . The  $D_{O-H}$  values (in  $\text{kJ mol}^{-1}$ ) for alicyclic carboxylic acids  $\text{cyclo-}C_nH_{2n-1}COOH$  depend on the ring strain energy,  $E_{rsc}(n)$

$$D_{O-H} = (441.9 \pm 1.0) + (5.0 \pm 1.2) \cdot 10^{-2} E_{rsc}(n), \quad (18)$$

where  $n$  is the number of carbon atoms in the ring (Fig. 1).<sup>38</sup>

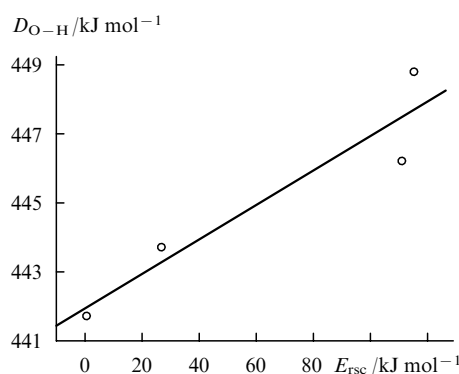
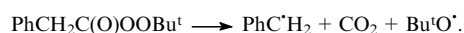


Figure 1. O–H bond dissociation energies ( $D_{O-H}$ ) in cyclocarboxylic acids  $C_nH_{2n-1}C(O)OH$  plotted vs. ring strain energy ( $E_{rsc}$ ).

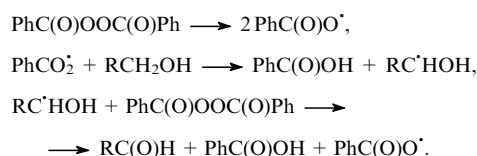
Limitations of the method for estimating the O–O bond strength ( $D_{O-O}$ ) are as follows.

1. The technique is applicable only to the compounds which decompose *via* homolysis of a single (the weakest) bond. If the decomposition occurs as concerted cleavage of two bonds, the activation energy for the process does not characterise the cleavage of the single bond. This is the case for, *e.g.*, the decomposition of many peracid esters.<sup>37</sup> For instance, the decomposition of the peroxy ester  $\text{PhCH}_2\text{C(O)OOBu}^t$  involves simultaneous cleavage of two bonds:



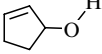
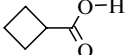
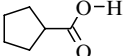
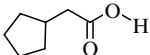
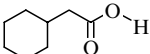
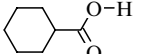
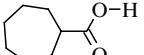
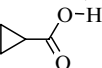
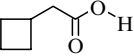
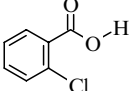
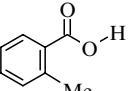
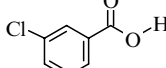
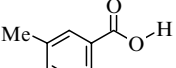
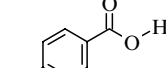
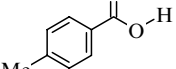
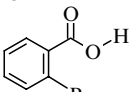
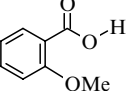
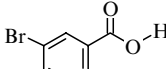
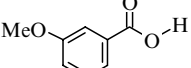
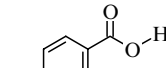
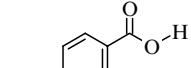
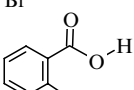
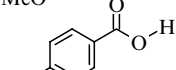
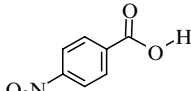
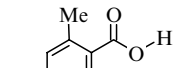
Experiments showed that in this case one has  $E_a < D_{O-O}$  and, at the same time,  $E_a > \Delta H(r)$  [ $\Delta H(r)$  is the enthalpy of reaction].

2. Radicals produced from solvent molecules and capable of attacking the initial peroxide molecule must not initiate an additional decomposition of the peroxide by the chain mechanism. For instance, the decomposition of dibenzoyl peroxide in alcohol ( $\text{RCH}_2\text{OH}$ ) is described by the following chain reaction:<sup>37</sup>



As a result, the rate of peroxide consumption becomes much higher than the peroxide homolysis rate and the activation energy for the decomposition no longer characterises the homolysis reaction. To exclude the chain decomposition of peroxide, an acceptor of free radicals, which does not react with the initial peroxide, is introduced into the solvent.

**Table 4.** O–H bond dissociation energies in alcohols and acids calculated from kinetic data on peroxide decompositions.<sup>38, 39</sup>

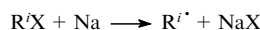
| Compound                                                                            | $D_{O-H}$ /kJ mol <sup>-1</sup> | Compound                                                                             | $D_{O-H}$ /kJ mol <sup>-1</sup> |
|-------------------------------------------------------------------------------------|---------------------------------|--------------------------------------------------------------------------------------|---------------------------------|
| <b>Alcohols</b>                                                                     |                                 |                                                                                      |                                 |
| MeO–H                                                                               | 431.7 (436–439)                 | Pr <sup>n</sup> CMe <sub>2</sub> O–H                                                 | 435.4                           |
| EtO–H                                                                               | 432.4 (436–440)                 | Pr <sup>i</sup> CMe <sub>2</sub> O–H                                                 | 434.4                           |
| Pr <sup>n</sup> O–H                                                                 | 431.9 (433–443)                 | Bu <sup>i</sup> CMe <sub>2</sub> O–H                                                 | 433.6                           |
| Pr <sup>i</sup> O–H                                                                 | 431.9 (438–443)                 |     | 434.8                           |
| Bu <sup>n</sup> O–H                                                                 | 432.3 (426)                     | PhCH <sub>2</sub> CMe <sub>2</sub> O–H                                               | 435.8                           |
| Bu <sup>i</sup> O–H                                                                 | 434.9 (440–446)                 | F <sub>3</sub> CO–H                                                                  | 451.3 (456–497)                 |
| Bu <sup>s</sup> O–H                                                                 | 434.8 (441)                     | ClCH <sub>2</sub> CMe <sub>2</sub> O–H                                               | 445.6                           |
| EtCMe <sub>2</sub> O–H                                                              | 436.0                           |                                                                                      |                                 |
| Bu <sup>i</sup> CH <sub>2</sub> O–H                                                 | 436.1                           |                                                                                      |                                 |
| Et <sub>2</sub> MeO–H                                                               | 431.1                           |                                                                                      |                                 |
| <b>Aliphatic acids</b>                                                              |                                 |                                                                                      |                                 |
| AcO–H                                                                               | 445.8 (443–445)                 |    | 446.2                           |
| EtC(O)O–H                                                                           | 439.3 (445)                     |    | 443.7                           |
| Pr <sup>n</sup> C(O)O–H                                                             | 439.8 (443)                     |    | 447.7                           |
| Bu <sup>n</sup> C(O)O–H                                                             | 442.1                           |    | 447.7                           |
| n-C <sub>5</sub> H <sub>11</sub> C(O)O–H                                            | 439.3                           |   | 441.7                           |
| n-C <sub>6</sub> H <sub>13</sub> C(O)O–H                                            | 444.4                           |  | 441.8                           |
| n-C <sub>7</sub> H <sub>15</sub> C(O)O–H                                            | 438.5                           |                                                                                      |                                 |
| n-C <sub>8</sub> H <sub>17</sub> C(O)O–H                                            | 443.0                           |                                                                                      |                                 |
| n-C <sub>9</sub> H <sub>19</sub> C(O)O–H                                            | 437.8                           |                                                                                      |                                 |
| n-C <sub>11</sub> H <sub>23</sub> C(O)O–H                                           | 445.8                           |                                                                                      |                                 |
| Pr <sup>i</sup> C(O)O–H                                                             | 435.2                           |                                                                                      |                                 |
| ClCH <sub>2</sub> C(O)O–H                                                           | 458.9                           |                                                                                      |                                 |
| PhCH <sub>2</sub> C(O)O–H                                                           | 448.0                           |                                                                                      |                                 |
|   | 448.8                           |                                                                                      |                                 |
|  | 448.3                           |                                                                                      |                                 |
| <b>Benzoic acids</b>                                                                |                                 |                                                                                      |                                 |
| PhC(O)O–H                                                                           | 438.0 (439.3)                   |  | 445.3                           |
|  | 444.2                           |  | 448.9                           |
|  | 448.6                           |  | 442.1                           |
|  | 451.1                           |  | 445.5                           |
|  | 443.5                           |  | 449.6                           |
|  | 447.8                           |  | 449.1                           |
|  | 447.0                           |  | 448.5                           |
|  | 448.2                           |  | 448.3                           |
|  | 445.4                           |                                                                                      |                                 |

**Note.** Data taken from handbook<sup>5</sup> are given in parentheses.

3. The decomposition of a molecule must follow a homolytic pathway only. The introduction of radical acceptor excludes a concurrent heterolytic decomposition of the peroxide. If only homolysis occurs, the rate of consumption of the radical acceptor equals the rate of peroxide decomposition within the accuracy to the escape probability ( $e$ ) of radicals from the cage to the bulk ( $e \approx 0.3-0.8$  for conventional solvents<sup>37</sup>).

#### IV. Linear correlations

Evans and Polanyi<sup>40</sup> were the first who found an empirical linear correlation between the activation energy and the enthalpy of reaction taking the reactions



as examples.

Semenov<sup>41</sup> extended this correlation to abstraction reaction involving various molecules and radicals and obtained the following averaged expression for such reactions:

$$E_a = A' + \alpha' \Delta H, \quad (19)$$

where  $\alpha' = 0.25$  and  $A' = 48 \text{ kJ mol}^{-1}$ . More recently, it was shown that this correlation equation correctly describes 'narrow' reaction series with the same reaction centre for each series characterised by its own coefficients  $\alpha'$  and  $A'$ . Listed below are the X–H bond dissociation energies<sup>5</sup> and the  $\alpha'$  and  $A'$  coefficients for a number of reaction series of  $X^{\cdot}$  radical (X atom) reacting with the C–H bonds of paraffin hydrocarbons:<sup>42</sup>

| $X^{\cdot}$ (X)               | $D_{X-H} / \text{kJ mol}^{-1}$ | $\alpha'$ | $A' / \text{kJ mol}^{-1}$ |
|-------------------------------|--------------------------------|-----------|---------------------------|
| HO $^{\cdot}$                 | 499.1                          | 0.25      | 31.6                      |
| H $^{\cdot}$                  | 436.0                          | 0.38      | 46.0                      |
| O $^{\cdot}$                  | 427.5                          | 0.52      | 64.0                      |
| H <sub>3</sub> C $^{\cdot}$   | 440                            | 0.52      | 62.0                      |
| MeO $^{\cdot}$                | 436.2                          | 0.59      | 49.0                      |
| F <sub>3</sub> C $^{\cdot}$   | 449.4                          | 0.66      | 60.0                      |
| MeC $^{\cdot}$ H <sub>2</sub> | 422                            | 0.70      | 53.0                      |
| Cl <sub>3</sub> C $^{\cdot}$  | 392.5                          | 0.94      | 67.0                      |
| Br $^{\cdot}$                 | 366.3                          | 0.86      | 16.0                      |
| I $^{\cdot}$                  | 298.4                          | 0.97      | 9.7                       |

In these ten reaction series the  $\alpha'$  coefficient varies from 0.25 to 0.97. The  $\alpha'$  and  $D_{X-H}$  values vary in antiparallel fashion, namely, the higher the  $D_{X-H}$  value, the smaller the  $\alpha'$  coefficient. The enthalpies of the investigated reactions of hydroxyl radical ( $D_{X-H} = 499.1 \text{ kJ mol}^{-1}$ ) vary in the range from  $-60$  to  $-100 \text{ kJ mol}^{-1}$  at  $\alpha' = 0.25$ . In contrast, similar reactions of iodine atoms ( $D_{I-H} = 298.4 \text{ kJ mol}^{-1}$ ) are highly endothermic ( $\Delta H \approx 100-140 \text{ kJ mol}^{-1}$ ) and the  $\alpha'$  coefficient approaches unity. Naturally, one can assume that the  $E_a$ -vs.- $\Delta H$  dependence is nonlinear and therefore the  $\alpha' = dE_a/d(\Delta H)$  parameter depends on the range of changes in  $\Delta H$  in each reaction series. This issue was considered in a review.<sup>43</sup>

Linear dependence (19) is often used for estimating the bond dissociation energy. To this end, it is written as follows:

$$D_i = D_1 + \frac{E_{ai} - E_{a1}}{\alpha'} \quad (20)$$

or

$$D_i = D_1 + \frac{RT}{\alpha'} \ln \left( \frac{n_i k_1}{n_1 k_i} \right), \quad (21)$$

where  $k_1$ ,  $E_{a1}$  and  $D_1$  are respectively the rate constant for, the activation energy for and the bond strength corresponding to the reaction of the  $X^{\cdot}$  radical with the compound  $R^1H$  with known strength of the X–H bond being formed,  $n_1$  is the number of

equally reactive bonds in the  $R^1H$  molecule involved in the reaction; and  $k_i$ ,  $n_i$ ,  $E_{ai}$  and  $D_i$  are the corresponding parameters of the reaction between the  $X^{\cdot}$  radical and  $R^1H$  compound. Calculations give  $\Delta D_i = \pm 2/\alpha' \text{ kJ mol}^{-1}$  provided that the error in determination of the activation energy is  $2 \text{ kJ mol}^{-1}$ . The accuracy of calculations can be improved by considering the partial rate constant,  $k$ , for the reaction per equally reactive C–H bond involved in the reaction of the  $X^{\cdot}$  radical with  $R^1H$  rather than the activation energy. The method is applicable to any reaction which belongs to the same series characterised by the  $\alpha'$  coefficient and lies within the difference  $\Delta H_{\min} - \Delta H_{\max}$  for this reaction series.

The kinetics of heterolytic reactions widely uses linear correlations based on linear relations for the free energy.<sup>44,45</sup> Correlations of the type

$$\log k_i = \log k_0 + \rho \sigma, \quad (22)$$

where  $\rho$  is the correlation coefficient,  $\sigma$  is the Hammett constant [or analogous Brown constants ( $\sigma^+$ ) and Taft constants ( $\sigma^*$ )] are also used in radical chemistry.<sup>46,47</sup> Equation (22) can be reduced to the Polanyi–Semenov equation (19) at a constant pre-exponent for a given reaction series. Seemingly, Eqn (22) can also be employed for estimating the bond strength from the kinetic data for corresponding series of compounds using the following transformation:

$$D_i = D_0 + \rho \sigma, \quad (23)$$

where  $D_i = D_0$  for the compound characterised by  $\sigma = 0$ . However, special care must be taken when using such correlations. Figure 2 shows the O–H bond strengths in monosubstituted phenols (the data for twenty-seven phenols were taken from handbook<sup>21</sup>) plotted vs. Hammett constants. Although we do observe a trend towards an increase in the  $D_{O-H}$  values as the  $\sigma$  constant increases, the correlation is very poor, because the correlation coefficient is only 0.75. The correlation equation of the straight line shown in Fig. 2 has the form

$$D_{O-H} (\text{kJ mol}^{-1}) = (364.8 \pm 1.4) + (19.22 \pm 3.44) \sigma. \quad (24)$$

For eight phenols the  $D_{O-H}$  values differ from the predicted results by more than  $10 \text{ kJ mol}^{-1}$ . Apparently, the reasons for poor correlation consist in fundamentally different stabilising effects of certain substituents Y on the acid anion  $YC_6H_4CO_2^-$  and the aroxyl radical  $YC_6H_4O^{\cdot}$  and in an additional solvation effect of the polar solvent on the benzoic acid anion, whereas the phenoxyl radical is generated in the non-polar solvent characterised by weaker solvation of reactants and transition state. Clearly, this type of correlation cannot serve as a reliable procedure for evaluating the bond strengths in molecules.

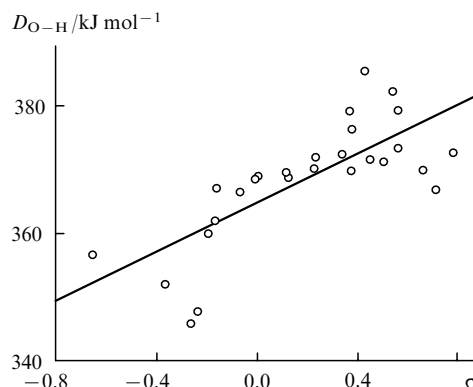
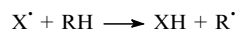


Figure 2. O–H bond dissociation energies ( $D_{O-H}$ ) in phenols 4- $YC_6H_4OH$  plotted vs. Hammett constants ( $\sigma$ ).

## V. Parabolic model for radical reactions

In the framework of the intersecting parabolas (IP) model the transition state of a radical reaction



is treated as a result of intersection of two potential energy curves.<sup>21, 37, 43, 45, 48</sup> One of them characterises the potential energy of the stretching vibration of the attacked R–H bond ( $U_{R-H}$ ) as a function of the vibration amplitude while the other characterises the potential energy of the vibration of the X–H bond being formed ( $U_{X-H}$ ). The stretching vibrations of the bonds are considered harmonic:

$$U_{R-H}^{1/2} = b\Delta r_{R-H},$$

$$U_{X-H}^{1/2} = b_f\Delta r_{X-H},$$

where  $\Delta r_{R-H}$  and  $\Delta r_{X-H}$  are the corresponding bond elongations in the transition state;  $b$  and  $b_f$  are the coefficients of proportionality ( $2b^2$  and  $2b_f^2$  are the force constants of the bond being cleaved and the bond being formed, respectively):

$$b = 2\pi\nu_{R-H}\mu_{R-H}^{1/2},$$

$$b_f = 2\pi\nu_{X-H}\mu_{X-H}^{1/2},$$

$\nu_{R-H}$  and  $\nu_{X-H}$  are the corresponding vibrational frequencies and  $\mu_{R-H}$  and  $\mu_{X-H}$  are the reduced masses of the atoms involved in the C–H and X–H bonds. Figure 3 presents the transition state diagram of the  $ROO^\bullet + RH$  reaction in the framework of the intersecting parabolas model.

A radical abstraction reaction is characterised by the following parameters:

- (1) enthalpy  $\Delta H_e$ , which includes the zero-point vibrational energy difference between the bond being cleaved and the bond being formed;
- (2) classical potential activation barrier  $E_e$ , which includes the zero-point vibrational energy of the bond being cleaved;
- (3) parameter  $r_e$  equal to the total elongation of the bond being cleaved and the bond being formed in the transition state;
- (4) coefficient  $b$ ;
- (5) parameter  $\alpha$  ( $\alpha^2$  is the force constant ratio of the bond being cleaved to the bond being formed);
- (6) pre-exponent  $A_0$  per equally reactive bond (in the molecule) involved in the reaction.

The parameters listed above are interrelated as follows:<sup>48</sup>

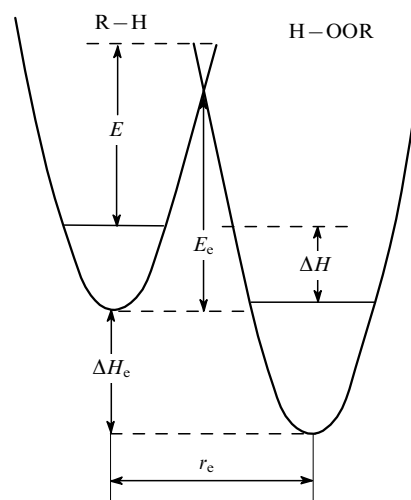


**Figure 3.** ‘Bond stretch – potential energy’ diagram for the  $ROO^\bullet + RH$  reaction in the framework of the intersecting parabolas model.

$$\Delta H_e = D_{R-H} - D_{X-H} + 0.5hN_A(\nu_{R-H} - \nu_{X-H}), \quad (25a)$$

$$br_e = \alpha\sqrt{E_e - \Delta H_e} + \sqrt{E_e}. \quad (25b)$$

Knowing the parameter  $br_e$ , one can calculate the classical potential barrier  $E_{e0}$  to a thermally neutral reaction characterised by  $\Delta H_e = 0$ :

$$E_{e0} = \frac{(br_e)^2}{(1 + \alpha)^2}. \quad (26)$$

The rate constant for the reaction is related to the activation energy,  $E_a$ , and the pre-exponent,  $A_0$ , by the Arrhenius relation:

$$k = nA_0 \exp\left(-\frac{E_a}{RT}\right), \quad (27)$$

where  $n$  is the number of equally reactive bonds in the reactant molecule.

The IP method allows the variety of radical reactions to be divided into classes using experimental data. Each class is characterised by the same set of parameters:  $\alpha$ ,  $br_e$ ,  $0.5hN_A\nu_{RH}$  ( $h$  is the Planck constant,  $N_A$  is the Avogadro constant) and  $A_0$  and an individual reaction belonging to a certain class is characterised by the enthalpy,  $\Delta H_e$ , and activation energy,  $E_e$ .

A method for estimating the bond strengths from the kinetic data, developed in the framework of the IP model, involves a number of versions.<sup>43, 49–51</sup>

1. With the measured rate constants  $k_i$  or the  $k_i/k_1$  ratios for a reaction class of the type  $X^\bullet + R^iH$  it is possible to estimate the bond strengths between the  $R^i-H$  and  $R^1-H$  compounds. The rate constant ratio,  $k_i/k_1$ , allows the activation energy difference,  $\Delta E_{ei}$ , between these reactions to be calculated:

$$\Delta E_{ei} = E_{ei} - E_{e1} = RT \ln \left( \frac{n_i k_i}{n_1 k_1} \right), \quad (28)$$

where  $n_1$  and  $n_i$  are respectively the numbers of equally reactive bonds in the  $R^1H$  and  $R^iH$  molecules attacked by the  $X^\bullet$  radical. From Eqns (25b) and (28) it follows that the relation between the  $\Delta E_{ei}$  value and the enthalpy difference  $\Delta(\Delta H_i)$  between these reactions has the form:<sup>49</sup>

$$\Delta(\Delta H_i) = 2br_e\alpha^{-2}(\sqrt{E_{ei}} - \sqrt{E_{e1}}) - (\alpha^{-2} - 1)\Delta E_{ei}. \quad (29)$$

On the other hand the enthalpy difference  $\Delta(\Delta H_i) = D_i - D_1$  and the energy of the  $R^i-H$  bond can be calculated using the equation

$$D_i = D_1 + 2br_e\alpha^{-2}(\sqrt{E_{ei}} - \sqrt{E_{e1}}) - (\alpha^{-2} - 1)\Delta E_{ei}. \quad (30)$$

Thus, calculations of the  $D_i$  values require knowledge of the  $D_1$ ,  $E_{e1}$ ,  $k_1/k_i$  ratio and the parameters characterising a given reaction class ( $br_e$  and  $\alpha$ ). Experience showed that the error in  $\Delta D$  measurements is 2–3 kJ mol<sup>−1</sup> (see Ref. 49). At low  $\Delta E_{ei}$  values ( $\Delta E_{ei} \ll E_{e1}$ ), Eqn (30) can be simplified:<sup>43</sup>

$$D_i = D_1 + \frac{1 + \alpha}{\alpha^2} \left( \sqrt{\frac{E_{e0}}{E_{e1}}} - 1 + \alpha \right) \Delta E_{ei}. \quad (31)$$

This approach was used for estimating  $D_{C-H}$  values in hydrocarbons,<sup>49, 50, 52</sup> oxygen-containing compounds,<sup>51, 53–55</sup> amines and amides,<sup>56, 57</sup> nitriles and nitro compounds;<sup>58</sup>  $D_{O-H}$  values in phenols<sup>59, 60</sup> and hydroxylamines;<sup>61</sup>  $D_{N-H}$  values in aromatic amines;<sup>62</sup>  $D_{S-H}$  values in thiophenols<sup>63, 64</sup> and  $D_{Si-H}$  values in silanes.<sup>65</sup>

2. Using different radicals  $X^\bullet$  (e.g.,  $X^i = R^iOO^\bullet$ ) in a series of radical reactions  $X^\bullet + RH$  belonging to the same class allows the approach to be employed for evaluating the  $X^i-H$  bond strengths. In this case Eqn (30) takes the form:

$$D_i = D_1 + 2br_e\alpha^{-2}(\sqrt{E_{e1}} - \sqrt{E_{ei}}) + (\alpha^{-2} - 1)\Delta E_{ei}. \quad (32)$$

This version of the technique was used in estimating the  $D_{O-H}$  values in hydroperoxides,<sup>66</sup> alcohols and acids.<sup>67</sup>

3. The  $D_i$  value for a reaction  $X^\bullet + R^iH$  can also be evaluated from the absolute value of the rate constant  $k_i$ . Since, according to the Arrhenius relation,

$$k_i = n_i A_0 \exp\left(-\frac{E_{ai}}{RT}\right),$$

the energy  $E_{ei}$  is calculated using the following equation

$$E_{ei} = RT \ln\left(\frac{A_0 n_i}{k_i}\right) + 0.5hN_A \nu_{R-H} - 0.5RT, \quad (33)$$

and  $\Delta H_e$  is calculated using the equation

$$\Delta H_e = E_{ei} - \alpha^{-2}(br_e - \sqrt{E_{ei}})^2, \quad (34)$$

from which after substituting expression (34) in Eqn (25a) we get:

$$D_i = D_{H-X} + E_{ei} - \alpha^{-2}(br_e - \sqrt{E_{ei}})^2 - 0.5hN_A(\nu_{R-H} - \nu_{X-H}). \quad (35)$$

In this case the error in the determination of  $D_i$  is usually higher than in the estimation using Eqn (32).

The parameters used for evaluating the  $D_i$  values in the radical abstraction reactions are listed in Table 5.

The limitation imposed on the method is associated with the enthalpy of reaction,  $\Delta H_e$  (see Refs 43 and 49). The case in point is that Eqn (26) is valid for reactions belonging to the same reaction class and characterised by enthalpies lying in the interval  $\Delta H_{e\min} < \Delta H_e < \Delta H_{e\max}$ . The activation energy for a highly exothermic reaction ( $\Delta H_e < \Delta H_{e\min}$ ) is nearly zero (more correctly,  $E = 0.5RT$ ) and independent of  $\Delta H$ . Therefore, the enthalpies,  $\Delta H_e$ , of such reactions cannot be estimated from the  $E_e$  values. The  $\Delta H_{e\min}$  value depends on the  $br_e$  and  $\alpha$  parameters and on the zero-point vibrational energy of the  $R-H$  bond being cleaved:

$$\alpha^2 \Delta H_{e\min} = -(br_e)^2 + 2br_e \sqrt{0.5hN_A \nu_{R-H}} + 0.5hN_A \nu_{R-H}(\alpha^2 - 1). \quad (36)$$

The activation energies of highly endothermic reactions ( $\Delta H_e > \Delta H_{e\max}$ ) approximately equal  $\Delta H_e$ , also being independent of the  $br_e$  and  $\alpha$  parameters:

$$E_e = \Delta H_e + 0.5RT. \quad (37)$$

The threshold value,  $\Delta H_{e\max}$ , depends on the  $\alpha$  and  $br_e$  parameters and on the zero-point vibrational energy of the bond being formed

$$\Delta H_{e\max} = (br_e)^2 - 2br_e \sqrt{0.5hN_A \nu_{X-H}} + 0.5hN_A \nu_{X-H}(\alpha^2 - 1). \quad (38)$$

An analogous method for evaluating the  $\Delta D$  values for two reactants from kinetic data ( $\Delta E$ ) was elaborated in the framework of the reaction model using two intersecting Morse curves.<sup>68, 69</sup> The results obtained by this technique and using the IP model are very similar.

**Table 5.** Parameters of the intersecting parabolas model used for calculating  $\Delta D$  values from experimental data.<sup>21, 37, 43, 48</sup>

| Reaction                 | $\alpha$ | $br_e / (\text{kJ mol}^{-1})^{1/2}$ | $E_{e0} / \text{kJ mol}^{-1}$ | $0.5hN_A(\nu - \nu_f) / \text{kJ mol}^{-1}$ | $A / \text{litre mol}^{-1} \text{ s}^{-1}$ |
|--------------------------|----------|-------------------------------------|-------------------------------|---------------------------------------------|--------------------------------------------|
| $H^\bullet + R^1H$       | 0.901    | 14.50                               | 58.2                          | -8.9                                        | $1.0 \times 10^{11}$                       |
| $H^\bullet + R^2H$       | 0.901    | 15.80                               | 69.1                          | -8.9                                        | $1.0 \times 10^{10}$                       |
| $H^\bullet + R^3H$       | 0.901    | 15.00                               | 62.3                          | -8.9                                        | $1.0 \times 10^{10}$                       |
| $R^1^\bullet + R^1H$     | 1.00     | 17.30                               | 74.8                          | 0                                           | $1.0 \times 10^9$                          |
| $R^1^\bullet + R^2H$     | 1.00     | 18.60                               | 86.5                          | 0                                           | $1.0 \times 10^8$                          |
| $R^1^\bullet + R^3H$     | 1.00     | 17.80                               | 79.2                          | 0                                           | $1.0 \times 10^8$                          |
| $R^2^\bullet + R^2H$     | 1.00     | 19.25                               | 92.6                          | 0                                           | $1.0 \times 10^8$                          |
| $R^2^\bullet + R^3H$     | 1.00     | 18.45                               | 85.1                          | 0                                           | $1.0 \times 10^8$                          |
| $R^3^\bullet + R^3H$     | 1.00     | 18.05                               | 81.4                          | 0                                           | $1.0 \times 10^8$                          |
| $Ph^\bullet + R^1H$      | 0.945    | 16.88                               | 75.3                          | -1.0                                        | $1.0 \times 10^9$                          |
| $Ph^\bullet + R^2H$      | 0.945    | 18.15                               | 87.1                          | -1.0                                        | $1.0 \times 10^8$                          |
| $Ph^\bullet + R^3H$      | 0.945    | 17.37                               | 79.7                          | -1.0                                        | $1.0 \times 10^8$                          |
| $RO^\bullet + R^1H$      | 0.796    | 12.73                               | 50.2                          | -4.3                                        | $1.0 \times 10^9$                          |
| $RO^\bullet + R^2H$      | 0.796    | 13.96                               | 60.4                          | -4.3                                        | $1.0 \times 10^8$                          |
| $RO^\bullet + R^3H$      | 0.796    | 13.54                               | 56.8                          | -4.3                                        | $1.0 \times 10^8$                          |
| $RO_2^\bullet + R^1H$    | 0.814    | 13.62                               | 56.14                         | -3.8                                        | $1.0 \times 10^8$                          |
| $RO_2^\bullet + R^2H$    | 0.814    | 15.20                               | 70.2                          | -3.8                                        | $1.0 \times 10^7$                          |
| $RO_2^\bullet + R^3H$    | 0.814    | 14.32                               | 62.3                          | -3.8                                        | $1.0 \times 10^7$                          |
| $R^1^\bullet + HSiR_3^4$ | 0.772    | 13.18                               | 55.3                          | -4.3                                        | $1.0 \times 10^9$                          |
| $R^1^\bullet + HGeR_3^4$ | 0.747    | 13.82                               | 62.6                          | -4.8                                        | $1.0 \times 10^9$                          |
| $R^1^\bullet + HSnR_3^4$ | 0.721    | 13.67                               | 63.1                          | -5.3                                        | $1.0 \times 10^9$                          |
| $R^1^\bullet + HSR^4$    | 0.808    | 11.80                               | 42.6                          | -3.6                                        | $2.0 \times 10^7$                          |
| $R^1^\bullet + Ar^1OH$   | 1.246    | 17.61                               | 61.5                          | 4.1                                         | $1.0 \times 10^8$                          |
| $R^1^\bullet + Ar^2OH$   | 1.246    | 20.58                               | 84.0                          | 4.1                                         | $1.0 \times 10^8$                          |
| $R^1^\bullet + AmOH$     | 1.246    | 17.82                               | 63.0                          | 4.1                                         | $1.0 \times 10^8$                          |
| $R^1^\bullet + AmH$      | 1.150    | 18.46                               | 73.7                          | 2.6                                         | $1.0 \times 10^9$                          |
| $H^\bullet + HPR_2^4$    | 0.736    | 12.61                               | 52.8                          | -12.4                                       | $2.0 \times 10^{10}$                       |
| $RO_2^\bullet + Ar^1OH$  | 1.014    | 13.16                               | 42.7                          | 0.3                                         | $3.2 \times 10^7$                          |
| $RO_2^\bullet + Ar^2OH$  | 1.014    | 14.30                               | 50.4                          | 0.3                                         | $3.2 \times 10^7$                          |
| $RO_2^\bullet + AmOH$    | 1.014    | 13.50                               | 44.9                          | 0.3                                         | $3.2 \times 10^7$                          |
| $RO_2^\bullet + AmH$     | 0.936    | 12.12                               | 39.2                          | -1.2                                        | $1.0 \times 10^8$                          |

Table 5 (continued).

| Reaction               | $\alpha$ | $br_e / (\text{kJ mol}^{-1})^{1/2}$ | $E_{e0} / \text{kJ mol}^{-1}$ | $0.5 h N_A (v - v_0) / \text{kJ mol}^{-1}$ | $A / \text{litre mol}^{-1} \text{ s}^{-1}$ |
|------------------------|----------|-------------------------------------|-------------------------------|--------------------------------------------|--------------------------------------------|
| $R'_s + R^4CH_2CN$     | 0.955    | 16.29                               | 69.4                          | -0.81                                      | $1.0 \times 10^9$                          |
| $R' + R^4CH_2CN$       | 1.000    | 14.29                               | 51.0                          | 0                                          | $1.0 \times 10^9$                          |
| $H' + R^1CH_2CN$       | 0.904    | 15.16                               | 63.4                          | -2.27                                      | $1.0 \times 10^{10}$                       |
| $R'_s + R^1NO_2$       | 0.955    | 16.88                               | 74.5                          | -0.55                                      | $1.0 \times 10^9$                          |
| $R^{1*} + R^1CH_2NO_2$ | 1.000    | 17.65                               | 77.9                          | 0                                          | $1.0 \times 10^9$                          |
| $H' + R^1Cl$           | 0.838    | 14.98                               | 66.4                          | -12.95                                     | $6.0 \times 10^{10}$                       |
| $H' + R^1Br$           | 0.672    | 11.36                               | 46.2                          | -12.56                                     | $4.0 \times 10^9$                          |
| $H' + R^1I$            | 0.502    | 9.22                                | 3.7                           | -11.52                                     | $1.0 \times 10^{11}$                       |
| $R^{1*} + CCl_3Br$     | 1.000    | 10.65                               | 28.4                          | 0                                          | $3.0 \times 10^9$                          |
| $H' + R^3Cl$           | 0.835    | 14.51                               | 62.5                          | -12.93                                     | $6.0 \times 10^9$                          |
| $H' + R^3Br$           | 0.672    | 11.56                               | 47.8                          | -12.56                                     | $8.0 \times 10^9$                          |
| $H' + R^1SO_2Cl$       | 1.906    | 27.18                               | 87.5                          | -9.66                                      | $1.0 \times 10^9$                          |
| $R'_s + R^3I$          | 1.000    | 4.77                                | 5.7                           | 0                                          | $4.0 \times 10^9$                          |
| $R' + R^1I$            | 1.000    | 10.60                               | 28.1                          | 0                                          | $4.0 \times 10^9$                          |
| $R' + R^1SH$           | 0.808    | 13.45                               | 55.3                          | -3.6                                       | $1.0 \times 10^9$                          |
| $RO' + R^1SH$          | 0.717    | 11.82                               | 47.4                          | -6.3                                       | $1.0 \times 10^9$                          |
| $RO'_2 + R^1SH$        | 0.733    | 11.82                               | 46.5                          | -5.8                                       | $1.0 \times 10^9$                          |
| $R^{3*} + ArSH$        | 0.904    | 13.45                               | 49.9                          | -2.0                                       | $1.0 \times 10^9$                          |

Note. In this Table,  $R^1H$ ,  $R^2H$  and  $R^3H$  denote paraffin, olefinic and alkylaromatic hydrocarbons, respectively.

## VI. Structure of molecular fragments and the C—H bond dissociation energies

The dissociation energies of the C—H bonds in hydrocarbon molecules were estimated from the experimental rate constants for abstraction reactions of the following radicals (the bond strengths were taken from Ref. 12):  $H_3C'$  ( $D_{C-H} = 440 \text{ kJ mol}^{-1}$ ),  $RC'H_2$  ( $D_{C-H} = 422 \text{ kJ mol}^{-1}$ ),  $Me_3C'$  ( $D_{C-H} = 400 \text{ kJ mol}^{-1}$ ),  $Ph'$  ( $D_{C-H} = 474 \text{ kJ mol}^{-1}$ ),  $PhC'H_2$  ( $D_{C-H} = 375 \text{ kJ mol}^{-1}$ ),  $RO'_2$  ( $D_{O-H} = 365.5 \text{ kJ mol}^{-1}$  for the secondary and  $D_{O-H} = 358.6 \text{ kJ mol}^{-1}$  for the tertiary alkylperoxy radicals).<sup>21</sup> The parameters for calculating the bond dissociation energies using the IP model are listed in Table 5 and the results of  $D_{C-H}$  calculations are presented in Tables 6–8.

The results obtained by this technique make it possible to significantly increase the number of hydrocarbons with known strengths of individual bonds.<sup>5</sup>

Attempts at evaluating the  $D_{C-H}$  values for various oxygen-containing compounds were found to be successful. In this case the limitation imposed on the IP method is as follows. All oxygen-containing molecules are polar and the reaction of a polar radical with a polar molecule leads to manifestation of the polar effect, which affects the activation energy.<sup>70–74</sup> Therefore, the C—H bond strengths in such compounds can be estimated only from the rate constants for reactions of non-polar alkyl radicals and hydrogen atom. The experimental  $D_{C-H}$  values for various alcohols, ketones and other oxygen-containing compounds are listed in Table 9.

Table 6. Dissociation energies (in  $\text{kJ mol}^{-1}$ ) of C—H bonds in linear and cyclic alkanes calculated using the intersecting parabolas model.<sup>37,49,50</sup>

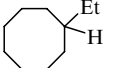
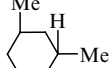
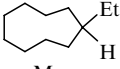
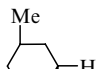
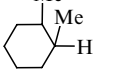
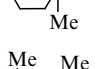
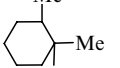
| Hydrocarbon                                                                         | $D_{R-H}$          | Hydrocarbon                                                                         | $D_{R-H}$ | Hydrocarbon                                                                         | $D_{R-H}$          | Hydrocarbon                                                                           | $D_{R-H}$          |
|-------------------------------------------------------------------------------------|--------------------|-------------------------------------------------------------------------------------|-----------|-------------------------------------------------------------------------------------|--------------------|---------------------------------------------------------------------------------------|--------------------|
| Linear alkanes                                                                      |                    |                                                                                     |           |                                                                                     |                    |                                                                                       |                    |
| $Bu^n(C-H)H_2$                                                                      | 422.0 <sup>a</sup> | $Et(C-H)HEt$                                                                        | 414.5     | $Pr^n(C-H)MeEt$                                                                     | 397.1              | $Me_3C-H$                                                                             | 400.0 <sup>a</sup> |
| $n-C_5H_{11}(C-H)H_2$                                                               | 422.0 <sup>a</sup> | $Pr^n(C-H)HEt$                                                                      | 414.5     | $n-C_5H_{11}(C-H)MeEt$                                                              | 396.6              | $Me_2(C-H)Et$                                                                         | 402.0              |
| $n-C_6H_{13}(C-H)H_2$                                                               | 422.0 <sup>a</sup> | $Bu^n(C-H)HEt$                                                                      | 414.5     | $Bu^i(C-H)H_2$                                                                      | 422.0 <sup>a</sup> | $Me_2(C-H)Pr^n$                                                                       | 399.3              |
| $Pr^n(C-H)HMe$                                                                      | 413.0 <sup>a</sup> | $n-C_5H_{11}(C-H)HEt$                                                               | 414.5     | $Bu^i(C-H)H_2$                                                                      | 422.0 <sup>a</sup> | $Me_2(C-H)Pr^i$                                                                       | 396.4              |
| $Bu^n(C-H)HMe$                                                                      | 413.0 <sup>a</sup> | $Pr^n(C-H)HPr^n$                                                                    | 415.7     | $Bu^i(C-H)HMe$                                                                      | 410.2              | $Me_2(C-H)Bu^i$                                                                       | 400.0              |
| $n-C_5H_{11}(C-H)HMe$                                                               | 413.0 <sup>a</sup> | $Bu^n(C-H)HPr^n$                                                                    | 415.7     | $Bu^i(C-H)Me_2$                                                                     | 399.6              | $Me_2(C-H)C_5H_{11}\text{-neo}$                                                       | 400.0              |
| $n-C_6H_{13}(C-H)HMe$                                                               | 413.0 <sup>a</sup> | $Et(C-H)MeEt$                                                                       | 399.7     | $Bu^i(CH_2)_2(C-H)Me_2$                                                             | 399.1              | $Me_2(C-H)C_5H_{11}\text{-sec}$                                                       | 405.4              |
|                                                                                     |                    |                                                                                     |           |                                                                                     |                    | $[Me_2(C-H)CH_2]_2$                                                                   | 400.0              |
| Cycloalkanes                                                                        |                    |                                                                                     |           |                                                                                     |                    |                                                                                       |                    |
|  | 429.0              |  | 392.3     |  | 403.9              |  | 393.0              |
|  | 418.5              |  | 392.2     |  | 401.9              |  | 390.3              |
|  | 408.4              |  | 392.8     |  | 402.9              |  | 392.0              |
|  | 408.8              |  | 407.7     |                                                                                     |                    |                                                                                       |                    |

Table 6 (continued).

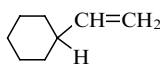
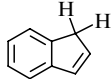
| Hydrocarbon  | $D_{R-H}$ | Hydrocarbon | $D_{R-H}$ | Hydrocarbon | $D_{R-H}$ | Hydrocarbon | $D_{R-H}$ |
|--------------|-----------|-------------|-----------|-------------|-----------|-------------|-----------|
| Cycloalkanes |           |             |           |             |           |             |           |
|              | 404.5     |             | 396.8     |             | 395.0     |             | 412.0     |
|              | 404.7     |             | 395.5     |             | 394.8     |             | 393.1     |
|              | 410.0     |             | 387.6     |             | 392.2     |             | 386.3     |
|              | 392.2     |             | 400.0     |             | 382.2     |             | 391.1     |
|              | 395.5     |             | 377.4     |             | 392.4     |             |           |
|              | 390.0     |             | 411.7     |             |           |             |           |

**Note.** From this point on the C–H bond for which the dissociation energy is calculated is given in parentheses. <sup>a</sup> The bond dissociation energies were taken from Ref. 12.

Table 7. Dissociation energies (in kJ mol<sup>−1</sup>) of C–H bonds in unsaturated hydrocarbons calculated using the intersecting parabolas model.<sup>37, 49, 50</sup>

| Hydrocarbon                                                                    | $D_{R-H}$          | Hydrocarbon                                    | $D_{R-H}$ | Hydrocarbon                                                  | $D_{R-H}$          |
|--------------------------------------------------------------------------------|--------------------|------------------------------------------------|-----------|--------------------------------------------------------------|--------------------|
| Linear compounds                                                               |                    |                                                |           |                                                              |                    |
| CH <sub>2</sub> = (C–H)H                                                       | 464.0 <sup>a</sup> | ( <i>E</i> )-MeCH = CH(C–H)H <sub>2</sub>      | 356.8     | ( <i>E</i> )-MeCH = CH(C–H)Me <sub>2</sub>                   | 333.9              |
| CH <sub>2</sub> = CH(C–H)H <sub>2</sub>                                        | 368.0 <sup>a</sup> | CH <sub>2</sub> = CEt(C–H)H <sub>2</sub>       | 367.7     | CH <sub>2</sub> = CH(C–H)HC <sub>5</sub> H <sub>11-n</sub>   | 348.8              |
| MeCH = (C–H)H                                                                  | 459.0 <sup>a</sup> | CH <sub>2</sub> = CMe(C–H)HMe                  | 347.2     | CH <sub>2</sub> = CMe(C–H)Me <sub>2</sub>                    | 351.1              |
| CH <sub>2</sub> = CH(C–H)HMe                                                   | 348.8              | ( <i>Z</i> )-MeCH = CH(C–H)HMe                 | 344.0     | ( <i>Z</i> )-MeCH = CH(C–H)HC <sub>5</sub> H <sub>11-n</sub> | 344.0              |
|                                                                                |                    | MeCH = CMe(C–H)H <sub>2</sub>                  | 352.4     | Me <sub>2</sub> C = CMe(C–H)H <sub>2</sub>                   | 352.8              |
| H(C–H)–CH=CHMe-( <i>E</i> )                                                    | 341.6              | ( <i>E</i> )-MeCH = CH(C–H)HMe                 | 346.2     | CH <sub>2</sub> = CHCH = CH(C–H)HPr <sup>n</sup>             | 331.9              |
| (CH <sub>2</sub> ) <sub>3</sub> CH=CHMe-( <i>E</i> )                           |                    | CH <sub>2</sub> = CHCHMe(C–H)H <sub>2</sub>    | 422.1     | ( <i>E</i> )-Me <sub>2</sub> (C–H)CH = CHPr <sup>i</sup>     | 336.1              |
|                                                                                |                    | MeCH = C = CH(C–H)H <sub>2</sub>               | 365.0     | HC ≡ C–H                                                     | 556.0 <sup>a</sup> |
| CH <sub>2</sub> = CHCH <sub>2</sub> (C–H)H <sub>2</sub>                        | 410.9              | CH <sub>2</sub> = CH(C–H)Me <sub>2</sub>       | 339.7     | HC ≡ C(C–H)H <sub>2</sub>                                    | 359.8              |
| CH <sub>2</sub> = CH(C–H)H(CH <sub>2</sub> ) <sub>4</sub> CH = CH <sub>2</sub> | 349.8              | CH <sub>2</sub> = CH(C–H)HCH = CH <sub>2</sub> | 318.0     | MeC ≡ C(C–H)H <sub>2</sub>                                   | 354.7              |
| ( <i>Z</i> )-MeCH = CH(C–H)H <sub>2</sub>                                      | 355.8              | Me <sub>2</sub> C = CH(C–H)HMe                 | 332.0     | HC ≡ C(C–H)HMe                                               | 346.8              |
| CH <sub>2</sub> = CMe(C–H)H <sub>2</sub>                                       | 357.9              | CH <sub>2</sub> = CH(C–H)HPr <sup>n</sup>      | 348.8     | Bu <sup>n</sup> C ≡ C(C–H)HPr <sup>n</sup>                   | 348.2              |
| Cyclic compounds                                                               |                    |                                                |           |                                                              |                    |
|                                                                                | 381.1              |                                                | 326.2     |                                                              | 329.3              |
|                                                                                | 338.9              |                                                | 346.6     |                                                              | 331.8              |
|                                                                                | 342.5              |                                                | 295.6     |                                                              | 288.8              |
|                                                                                | 332.7              |                                                | 357.2     |                                                              | 336.4              |
|                                                                                | 341.5              |                                                | 347.1     |                                                              | 330.9              |

Table 7 (continued).

| Hydrocarbon                                                                       | $D_{R-H}$ | Hydrocarbon                                                                       | $D_{R-H}$ | Hydrocarbon                                                                         | $D_{R-H}$ |
|-----------------------------------------------------------------------------------|-----------|-----------------------------------------------------------------------------------|-----------|-------------------------------------------------------------------------------------|-----------|
|  | 336.5     |  | 312.6     |  | 301.0     |
|                                                                                   |           |  | 341.8     |  | 339.9     |

<sup>a</sup> The bond dissociation energies were taken from Ref. 12.

Table 8. Dissociation energies (in kJ mol<sup>-1</sup>) of C–H bonds in aromatic hydrocarbons, pyridines and quinolines calculated using the intersecting parabolas model.<sup>37, 49, 52</sup>

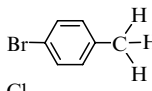
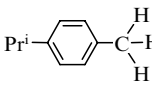
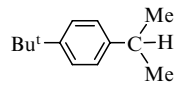
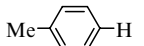
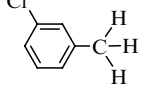
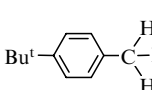
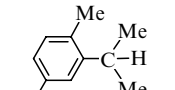
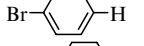
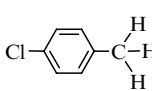
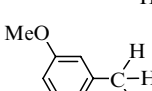
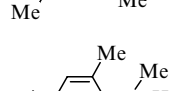
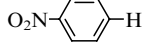
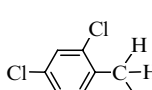
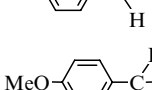
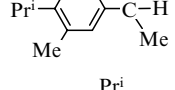
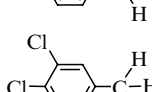
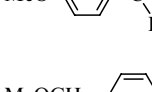
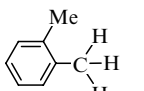
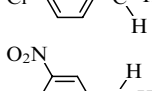
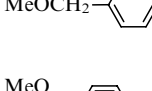
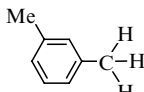
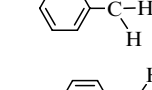
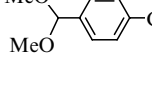
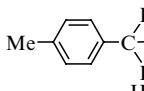
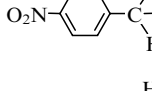
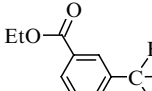
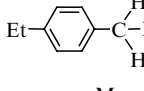
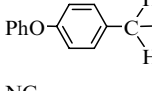
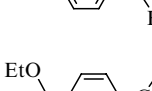
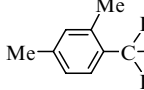
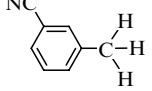
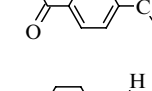
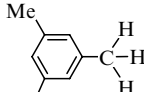
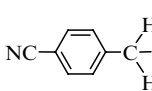
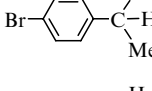
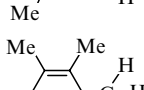
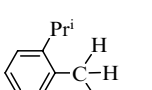
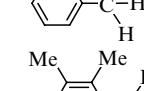
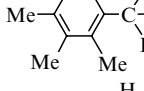
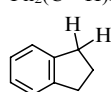
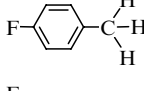
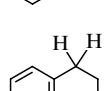
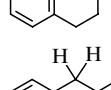
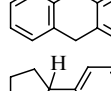
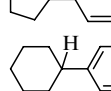
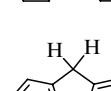
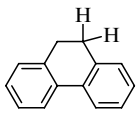
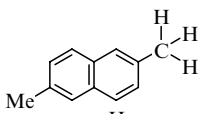
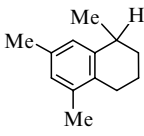
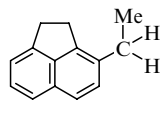
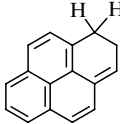
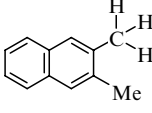
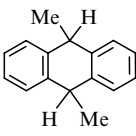
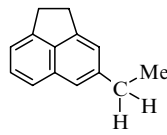
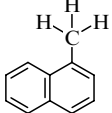
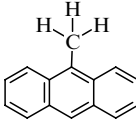
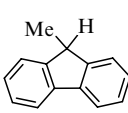
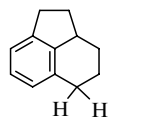
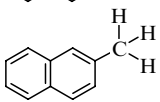
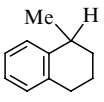
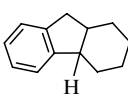
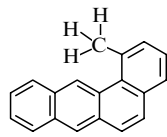
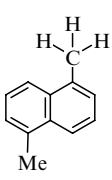
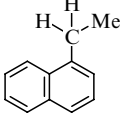
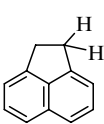
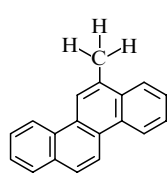
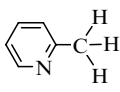
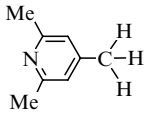
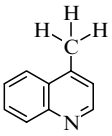
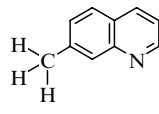
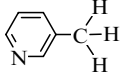
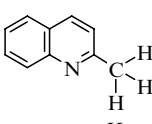
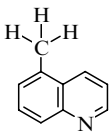
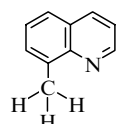
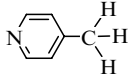
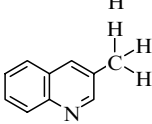
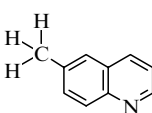
| Compound                                                                            | $D_{C-H}$          | Compound                                                                            | $D_{C-H}$ | Compound                                                                            | $D_{C-H}$ | Compound                                                                              | $D_{C-H}$ |
|-------------------------------------------------------------------------------------|--------------------|-------------------------------------------------------------------------------------|-----------|-------------------------------------------------------------------------------------|-----------|---------------------------------------------------------------------------------------|-----------|
| Aromatic hydrocarbons                                                               |                    |                                                                                     |           |                                                                                     |           |                                                                                       |           |
| Ph–H                                                                                | 474.0 <sup>a</sup> |    | 380.1     |    | 353.0     |    | 349.3     |
|    | 474.8              |    | 376.1     |    | 373.8     |    | 362.9     |
|    | 483.1              |   | 375.3     |   | 378.8     |   | 367.8     |
|    | 490.7              |  | 370.9     |  | 362.5     |  | 375.3     |
| Ph(C–H) <sub>2</sub>                                                                | 375.0 <sup>a</sup> |  | 369.6     |  | 357.5     |                                                                                       |           |
|   | 374.6              |  | 375.0     |  | 353.2     | PhCH <sub>2</sub> (C–H)HPh                                                            | 364.1     |
|  | 374.3              |  | 371.4     |  | 372.7     | Ph(C–H)HEt                                                                            | 366.2     |
|  | 372.5              |  | 377.3     |  | 374.1     | Ph(C–H)HMe                                                                            | 364.1     |
|  | 363.9              |  | 371.2     |  | 364.6     | Ph(C–H)Me <sub>2</sub>                                                                | 351.6     |
|  | 373.0              |  | 368.0     |  | 362.1     | PhCMe <sub>2</sub> (C–H)H <sub>2</sub>                                                | 412.6     |
|  | 373.9              |  | 366.6     |  | 380.2     | Ph <sub>2</sub> (C–H)H                                                                | 356.8     |
|  | 374.3              |  | 363.2     |                                                                                     |           | Ph <sub>3</sub> C–H                                                                   | 357.3     |
|  | 370.9              |                                                                                     |           |                                                                                     |           | Ph <sub>2</sub> (C–H)Me                                                               | 348.8     |
|  | 371.0              |                                                                                     |           |                                                                                     |           |  | 357.0     |
|  | 373.0              |                                                                                     |           |                                                                                     |           |  | 345.6     |
|                                                                                     |                    |                                                                                     |           |                                                                                     |           |  | 316.9     |
|                                                                                     |                    |                                                                                     |           |                                                                                     |           |  | 368.2     |
|                                                                                     |                    |                                                                                     |           |                                                                                     |           |  | 356.4     |
|                                                                                     |                    |                                                                                     |           |                                                                                     |           |  | 332.6     |



Table 8 (continued).

| Compound                                                                            | $D_{C-H}$ | Compound                                                                            | $D_{C-H}$ | Compound                                                                            | $D_{C-H}$ | Compound                                                                              | $D_{C-H}$ |
|-------------------------------------------------------------------------------------|-----------|-------------------------------------------------------------------------------------|-----------|-------------------------------------------------------------------------------------|-----------|---------------------------------------------------------------------------------------|-----------|
| Aromatic hydrocarbons                                                               |           |                                                                                     |           |                                                                                     |           |                                                                                       |           |
|    | 341.6     |    | 363.2     |    | 338.4     |    | 352.7     |
|    | 341.4     |    | 363.3     |    | 326.7     |    | 352.7     |
|    | 365.1     |    | 366.9     |    | 328.5     |    | 317.0     |
|    | 358.3     |    | 336.4     |    | 332.0     |    | 370.8     |
|   | 363.1     |    | 364.4     |    | 351.3     |   | 358.7     |
| Pyridines, quinolines                                                               |           |                                                                                     |           |                                                                                     |           |                                                                                       |           |
|  | 365.0     |  | 381.2     |  | 360.1     |  | 371.0     |
|  | 378.2     |  | 366.6     |  | 366.3     |  | 377.8     |
|  | 362.1     |  | 372.1     |  | 371.0     |                                                                                       |           |

<sup>a</sup> The bond dissociation energies were taken from Ref. 12.

In Table 10 we compare the  $D_{C-H}$  values obtained using the IP method with the published data. By and large, the results obtained are in reasonable agreement with one another, the differences between them lying within the scatter of the data that are also characteristic of other methods. Comparison of the two lists of compounds given in Tables 10 and 9 shows how the IP method made it possible to increase the number of compounds with known  $D_{C-H}$  values.

The strengths of the most reactive C–H bonds in aliphatic amines, nitriles, nitro compounds and sulfides (information on these parameters is scarce) were determined analogously. The results of calculations are listed in Table 11.

Empirical analysis of the effect of the structure of molecular fragments on the  $D_{C-H}$  values using the C–H bond strengths in various molecules (see Tables 6–11) makes it possible to draw some conclusions.

1. The presence of  $\alpha$ -C=C bonds causes the  $D_{C-H}$  value to decrease. Owing to stabilisation of the allyl radical the  $\alpha$ -C–H

bonds in olefins are much weaker than in paraffins. The effect of the neighbouring methyl groups on the allyl C–H bond is illustrated below (see also Table 7; the  $D$  values are given in  $\text{kJ mol}^{-1}$ ).

| Compound                                              | $D_{C-H}$ | $\Delta D$ |
|-------------------------------------------------------|-----------|------------|
| $\text{MeCH}_2(\text{C}-\text{H})\text{H}_2$          | 422       | 0          |
| $\text{CH}_2=\text{CH}(\text{C}-\text{H})\text{H}_2$  | 368       | –54.0      |
| $\text{CH}_2=\text{CH}(\text{C}-\text{H})\text{HMe}$  | 349.8     | –72.2      |
| $\text{CH}_2=\text{CH}(\text{C}-\text{H})\text{Me}_2$ | 339.6     | –82.4      |

As can be seen, not only the double bond but also the neighbouring methyl groups strongly affect the strength of the C–H bond in the  $\alpha$ -position with respect to the double bond. Replacement of a hydrogen atom at the carbon atom involved in the double bond by a methyl group also leads to reduction of  $D_{C-H}$  values, although to a somewhat lesser extent (see Table 4; the  $D_{C-H}$  values are given in  $\text{kJ mol}^{-1}$ ).

**Table 9.** Dissociation energies of C–H bonds in oxygen-containing compounds calculated using the intersecting parabolas model.<sup>51, 53–55</sup>

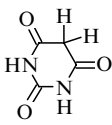
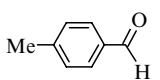
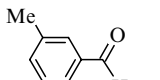
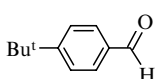
| Compound                                                                            | $D_{C-H} / \text{kJ mol}^{-1}$ | Compound                                                                            | $D_{C-H} / \text{kJ mol}^{-1}$ |
|-------------------------------------------------------------------------------------|--------------------------------|-------------------------------------------------------------------------------------|--------------------------------|
| <b>Alcohols</b>                                                                     |                                |                                                                                     |                                |
| H–CH <sub>2</sub> OH                                                                | 411.0 <sup>a</sup>             | MeCH(OH)(C–H)(OH)Me                                                                 | 383.1                          |
| Me(C–H)(OH)H                                                                        | 399.8                          | n-C <sub>6</sub> H <sub>19</sub> (C–H)(OH)H                                         | 395.5                          |
| Et(C–H)(OH)H                                                                        | 399.5                          | CH <sub>2</sub> =CH(C–H)(OH)H                                                       | 356.2                          |
|    | 388.4                          |    | 330.7                          |
| Pr <sup>n</sup> (C–H)(OH)H                                                          | 397.2                          | Me <sub>2</sub> (C–H)OH                                                             | 390.5                          |
| H–CH <sub>2</sub> (OH)CH <sub>2</sub> OH                                            | 401.5                          | Ph(C–H)(OH)H                                                                        | 366.9                          |
| EtMe(C–H)OH                                                                         | 389.7                          | Bu <sup>t</sup> (C–H)(OH)H                                                          | 395.2                          |
| HO(CH <sub>2</sub> ) <sub>3</sub> (C–H)(OH)H                                        | 404.2                          | Ph(C–H)(OH)Me                                                                       | 366.4                          |
| n-C <sub>5</sub> H <sub>11</sub> (C–H)(OH)H                                         | 391.4                          | H–CH <sub>2</sub> (OH)CMe <sub>2</sub> CH <sub>3</sub> OH                           | 408.3                          |
| HOCH <sub>2</sub> CH <sub>2</sub> (C–H)(OH)Me                                       | 387.7                          | H–CH <sub>2</sub> CMe <sub>2</sub> OH                                               | 417.4                          |
| n-C <sub>8</sub> H <sub>17</sub> (C–H)(OH)H                                         | 395.8                          |                                                                                     |                                |
| <b>Ketones</b>                                                                      |                                |                                                                                     |                                |
| MeC(O)(C–H)H <sub>2</sub>                                                           | 411.8                          | Me <sub>2</sub> (C–H)C(O)Pr <sup>i</sup>                                            | 387.5                          |
| MeC(O)C(O)(C–H)H <sub>2</sub>                                                       | 411.6                          | PhC(O)CH <sub>2</sub> (C–H)Me <sub>2</sub>                                          | 385.2                          |
| MeC(O)(C–H)HMe                                                                      | 392.6                          |                                                                                     |                                |
| MeC(O)(C–H)HC(O)Me                                                                  | 399.1                          |    | 401.2                          |
| MeC(O)(C–H)Me <sub>2</sub>                                                          | 383.8                          |                                                                                     |                                |
| MeC(O)(C–H)HC(O)OEt                                                                 | 396.5                          | PhC(O)(C–H)HC <sub>8</sub> H <sub>17-n</sub>                                        | 394.3                          |
| MeC(O)(C–H)HEt                                                                      | 397.2                          |                                                                                     |                                |
| PhC(O)(C–H)H <sub>2</sub>                                                           | 402.8                          |   | 394.1                          |
| Me(C–H)HC(O)Et                                                                      | 396.5                          |                                                                                     |                                |
| PhC(O)(C–H)HMe                                                                      | 394.4                          |  | 397.8                          |
| Et(C–H)HC(O)Pr <sup>n</sup>                                                         | 394.6                          |                                                                                     |                                |
| PhC(O)(C–H)Me <sub>2</sub>                                                          | 385.3                          |                                                                                     |                                |
| Pr <sup>n</sup> (C–H)HC(O)Bu <sup>n</sup>                                           | 395.8                          |                                                                                     |                                |
| PhC(O)(C–H)HEt                                                                      | 394.3                          |                                                                                     |                                |
| MeC(O)CH <sub>2</sub> (C–H)Me <sub>2</sub>                                          | 388.7                          |                                                                                     |                                |
| PhC(O)CMe <sub>2</sub> (C–H)H <sub>2</sub>                                          | 413.3                          |                                                                                     |                                |
| <b>Aldehydes</b>                                                                    |                                |                                                                                     |                                |
| HC(O)–H                                                                             | 377.8 <sup>a</sup>             | Bu <sup>t</sup> -4-CHO                                                              | 345.4                          |
| H–CH <sub>2</sub> C(O)H                                                             | 394.3 <sup>a</sup>             | O <sub>2</sub> N-3-CHO                                                              | 343.7                          |
| MeC(O)–H                                                                            | 373.8 <sup>a</sup>             | O <sub>2</sub> N-4-CHO                                                              | 340.4                          |
|                                                                                     | 373.8                          | MeO-3-CHO                                                                           | 350.9                          |
| Pr <sup>n</sup> C(O)–H                                                              | 371.2                          | MeO-4-CHO                                                                           | 346.4                          |
| Pr <sup>i</sup> C(O)–H                                                              | 364.5                          | PhO-4-CHO                                                                           | 347.1                          |
| Bu <sup>n</sup> C(O)–H                                                              | 372.0                          | Cl-4-CHO                                                                            | 352.3                          |
| Bu <sup>i</sup> C(O)–H                                                              | 362.6                          | Cl-3-CHO                                                                            | 353.6                          |
| Bu <sup>s</sup> C(O)–H                                                              | 360.8                          | Br-3-CHO                                                                            | 353.8                          |
| Bu <sup>t</sup> C(O)–H                                                              | 375.1                          |                                                                                     |                                |
| Et <sub>2</sub> CHC(O)–H                                                            | 367.2                          |                                                                                     |                                |
| n-C <sub>9</sub> H <sub>19</sub> C(O)–H                                             | 373.3                          |                                                                                     |                                |
| PhC(O)–H                                                                            | 348.0                          |                                                                                     |                                |
| PhCH <sub>2</sub> C(O)–H                                                            | 362.0                          |                                                                                     |                                |
| PhCMe <sub>2</sub> C(O)–H                                                           | 362.9                          |                                                                                     |                                |
| H–C(O)CO <sub>2</sub> H                                                             | 375.3                          |                                                                                     |                                |
| HOCH <sub>2</sub> (CHOH) <sub>3</sub> C(O)–H                                        | 370.0                          |                                                                                     |                                |
| HOCH <sub>2</sub> (CHOH) <sub>4</sub> C(O)–H                                        | 371.4                          |                                                                                     |                                |
|  | 345.8                          |                                                                                     |                                |
|  | 347.0                          |                                                                                     |                                |
|  | 337.1                          |                                                                                     |                                |

Table 9 (continued).

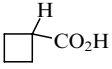
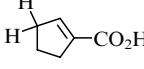
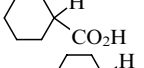
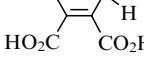
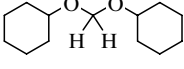
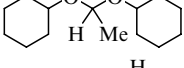
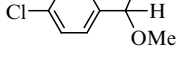
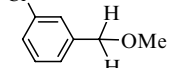
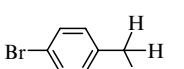
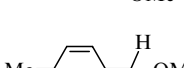
| Compound                                                                                               | $D_{C-H} / \text{kJ mol}^{-1}$ | Compound                                                                                  | $D_{C-H} / \text{kJ mol}^{-1}$ |
|--------------------------------------------------------------------------------------------------------|--------------------------------|-------------------------------------------------------------------------------------------|--------------------------------|
| <b>Acids</b>                                                                                           |                                |                                                                                           |                                |
| H – CO <sub>2</sub> H                                                                                  | 392.7                          | n-C <sub>5</sub> H <sub>11</sub> (C – H)HCO <sub>2</sub> H                                | 399.1                          |
| H – CH(CO <sub>2</sub> H) <sub>2</sub>                                                                 | 400.1                          | Ph(C – H)HCO <sub>2</sub> H                                                               | 367.0                          |
| H – CH <sub>2</sub> CO <sub>2</sub> H                                                                  | 414.1                          | n-C <sub>8</sub> H <sub>17</sub> (C – H)HCO <sub>2</sub> H                                | 399.0                          |
| HO <sub>2</sub> C(C – H)HCH <sub>2</sub> CO <sub>2</sub> H                                             | 397.8                          | Cl(C – H)HCO <sub>2</sub> H                                                               | 398.9                          |
| Me(C – H)HCO <sub>2</sub> H                                                                            | 398.9                          |          | 399.0                          |
| [(C – H)(OH)CO <sub>2</sub> H] <sub>2</sub>                                                            | 392.7                          |          | 359.8                          |
| Me <sub>2</sub> (C – H)CO <sub>2</sub> H                                                               | 388.3                          |          | 388.2                          |
| NC(C – H)HCO <sub>2</sub> H                                                                            | 398.4                          |          | 370.0                          |
| Et(C – H)HCO <sub>2</sub> H                                                                            | 398.7                          |                                                                                           |                                |
| MeC(O)NH(C – H)HCO <sub>2</sub> H                                                                      | 402.2                          |                                                                                           |                                |
| H – CH <sub>2</sub> CMe <sub>2</sub> CO <sub>2</sub> H                                                 | 415.2                          |                                                                                           |                                |
| MeC(O)NH(C – H)MeCO <sub>2</sub> H                                                                     | 393.0                          |                                                                                           |                                |
| Pr <sup>n</sup> (C – H)HCO <sub>2</sub> H                                                              | 399.4                          |                                                                                           |                                |
| Bu <sup>n</sup> (C – H)HCO <sub>2</sub> H                                                              | 397.1                          |                                                                                           |                                |
| H – C(OH)(CO <sub>2</sub> H)H                                                                          | 397.8                          |                                                                                           |                                |
| H – C(OH)(CO <sub>2</sub> H)Me                                                                         | 386.0                          |                                                                                           |                                |
| <b>Esters</b>                                                                                          |                                |                                                                                           |                                |
| MeCO <sub>2</sub> (C – H)H <sub>2</sub>                                                                | 404.0 <sup>a</sup>             | Bu <sup>n</sup> CO <sub>2</sub> (C – H)HC <sub>7</sub> H <sub>15-n</sub>                  | 391.9                          |
| MeC(O)(CH <sub>2</sub> ) <sub>6</sub> (C – H)HCO <sub>2</sub> Me                                       | 392.6                          | Bu <sup>i</sup> CO <sub>2</sub> CMe <sub>2</sub> (C – H)H <sub>2</sub>                    | 415.0                          |
| Et(C – H)HCO <sub>2</sub> Me                                                                           | 394.9                          | Bu <sup>i</sup> O <sub>2</sub> CCH <sub>2</sub> (C – H)HCO <sub>2</sub> H                 | 393.1                          |
| EtO <sub>2</sub> CCO <sub>2</sub> (C – H)HMe                                                           | 396.2                          | Bu <sup>i</sup> O <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub> (C – H)HCO <sub>2</sub> H | 391.0                          |
| Pr <sup>n</sup> (C – H)HCO <sub>2</sub> Me                                                             | 394.9                          | Bu <sup>i</sup> O <sub>2</sub> C(CH <sub>2</sub> ) <sub>3</sub> (C – H)HCO <sub>2</sub> H | 391.5                          |
| Bu <sup>n</sup> (C – H)HCO <sub>2</sub> Me                                                             | 394.5                          | Bu <sup>i</sup> O <sub>2</sub> C(CH <sub>2</sub> ) <sub>4</sub> (C – H)HCO <sub>2</sub> H | 391.3                          |
| Pr <sup>i</sup> O <sub>2</sub> CCO <sub>2</sub> (C – H)Me <sub>2</sub>                                 | 396.2                          | Bu <sup>i</sup> O <sub>2</sub> C(CH <sub>2</sub> ) <sub>7</sub> (C – H)HCO <sub>2</sub> H | 391.3                          |
| Pr <sup>i</sup> O <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> (C – H)Me <sub>2</sub> | 395.5                          | MeO <sub>2</sub> C(C – H)HCO <sub>2</sub> Me                                              | 391.7                          |
| Pr <sup>i</sup> O <sub>2</sub> C(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> (C – H)Me <sub>2</sub> | 391.7                          | MeO <sub>2</sub> CCO <sub>2</sub> (C – H)H <sub>2</sub>                                   | 403.9                          |
| Pr <sup>i</sup> O <sub>2</sub> C(CH <sub>2</sub> ) <sub>5</sub> CO <sub>2</sub> (C – H)Me <sub>2</sub> | 391.2                          | MeO <sub>2</sub> CCH <sub>2</sub> (C – H)HCO <sub>2</sub> Me                              | 404.8                          |
| Pr <sup>i</sup> O <sub>2</sub> C(CH <sub>2</sub> ) <sub>8</sub> CO <sub>2</sub> (C – H)Me <sub>2</sub> | 391.1                          | MeO <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub> (C – H)HCO <sub>2</sub> Me              | 393.1                          |
| Bu <sup>n</sup> CO <sub>2</sub> (C – H)HMe                                                             | 392.3                          | MeO <sub>2</sub> C(CH <sub>2</sub> ) <sub>4</sub> (C – H)HCO <sub>2</sub> Me              | 393.2                          |
| Bu <sup>n</sup> CO <sub>2</sub> (C – H)HEt                                                             | 392.1                          | PhCO <sub>2</sub> (C – H)H <sub>2</sub>                                                   | 418.4                          |
| Bu <sup>n</sup> CO <sub>2</sub> (C – H)Me <sub>2</sub>                                                 | 387.9                          | PhSiMe <sub>2</sub> (C – H)H <sub>2</sub>                                                 | 410.1                          |
| <b>Ethers and acetals</b>                                                                              |                                |                                                                                           |                                |
| MeO(C – H)H <sub>2</sub>                                                                               | 411.9                          | (EtO) <sub>2</sub> (C – H)Pr <sup>i</sup>                                                 | 380.5                          |
| PhO(C – H)H <sub>2</sub>                                                                               | 385.0                          | (iso-C <sub>5</sub> H <sub>11</sub> O) <sub>2</sub> (C – H)Me                             | 378.3                          |
| EtO(C – H)HMe                                                                                          | 399.5                          | (Pr <sup>n</sup> O) <sub>2</sub> (C – H)Pr <sup>i</sup>                                   | 379.5                          |
| Bu <sup>i</sup> OCMe <sub>2</sub> (C – H)H <sub>2</sub>                                                | 402.1                          | (Pr <sup>i</sup> O) <sub>2</sub> (C – H)Pr <sup>i</sup>                                   | 381.4                          |
| Pr <sup>i</sup> O(C – H)Me <sub>2</sub>                                                                | 390.8                          | (Bu <sup>n</sup> O) <sub>2</sub> (C – H)Pr <sup>i</sup>                                   | 379.0                          |
| Bu <sup>n</sup> O(C – H)HPr <sup>n</sup>                                                               | 392.2                          | (Bu <sup>s</sup> O) <sub>2</sub> (C – H)Pr <sup>i</sup>                                   | 380.5                          |
| MeO(C – H)HPh                                                                                          | 359.0                          | (Pr <sup>i</sup> O) <sub>2</sub> (C – H)Me                                                | 382.9                          |
| MeO(C – H)Ph <sub>2</sub>                                                                              | 354.1                          | (Bu <sup>n</sup> O) <sub>2</sub> (C – H)Me                                                | 379.0                          |
| PhCH <sub>2</sub> O(C – H)HPh                                                                          | 359.0                          | (MeO) <sub>2</sub> (C – H)Pr <sup>n</sup>                                                 | 378.8                          |
| (MeO) <sub>2</sub> (C – H)H                                                                            | 391.0                          | (EtO) <sub>2</sub> (C – H)Pr <sup>n</sup>                                                 | 378.3                          |
| (MeO) <sub>2</sub> (C – H)Me                                                                           | 381.2                          |       | 384.3                          |
| (Bu <sup>n</sup> O) <sub>2</sub> (C – H)H                                                              | 390.2                          |       | 380.2                          |
| (EtO) <sub>2</sub> (C – H)H                                                                            | 390.1                          |       | 359.5                          |
| (MeO) <sub>2</sub> (C – H)Ph                                                                           | 353.9                          |       | 360.9                          |
| (EtO) <sub>2</sub> (C – H)Me                                                                           | 380.2                          |       | 357.9                          |
| (MeO) <sub>2</sub> (C – H)Pr <sup>i</sup>                                                              | 381.4                          |       | 357.3                          |
| (Pr <sup>n</sup> O) <sub>2</sub> (C – H)H                                                              | 391.8                          |                                                                                           |                                |
| (EtO) <sub>2</sub> (C – H)Ph                                                                           | 376.5                          |                                                                                           |                                |
| (Pr <sup>n</sup> O) <sub>2</sub> (C – H)Me                                                             | 379.6                          |                                                                                           |                                |
| (Pr <sup>i</sup> O) <sub>2</sub> (C – H)Pr <sup>n</sup>                                                | 379.6                          |                                                                                           |                                |
| (Pr <sup>i</sup> O) <sub>2</sub> (C – H)H                                                              | 390.5                          |                                                                                           |                                |
| (Pr <sup>i</sup> O) <sub>2</sub> (C – H)Me                                                             | 380.7                          |                                                                                           |                                |
| (Bu <sup>n</sup> O) <sub>2</sub> (C – H)Me                                                             | 378.9                          |                                                                                           |                                |
| (Bu <sup>i</sup> O) <sub>2</sub> (C – H)Me                                                             | 380.1                          |                                                                                           |                                |
| (Bu <sup>s</sup> O) <sub>2</sub> (C – H)H                                                              | 389.5                          |                                                                                           |                                |
| (n-C <sub>5</sub> H <sub>11</sub> O) <sub>2</sub> (C – H)Pr <sup>i</sup>                               | 378.3                          |                                                                                           |                                |
| (sec-C <sub>5</sub> H <sub>11</sub> O)(C – H)Pr <sup>i</sup>                                           | 379.6                          |                                                                                           |                                |
| [iso-C <sub>5</sub> H <sub>11</sub> O] <sub>2</sub> (C – H)H                                           | 388.4                          |                                                                                           |                                |
| (Bu <sup>s</sup> O) <sub>2</sub> (C – H)H                                                              | 391.5                          |                                                                                           |                                |
| (n-C <sub>5</sub> H <sub>11</sub> O) <sub>2</sub> (C – H)Me                                            | 378.3                          |                                                                                           |                                |
| (sec-C <sub>5</sub> H <sub>11</sub> O) <sub>2</sub> (C – H)H                                           | 390.2                          |                                                                                           |                                |

Table 9 (continued).

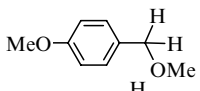
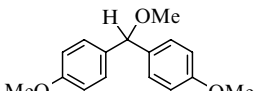
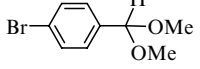
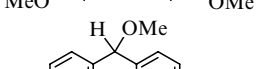
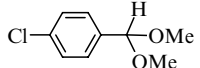
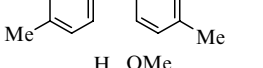
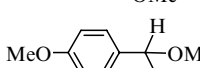
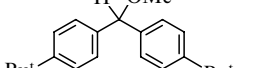
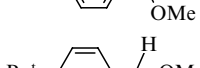
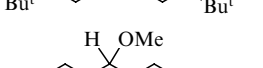
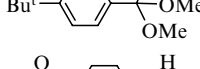
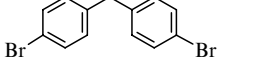
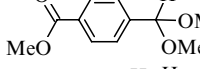
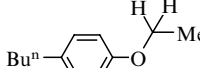
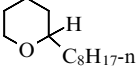
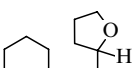
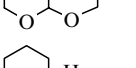
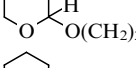
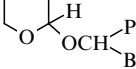
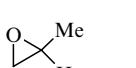
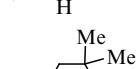
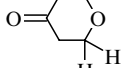
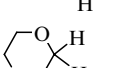
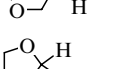
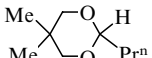
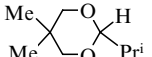
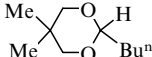
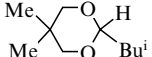
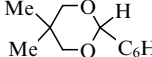
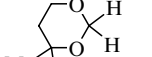
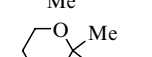
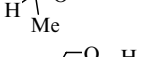
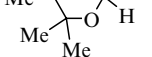
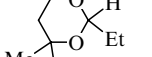
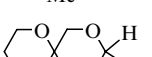
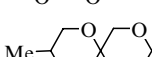
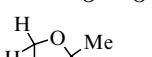
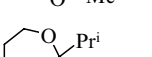
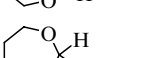
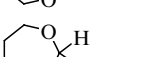
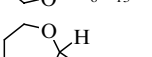
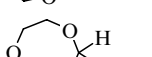
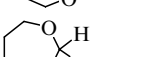
| Compound                                                                            | $D_{C-H}/\text{kJ mol}^{-1}$ | Compound                                                                            | $D_{C-H}/\text{kJ mol}^{-1}$ |
|-------------------------------------------------------------------------------------|------------------------------|-------------------------------------------------------------------------------------|------------------------------|
| Ethers and acetals                                                                  |                              |                                                                                     |                              |
|    | 354.5                        |   | 342.8                        |
|    | 354.3                        |   | 346.6                        |
|    | 354.3                        |   | 347.6                        |
|    | 353.2                        |   | 350.1                        |
|    | 353.1                        |   | 353.5                        |
|    | 355.2                        |   | 352.4                        |
|    | 357.7                        |                                                                                     |                              |
|    | 350.0                        |                                                                                     |                              |
| Cyclic ethers and acetals                                                           |                              |                                                                                     |                              |
|  | 391.6                        |  | 380.5                        |
|  | 384.1                        |  | 377.1                        |
|  | 387.5                        |  | 383.7                        |
|  | 381.4                        |  | 380.5                        |
|  | 378.5                        |  | 376.0                        |
|  | 374.3                        |  | 389.6                        |
|  | 375.3                        |  | 405.7                        |
|  | 401.7                        |  | 381.2                        |
|  | 386.0                        |  | 373.4                        |
|  | 385.0                        |  | 372.5                        |
|  | 386.0                        |                                                                                     |                              |
|  | 381.8                        |                                                                                     |                              |

Table 9 (continued).

| Compound                                                                            | $D_{C-H}/\text{kJ mol}^{-1}$ | Compound                                                                            | $D_{C-H}/\text{kJ mol}^{-1}$ |
|-------------------------------------------------------------------------------------|------------------------------|-------------------------------------------------------------------------------------|------------------------------|
| Cyclic ethers and acetals                                                           |                              |                                                                                     |                              |
|    | 373.1                        |    | 379.4                        |
|    | 372.2                        |    | 380.1                        |
|    | 371.3                        |    | 379.1                        |
|    | 373.6                        |    | 378.5                        |
|    | 371.6                        |    | 378.1                        |
|    | 373.2                        |    | 389.8                        |
|    | 381.7                        |    | 389.7                        |
|    | 388.0                        |    | 388.4                        |
|   | 378.0                        |   | 381.4                        |
|  | 381.7                        |  | 390.8                        |
|  | 377.7                        |  | 375.5                        |
|  | 377.0                        |  | 404.8                        |
|  | 376.5                        |  | 377.4                        |
|  | 378.4                        |  | 378.1                        |
|  | 383.6                        |  | 373.6                        |
|  | 378.9                        |  | 385.5                        |
|  | 396.2                        |  | 400.9                        |
|  | 388.7                        |  | 380.8                        |
|  | 380.3                        |  | 379.2                        |

<sup>a</sup> The bond dissociation energies were taken from Ref. 12.

**Table 10.** Dissociation energies of C–H bonds in oxygen-containing compounds calculated using the intersecting parabolas model as compared with published data.

| Compound                                                                          | $D_{C-H}/\text{kJ mol}^{-1}$ |                                                                                                        |
|-----------------------------------------------------------------------------------|------------------------------|--------------------------------------------------------------------------------------------------------|
|                                                                                   | IP model                     | Published data                                                                                         |
| H–CH <sub>2</sub> OH                                                              | 411.0                        | 401.9, <sup>5</sup> 402.1, <sup>10</sup> 411.0, <sup>12</sup> 384.9, <sup>13</sup> 401.8 <sup>75</sup> |
| Me(C–H)(OH)H                                                                      | 399.8                        | 401.3, <sup>5</sup> 389.1, <sup>9</sup> 384.9, <sup>13</sup> 389.2, <sup>75</sup> 392.5 <sup>76</sup>  |
| Et(C–H)(OH)H                                                                      | 399.5                        | 392.0, <sup>12</sup> 394.6 <sup>76</sup>                                                               |
| Me <sub>2</sub> (C–H)OH                                                           | 390.5                        | 381.2, <sup>5</sup> 380.7, <sup>9</sup> 372.4, <sup>13</sup> 383.7 <sup>76</sup>                       |
| H–CH <sub>2</sub> CMe <sub>2</sub> OH                                             | 417.4                        | 418.4, <sup>5</sup> 414.2, <sup>13</sup> 383.3 <sup>76</sup>                                           |
|  | 388.4                        | 386.6 <sup>5</sup>                                                                                     |
| H–CH <sub>2</sub> (OH)CH <sub>2</sub> OH                                          | 401.5                        | 376.6, <sup>13</sup> 385.4 <sup>76</sup>                                                               |
| CH <sub>2</sub> =CH(C–H)(OH)H                                                     | 356.2                        | 341.4 <sup>5</sup>                                                                                     |
| H–C(O)H                                                                           | 377.8                        | 368.2, <sup>10</sup> 376.0, <sup>12</sup> 386.4 <sup>75</sup>                                          |
| MeC(O)–H                                                                          | 373.8                        | 372.0, <sup>12</sup> 373.8 <sup>75</sup>                                                               |
| H–CH <sub>2</sub> C(O)H                                                           | 394.3                        | 394.6, <sup>12</sup> 394.3 <sup>75</sup>                                                               |
| MeC(O)(C–H)H <sub>2</sub>                                                         | 411.8                        | 389.1, <sup>76</sup> 411.3 <sup>75</sup>                                                               |
| MeC(O)(C–H)HMe                                                                    | 392.6                        | 386.2 <sup>9</sup>                                                                                     |
| EtO(C–H)HMe                                                                       | 399.5                        | 386.2, <sup>9</sup> 384.9 <sup>13</sup>                                                                |

**Table 11.** Dissociation energies of C–H bonds in nitrogen- and sulfur-containing compounds calculated from experimental data using the intersecting parabolas model.

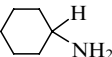
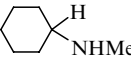
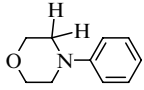
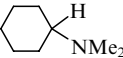
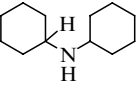
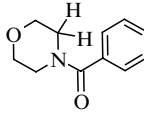
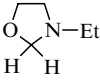
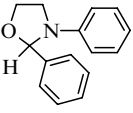
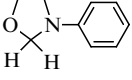
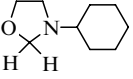
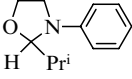
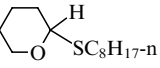
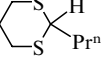
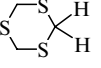
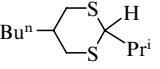
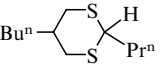
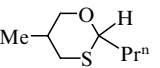
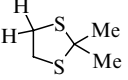
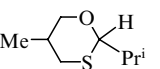
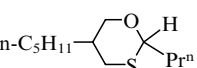
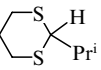
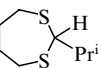
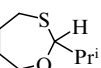
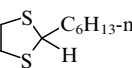
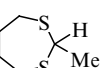
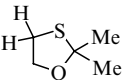
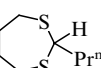
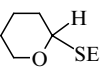
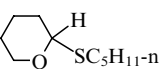
| Compound                                                                            | $D_{C-H}/\text{kJ mol}^{-1}$ | Compound                                                                            | $D_{C-H}/\text{kJ mol}^{-1}$ |
|-------------------------------------------------------------------------------------|------------------------------|-------------------------------------------------------------------------------------|------------------------------|
| Amines and amides <sup>56,57</sup>                                                  |                              |                                                                                     |                              |
| H <sub>2</sub> N(C–H)H <sub>2</sub>                                                 | 400.0                        |  | 385.6                        |
| MeNH(C–H)H <sub>2</sub>                                                             | 389.0                        |                                                                                     |                              |
| Me <sub>2</sub> N(C–H)H <sub>2</sub>                                                | 376.6                        | CH <sub>2</sub> =CH(C–H)HN(CH <sub>2</sub> CH=CH <sub>2</sub> ) <sub>2</sub>        | 345.6                        |
| H <sub>2</sub> N(C–H)HMe                                                            | 389.6                        | CH <sub>2</sub> =CH(C–H)HN(CH <sub>2</sub> CH=CH <sub>2</sub> )Ph                   | 339.3                        |
| EtNH(C–H)HMe                                                                        | 384.6                        | H <sub>2</sub> N(C–H)HPh                                                            | 368.0                        |
| Et <sub>2</sub> N(C–H)HMe                                                           | 379.5                        | Me <sub>2</sub> N(C–H)HPh                                                           | 370.8                        |
| H <sub>2</sub> N(C–H)Me <sub>2</sub>                                                | 379.5                        | (PhCH <sub>2</sub> ) <sub>2</sub> N(C–H)HPh                                         | 372.8                        |
| Pr <sup>i</sup> NH(C–H)Me <sub>2</sub>                                              | 375.0                        | PhMeN(C–H)H <sub>2</sub>                                                            | 383.7                        |
| Pr <sup>i</sup> <sub>2</sub> N(C–H)Me <sub>2</sub>                                  | 370.0                        | PhEtN(C–H)HMe                                                                       | 383.2                        |
|                                                                                     |                              | Ph <sub>2</sub> N(C–H)H <sub>2</sub>                                                | 379.5                        |
|  | 395.9                        |                                                                                     |                              |
|  | 388.0                        |  | 361.0                        |
|  | 381.0                        |                                                                                     |                              |
|  | 387.3                        |  | 401.0                        |
|                                                                                     |                              | AcNH(C–H)HMe                                                                        | 399.2                        |
|                                                                                     |                              | AcNH(C–H)Me <sub>2</sub>                                                            | 395.5                        |
|                                                                                     |                              | AcMeN(C–H)H <sub>2</sub>                                                            | 386.9                        |
| Nitriles <sup>58</sup>                                                              |                              |                                                                                     |                              |
| NC(C–H)H <sub>2</sub>                                                               | 401.7 <sup>a</sup>           | NCCH <sub>2</sub> (C–H)HCO <sub>2</sub> Me                                          | 383.8                        |
| NC(C–H)HMe                                                                          | 387.2                        | NCCMePh(C–H)H <sub>2</sub>                                                          | 408.7                        |
| NC(C–H)Me <sub>2</sub>                                                              | 372.2                        | NCCH=(C–H)H                                                                         | 439.8 <sup>a</sup>           |
| NCCMe <sub>2</sub> (C–H)H <sub>2</sub>                                              | 402.9                        | NCC≡C–H                                                                             | 471.3 <sup>a</sup>           |
| [NCCMe(C–H)H <sub>2</sub> ] <sub>2</sub>                                            | 404.4                        | N≡C–H                                                                               | 518.0 <sup>a</sup>           |

Table 11 (continued).

| Compound                                                                            | $D_{C-H}/\text{kJ mol}^{-1}$ | Compound                                                                             | $D_{C-H}/\text{kJ mol}^{-1}$     |
|-------------------------------------------------------------------------------------|------------------------------|--------------------------------------------------------------------------------------|----------------------------------|
| Cyclic aminoethers <sup>55</sup>                                                    |                              |                                                                                      |                                  |
|    | 371.2                        |     | 362.6                            |
|    | 369.9                        |     | 370.1                            |
|    | 364.8                        |                                                                                      |                                  |
| Nitro compounds <sup>58</sup>                                                       |                              |                                                                                      |                                  |
| H-CH <sub>2</sub> NO <sub>2</sub>                                                   | 415.4                        | Me(C-H)HNO <sub>2</sub>                                                              | 402.4                            |
| Me <sub>2</sub> (C-H)NO <sub>2</sub>                                                | 394.0                        | O <sub>2</sub> N-H                                                                   | 327.6 ( $D_{N-H}$ ) <sup>a</sup> |
| Thio- and dithioacetals <sup>53, 55, 64</sup>                                       |                              |                                                                                      |                                  |
| (EtS) <sub>2</sub> (C-H)H                                                           | 390.2                        |     | 378.0                            |
| (EtS) <sub>2</sub> (C-H)Me                                                          | 376.1                        |     | 373.1                            |
| (EtS) <sub>2</sub> (C-H)Pr <sup>i</sup>                                             | 376.5                        |    | 388.8                            |
| (n-C <sub>5</sub> H <sub>11</sub> S) <sub>2</sub> (C-H)Pr <sup>i</sup>              | 385.6                        |   | 373.9                            |
|   | 367.3                        |   | 371.5                            |
|  | 369.1                        |   | 374.2                            |
|  | 404.0                        |   | 374.7                            |
|  | 378.3                        |  | 374.6                            |
|  | 370.8                        |   | 388.0                            |
|  | 371.1                        |   | 370.1                            |
|  | 370.6                        |   | 384.7                            |
|  | 367.5                        |   | 369.4                            |
|  | 394.7                        |   | 369.8                            |
|  | 377.8                        |                                                                                      |                                  |
|  | 374.6                        |                                                                                      |                                  |
|  | 374.1                        |                                                                                      |                                  |

<sup>a</sup> The bond dissociation energies were taken from Ref. 12.

| Compound                      | $D_{C-H}$ | $\Delta D$ |
|-------------------------------|-----------|------------|
| $CH_2=CH(C-H)H_2$             | 368.0     | 0          |
| $CH_2=CMe(C-H)H_2$            | 357.9     | -10.1      |
| $(E)\text{-}MeCH=CMe(C-H)H_2$ | 356.8     | -11.2      |
| $Me_2C=CMe(C-H)H_2$           | 350.2     | -17.8      |

Two double bonds have an even more pronounced effect on the  $\alpha$ -C-H bond (see Table 4; the  $D_{C-H}$  values are given in  $\text{kJ mol}^{-1}$ ).

| Compound               | $D_{C-H}$ | $\Delta D_{C-H}$ |
|------------------------|-----------|------------------|
| $CH_2=CH(C-H)H_2$      | 368.0     | 0                |
| $CH_2=CHCH=CH(C-H)H_2$ | 343.0     | -25.0            |
| $(CH_2=CH)_2(C-H)H$    | 318.0     | -50.0            |
| $(CH_2=CH)_2(C-H)Me$   | 321.1     | -46.9            |

|                                                                                     |       |        |
|-------------------------------------------------------------------------------------|-------|--------|
|    | 408.4 | 0      |
|    | 342.5 | -65.9  |
|    | 329.3 | -79.1  |
|    | 288.8 | -119.6 |
|    | 408.8 | 0      |
|   | 341.5 | -67.3  |
|  | 330.9 | -77.9  |
|  | 312.6 | -96.2  |
|  | 338.9 | -69.9  |

2. The benzene ring has a similar effect on the  $\alpha$ -C-H bond (see Table 8; the  $D_{C-H}$  values are given in  $\text{kJ mol}^{-1}$ ).

| Compound      | $D_{C-H}$ | $\Delta D_{C-H}$ |
|---------------|-----------|------------------|
| $Me(C-H)H_2$  | 422       | 0                |
| $Ph(C-H)H_2$  | 375.0     | -47.0            |
| $Ph(C-H)HMe$  | 364.1     | -57.9            |
| $Ph(C-H)Me_2$ | 354.2     | -67.8            |
| $Ph_2(C-H)H$  | 356.8     | -65.2            |

3. The C-H bond weakens if a nitrogen-containing functional group X-NH<sub>2</sub>, NH<sub>2</sub> or CN is in the  $\alpha$ -position with respect to this bond (see Table 11; the  $D_{C-H}$  values are given in  $\text{kJ mol}^{-1}$ ).

| Compound    | X               | $D_{C-H}$ | $\Delta D_{C-H}$ |
|-------------|-----------------|-----------|------------------|
| $X(C-H)H_2$ | Me              | 422.0     | 0                |
|             | NH <sub>2</sub> | 400.0     | -22.0            |
|             | NHR             | 398.0     | -33.0            |
|             | CN              | 401.7     | -20.3            |
|             | NO <sub>2</sub> | 415.4     | -6.6             |
| $X(C-H)HMe$ | Me              | 412.0     | 0                |
|             | NH <sub>2</sub> | 389.6     | -22.4            |
|             | NHR             | 384.6     | -27.4            |
|             | CN              | 387.2     | -24.8            |
|             | NO <sub>2</sub> | 402.4     | -9.6             |

| Compound     | X               | $D_{C-H}$ | $\Delta D_{C-H}$ |
|--------------|-----------------|-----------|------------------|
| $X(C-H)Me_2$ | Me              | 400.0     | 0                |
|              | NH <sub>2</sub> | 379.5     | -20.5            |
|              | NHR             | 375.0     | -25.0            |
|              | CN              | 372.2     | -27.8            |
|              | NO <sub>2</sub> | 394.9     | -5.1             |

This is due to stabilisation of free valence caused by the neighbouring group containing p- or  $\pi$ -electrons. With respect to their ability to stabilise the free valence on the neighbouring carbon atom the groups considered are in the same order: NO<sub>2</sub> < CN < NH<sub>2</sub> < NHR. Replacement of a hydrogen atom by a methyl group in the X(C-H)H<sub>2</sub> fragment reduces the  $D_{C-H}$  value by  $10.5 \pm 3.4 \text{ kJ mol}^{-1}$  (cf.  $19.2 \pm 2.6 \text{ kJ mol}^{-1}$  for replacement of two molecules).

4. Oxygen-containing groups X have a similar effect on the  $\alpha$ -C-H bond (see Table 9; the  $D_{C-H}$  values are given in  $\text{kJ mol}^{-1}$ ).

| Compound     | X      | $D_{C-H}$ | $\Delta D_{C-H}$ |
|--------------|--------|-----------|------------------|
| $X(C-H)H_2$  | Me     | 422.0     | 0                |
|              | OH     | 411.0     | -11.0            |
|              | OR     | 411.9     | -10.1            |
|              | C=O    | 411.8     | -10.2            |
|              | C(O)OH | 414.1     | -7.9             |
| $X(C-H)HMe$  | Me     | 412.0     | 0                |
|              | OH     | 399.8     | -12.2            |
|              | OR     | 399.5     | -12.5            |
|              | C=O    | 397.2     | -14.8            |
|              | C(O)OH | 398.9     | -13.1            |
| $X(C-H)Me_2$ | Me     | 400.0     | 0                |
|              | OH     | 390.5     | -9.5             |
|              | OR     | 390.8     | -9.2             |
|              | C=O    | 387.6     | -12.4            |
|              | C(O)OH | 388.3     | -11.7            |

With respect to their ability to stabilise the free valence the oxygen-containing groups can be ordered as follows: OH > OR > C=O > CO<sub>2</sub>H. The increments characterising the effect of one and two methyl groups on the  $D_{C-H}$  value are similar to those of hydrocarbons and N-containing groups:

$$D_{C-H}(XC-H)H_2 - D_{C-H}(XMeC-H)H = 13.3 \pm 1.6 \text{ kJ mol}^{-1};$$

$$D_{C-H}(XC-H)H_2 - D_{C-H}(XMeC-H)H = 15.9 \pm 3.0 \text{ kJ mol}^{-1}.$$

5. The C-H bond strengths in cyclic acetals are affected by the ring strain energy. Table 9 shows that the smaller the  $E_{\text{rsc}}$  (see Ref. 55) the larger the  $D_{C-H}$  value.

| Cyclic acetal                                                                       | $D_{C-H}/\text{kJ mol}^{-1}$ | $E_{\text{rsc}}/\text{kJ mol}^{-1}$<br>(see Refs 6, 7) |
|-------------------------------------------------------------------------------------|------------------------------|--------------------------------------------------------|
|  | 381.2                        | 29.16                                                  |
|  | 385.5                        | 25.52                                                  |
|  | 388.0                        | 13.09                                                  |

The C-H bond dissociation energies in 1,3-dioxolane, 1,3-dioxane and 1,3-dioxepane are related to the ring strain energy  $E_{\text{rsc}}$  (in  $\text{kJ mol}^{-1}$ ) by the following correlation equation:



$$D_{C-H} = 393.17 - 0.37 E_{rsc}. \quad (39)$$

The C–H bond strength difference between 1,3-dioxane and diethoxymethane is  $-2.4 \text{ kJ mol}^{-1}$ , *i.e.*, at minimum ring strain energy the C–H bond strength in 1,3-dioxane is similar to that of acyclic acetals ( $390.4 \text{ kJ mol}^{-1}$ ).

6. In the text below the C–H bond dissociation energies in SCHR (R = H, Me, Pr<sup>i</sup>) fragments are compared with the C–H bond strengths in similar hydrocarbons<sup>12</sup> (the  $D_{C-H}$  values are given in  $\text{kJ mol}^{-1}$ ).

| Compound                | (EtX) <sub>2</sub> (C–H)H | (EtX) <sub>2</sub> (C–H)Pr <sup>i</sup> | (EtX) <sub>2</sub> (C–H)Me |
|-------------------------|---------------------------|-----------------------------------------|----------------------------|
| $D_{C-H}$               | 390                       | 389                                     | 376                        |
| for X = S               |                           |                                         |                            |
| $D_{C-H}$               | 412                       | 400                                     | 396                        |
| for X = CH <sub>2</sub> |                           |                                         |                            |
| $\Delta D$              | –22                       | –11                                     | –20                        |

As can be seen, the sulfur atoms lead to an appreciable (by  $11\text{--}22 \text{ kJ mol}^{-1}$ ) decrease in the strength of the neighbouring C–H bond.

## VII. Dissociation energies of O–H bonds in alcohols, acids, hydroperoxides, hydroxylamines and phenols

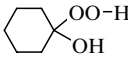
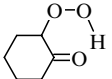
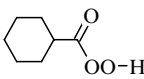
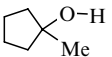
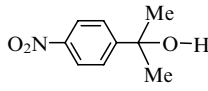
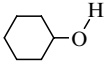
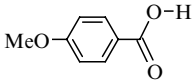
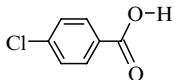
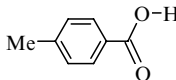
The O–H bond strengths in various hydroperoxides were first calculated<sup>66</sup> from experimental data (parameters of co-oxidation). The estimates of the  $\Delta D_{O-H}$  values were obtained using the

ratio of the rate constants for reactions of two different peroxy radicals with the same hydrocarbon. The parameters of the IP model used in the  $\Delta D_{O-H}$  calculations are listed in Table 5. Dimethylethyl hydroperoxide ( $D_{O-H} = 358.6 \text{ kJ mol}^{-1}$ )<sup>76</sup> was used as a reference hydroperoxide. The results of calculations are presented in Table 12.

As can be seen from the data in Table 12, the  $D_{O-H}$  values vary over a wide range from 360 to  $413 \text{ kJ mol}^{-1}$  depending on the hydroperoxide structure. The hydroperoxides studied can be ordered as follows with respect to the O–H bond strength ( $D_{O-H}$ , in  $\text{kJ mol}^{-1}$ ):  $R_2CHOC(OO-H)R_2$  (358.4) <  $RPhC(O-H)OO-H$  (359.8) < 1-hydroxycyclohexyl 1-hydroperoxide (362.1) <  $ROCH(OO-H)R$  (367.3) < 2-hydroperoxytetrahydrofuran (367.6) <  $\alpha$ -ketocyclohexyl peroxide (369.8) <  $ROCH(OO-H)Ph$  (374.8) <  $\alpha$ -RC(O)OCH(OO-H)Ph (376.4) < cyclohexylperacid (376.9),  $R_3CC(O)(OO-H)$  (376.9) <  $RC(O)(OO-H)$  (387.1) <  $PhC(O)(OO-H)$  (403.9) <  $Cl_2CH.CCl_2(OO-H)$  (411.6) <  $Cl_3CCCl_2(OO-H)$  (413.1). The highest  $D_{O-H}$  values were obtained for peracids and chlorine-containing hydroperoxides.

The  $D_{O-H}$  values in alcohols (dimethylethoxyl radical with  $D_{O-H} = 439.4 \text{ kJ mol}^{-1}$  was used as a reference alkoxyl radical)<sup>38</sup> and acids (benzoyloxy radical with  $D_{O-H} = 439.3 \text{ kJ mol}^{-1}$  was used as a reference radical)<sup>5</sup> were estimated in a similar fashion.<sup>67</sup> The results of evaluation of the O–H bond strength are given in Table 12. As can be seen, the  $D_{O-H}$  values vary only slightly on going from one alcohol to another. As was mentioned above, the O–H bond strengths of various acids are also similar (see Table 4). The EtX compounds form the following sequence with respect to the O–H bond dissociation energy (in

**Table 12.** Dissociation energies of O–H bonds in hydroperoxides, alcohols and acids calculated from experimental data using the intersecting parabolas model.

| Compound                                                                                                    | $D_{O-H} / \text{kJ mol}^{-1}$ | Compound                                                                             | $D_{O-H} / \text{kJ mol}^{-1}$ |
|-------------------------------------------------------------------------------------------------------------|--------------------------------|--------------------------------------------------------------------------------------|--------------------------------|
| Hydroperoxides <sup>66</sup> [ $D_{O-H}(\text{Bu}^t\text{OO-H}) = 358.6 \text{ kJ mol}^{-1}$ (see Ref. 76)] |                                |                                                                                      |                                |
| HOO–H                                                                                                       | 369.0                          |   | 362.1                          |
| $RCH_2OO-H$                                                                                                 | 365.5                          |   | 369.8                          |
| $R_2CHOO-H$                                                                                                 | 365.5                          |                                                                                      |                                |
| $R_3COO-H$                                                                                                  | 358.6                          |                                                                                      |                                |
| $RPhC(OH)OO-H$                                                                                              | 359.8                          |   | 376.9                          |
| $R_3CC(O)OO-H$                                                                                              | 376.9                          |                                                                                      |                                |
| $ROCH(OO-H)R$                                                                                               | 367.3                          |                                                                                      |                                |
| $PhC(O)OO-H$                                                                                                | 403.9                          |                                                                                      |                                |
| $R_2CHOC(OO-H)R_2$                                                                                          | 358.4                          |                                                                                      |                                |
| $RC(O)CH(OO-H)R$                                                                                            | 369.8                          |                                                                                      |                                |
| $ROCH(OO-H)Ph$                                                                                              | 374.8                          |                                                                                      |                                |
| $RC(O)OCH(OO-H)Ph$                                                                                          | 376.4                          |                                                                                      |                                |
|                          | 367.6                          | $Cl_2CHCCl_2(OO-H)$                                                                  | 411.6                          |
|                                                                                                             |                                | $Cl_3CCCl_2(OO-H)$                                                                   | 413.1                          |
|                                                                                                             |                                | $RC(O)(OO-H)$                                                                        | 387.1                          |
| Alcohols <sup>67</sup> [ $D_{O-H}(\text{Bu}^t\text{O-H}) = 439.4 \text{ kJ mol}^{-1}$ (see Ref. 5)]         |                                |                                                                                      |                                |
| $EtMe_2CO-H$                                                                                                | 439.7                          |   | 425.1                          |
| $PhMe_2CO-H$                                                                                                | 438.2                          |                                                                                      |                                |
|                          | 437.6                          |   | 438.5                          |
| Acids <sup>67</sup> [ $D_{O-H}[PhC(O)O-H] = 439.3 \text{ kJ mol}^{-1}$ (see Ref. 5)]                        |                                |                                                                                      |                                |
| $Pr^iOC(O)O-H$                                                                                              | 432.5                          |  | 438.5                          |
| $Bu^tOC(O)O-H$                                                                                              | 431.9                          |                                                                                      |                                |
| $PhC \equiv CC(O)O-H$                                                                                       | 436.9                          |   | 432.2                          |
|                          | 437.0                          |                                                                                      |                                |

$\text{kJ mol}^{-1}$ ):  $\text{EtOO-H}$  (365.5) <  $\text{EtO-H}$  (432.4) <  $\text{EtC(O)O-H}$  (439.3). It was found that the O–H bond strengths in *para*-substituted benzoic acids  $4\text{-YC}_6\text{H}_4\text{CO}_2\text{H}$  are independent of the substituent Y and only at Y = Cl is the  $D_{\text{O-H}}$  value  $7 \text{ kJ mol}^{-1}$  lower than in unsubstituted benzoic acid.

| Y   | $\sigma$ | $D_{\text{O-H}}/\text{kJ mol}^{-1}$ |
|-----|----------|-------------------------------------|
| MeO | –0.268   | 438.5                               |
| Me  | –0.170   | 437.0                               |
| H   | 0.0      | 439.3                               |
| Cl  | 0.227    | 432.2                               |

Tables 13 and 14 list the  $D_{\text{O-H}}$  values for phenols, calculated from experimental data in the framework of the IP model. The  $\Delta D_{\text{O-H}}$  values were estimated from the rate constant ratio for the reactions of the same peroxy radical with two phenols. The reference compounds were unsubstituted phenol ( $D_{\text{O-H}} = 369.0 \text{ kJ mol}^{-1}$ ) and 2,4,6-tri-*tert*-butylphenol ( $D_{\text{O-H}} = 339.7 \text{ kJ mol}^{-1}$ ).<sup>19</sup> The parameters of the IP model used in calculations are given in Table 5.

Comparison shows that in most cases the O–H bond strengths thus obtained are in good agreement with the  $D_{\text{O-H}}$  values found from the chemical equilibrium (see Table 1). The

$D_{\text{O-H}}$  values (in  $\text{kJ mol}^{-1}$ ) for phenols  $4\text{-YC}_6\text{H}_4\text{OH}$ , calculated from the equilibrium constants and from the kinetic data using the IP model are listed below.

| Y               | $D_{\text{O-H}}$ (equilibrium) | $D_{\text{O-H}}$ (IP model) |
|-----------------|--------------------------------|-----------------------------|
| MeO             | 346.3                          | 347.5                       |
| Me              | 360.5                          | 362.2                       |
| H               | 369.2                          | 369.0                       |
| Bu <sup>t</sup> | 356.7                          | 360.1                       |

An analogous picture is also observed for *para*-substituted 4-Y-2,6-di-*tert*-butylphenols ( $D_{\text{O-H}}$  values are given in  $\text{kJ mol}^{-1}$ ).<sup>21</sup>

| Y   | $D_{\text{O-H}}$ (equilibrium) | $D_{\text{O-H}}$ (IP model) |
|-----|--------------------------------|-----------------------------|
| H   | 346.2                          | 347.4                       |
| Me  | 338.8                          | 339.7                       |
| MeO | 327.5                          | 331.4                       |
| Ph  | 337.9                          | 338.4                       |
| Cl  | 344.5                          | 345.2                       |
| CN  | 356.9                          | 353.1                       |

**Table 13.** Dissociation energies of O–H bonds in phenols calculated from experimental data using the intersecting parabolas model, [ $D_{\text{O-H}}(\text{PhO-H}) = 369.0 \text{ kJ mol}^{-1}$ ].<sup>59, 60</sup>

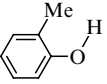
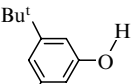
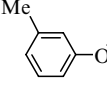
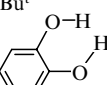
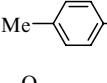
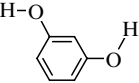
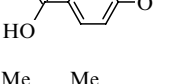
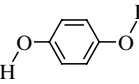
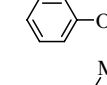
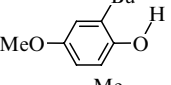
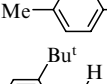
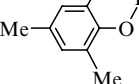
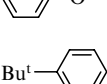
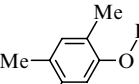
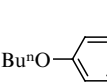
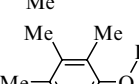
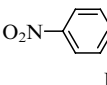
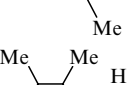
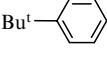
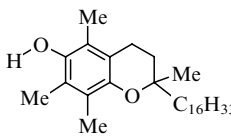
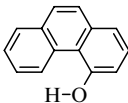
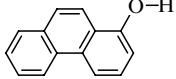
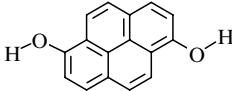
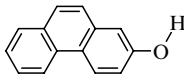
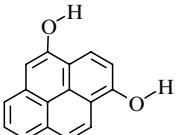
| Phenol                                                                              | $D_{\text{O-H}}/\text{kJ mol}^{-1}$ | Phenol                                                                              | $D_{\text{O-H}}/\text{kJ mol}^{-1}$ |
|-------------------------------------------------------------------------------------|-------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------|
|  | 359.9                               |  | 362.4                               |
|  | 366.7                               |  | 339.6                               |
|  | 362.2                               |  | 369.1                               |
|  | 371.7                               |  | 352.0                               |
|  | 355.5                               |  | 343.4                               |
|  | 360.5                               |  | 347.5                               |
|  | 353.8                               |  | 356.8                               |
|  | 360.1                               |  | 347.4                               |
|  | 347.8                               |  | 351.2                               |
|  | 372.8                               |                                                                                     |                                     |
|  | 359.5                               |                                                                                     |                                     |

Table 13 (continued).

| Phenol | $D_{O-H} / \text{kJ mol}^{-1}$ | Phenol | $D_{O-H} / \text{kJ mol}^{-1}$ |
|--------|--------------------------------|--------|--------------------------------|
|        | 340.5                          |        | 333.5                          |
|        | 342.4                          |        | 330.8                          |
|        | 340.3                          |        | 326.4                          |
|        | 339.5                          |        | 328.9                          |
|        | 349.8                          |        | 333.3                          |
|        | 344.7                          |        | 329.7                          |
|        | 343.8                          |        | 328.4                          |
|        | 329.7                          |        | 334.7                          |
|        | 326.4                          |        | 331.0                          |
|        | 326.0                          |        | 342.8                          |
|        | 334.0                          |        | 335.1                          |
|        | 343.4                          |        | 335.6                          |
|        | 353.8                          |        |                                |
|        | 338.3                          |        |                                |

Table 13 (continued).

| Phenol                                                                                                   | $D_{O-H} / \text{kJ mol}^{-1}$ | Phenol                                                                             | $D_{O-H} / \text{kJ mol}^{-1}$ |
|----------------------------------------------------------------------------------------------------------|--------------------------------|------------------------------------------------------------------------------------|--------------------------------|
| <br>(see <sup>a</sup> ) | 330.0                          |   | 356.2                          |
|                         | 354.7                          |  | 315.9                          |
|                         | 367.0                          |   | 317.7                          |

<sup>a</sup>  $\text{C}_{16}\text{H}_{33} = [(\text{CH}_2)_3\text{CHMe}]_3\text{Me}$ .Table 14. Dissociation energies of O–H bonds in sterically hindered phenols calculated from experimental data using the intersecting parabolas model [ $D_{O-H}(2,4,6\text{-Bu}^t\text{C}_6\text{H}_2\text{O}-\text{H}) = 339.7 \text{ kJ mol}^{-1}$ ].<sup>59,60</sup>

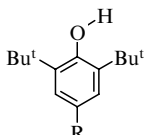
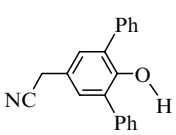
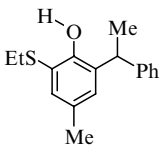
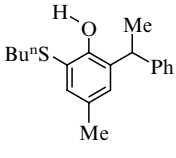
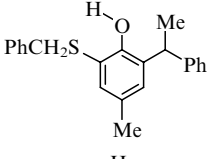
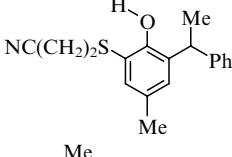
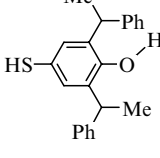
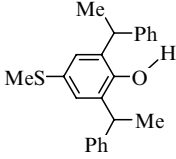
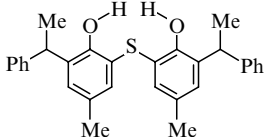
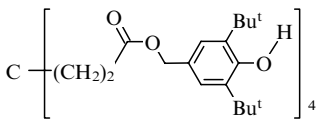
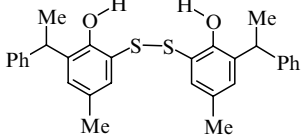
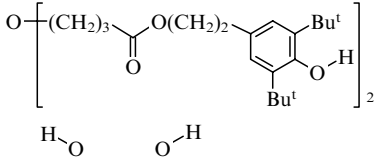
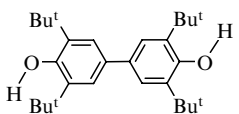
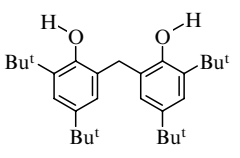
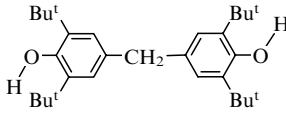
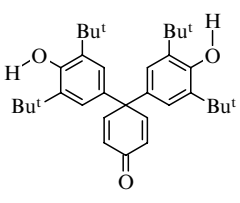
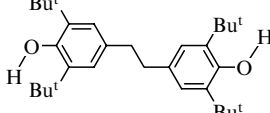
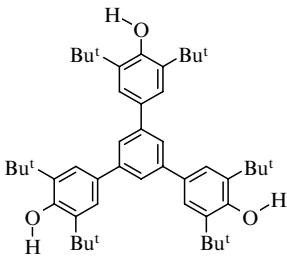
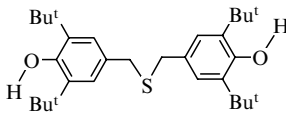
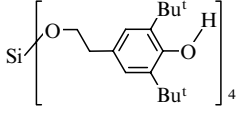
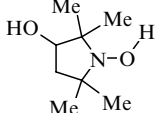
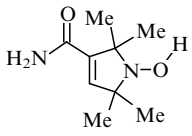
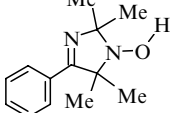
| Phenol                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | $D_{O-H} / \text{kJ mol}^{-1}$                                                                                                                                                                     | Phenol                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | $D_{O-H} / \text{kJ mol}^{-1}$                              |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| <br>R = H<br>R = Me<br>R = CH <sub>2</sub> Ph<br>R = Ph<br>R = Me <sub>2</sub> PhC<br>R = Ph <sub>2</sub> CH<br>R = OMe<br>R = OBu <sup>t</sup><br>R = Cl<br>R = NO<br>R = NO <sub>2</sub><br>R = CH <sub>2</sub> NH <sub>2</sub><br>R = NHAc<br>R = HCO<br>R = Ac<br>R = CN<br>R = CO <sub>2</sub> H<br>R = CO <sub>2</sub> Bu <sup>t</sup><br>R = CH <sub>2</sub> CO <sub>2</sub> H<br>R = CH <sub>2</sub> CO <sub>2</sub> Me<br>R = CH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> C <sub>18</sub> H <sub>37-n</sub><br>R = SPh | 347.4<br>339.7<br>340.4<br>338.4<br>340.8<br>343.0<br>331.4<br>332.0<br>345.2<br>346.7<br>358.7<br>335.5<br>327.4<br>348.5<br>346.2<br>353.1<br>349.5<br>348.5<br>337.6<br>343.5<br>340.3<br>347.1 | <br><br><br><br><br><br> | 312.0<br>339.4<br>339.2<br>338.7<br>346.2<br>340.7<br>341.1 |

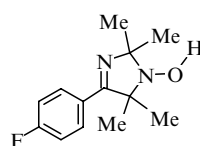
Table 14 (continued).

| Phenol                                                                              | $D_{O-H} / \text{kJ mol}^{-1}$ | Phenol                                                                              | $D_{O-H} / \text{kJ mol}^{-1}$ |
|-------------------------------------------------------------------------------------|--------------------------------|-------------------------------------------------------------------------------------|--------------------------------|
|    | 335.9                          |   | 341.7                          |
|    | 335.3                          |   | 339.6                          |
|    | 343.3                          |   | 341.2                          |
|    | 340.9                          |   | 347.0                          |
|   | 339.4                          |  | 345.6                          |
|  | 340.6                          |                                                                                     |                                |
|  | 341.6                          |                                                                                     |                                |

The O–H bond strengths in hydroxylamines were calculated using the IP model from the characteristics of reactions of various iminoxyl radicals with 1,2-diphenylhydrazine<sup>61</sup> using 1-hydroxy-2,2,6,6-tetramethylpiperidin-4-one ( $D_{O-H} = 300.4 \text{ kJ mol}^{-1}$ ) as the reference hydroxylamine. The results of calculations are listed in Table 15. They are in good agreement with the data presented in Table 3 and obtained from the equilibrium constants ( $D_{O-H}$  values are given in  $\text{kJ mol}^{-1}$ ).

| Hydroxylamine                                                                       | $D_{O-H} \text{ (equilibrium)}$ | $D_{O-H} \text{ (IP model)}$ |
|-------------------------------------------------------------------------------------|---------------------------------|------------------------------|
|  | 287.3                           | 289.1                        |
|  | 293.1                           | 292.6                        |
|  | 294.2                           | 294.0                        |

| Hydroxylamine | $D_{O-H} \text{ (equilibrium)}$ | $D_{O-H} \text{ (IP model)}$ |
|---------------|---------------------------------|------------------------------|
|---------------|---------------------------------|------------------------------|



296.1

295.1

Comparison of the  $D_{O-H}$  values in alcohols, phenols, hydroperoxides and hydroxylamines indicates that the O–H bond strength is strongly affected by conjugation of free valence of the oxygen atom with adjacent  $\pi$ -bonds and p electrons of heteroatoms (N, O).

| Bond                  | Compound            | $D_{O-H} / \text{kJ mol}^{-1}$ | $\Delta D_{O-H} / \text{kJ mol}^{-1}$ |
|-----------------------|---------------------|--------------------------------|---------------------------------------|
| AlkO–H                | Bu <sup>t</sup> OH  | 439.4                          | 0                                     |
| ArO–H                 | PhOH                | 369.0                          | 70.4                                  |
| AlkOO–H               | EtOOH               | 365.5                          | 73.9                                  |
| Alk <sub>2</sub> NO–H | Et <sub>2</sub> NOH | 304.3                          | 135.1                                 |

**Table 15.** Dissociation energies (in  $\text{kJ mol}^{-1}$ ) of O–H bonds in hydroxylamines and oximes calculated from experimental data using the intersecting parabolas model [ $D_{\text{O-H}}(1\text{-OH-2,2,6,6-Me}_4\text{-piperidin-4-one}) = 300.4 \text{ kJ mol}^{-1}$ ].<sup>61</sup>

| Compound | $D_{\text{O-H}}$ | Compound | $D_{\text{O-H}}$ | Compound | $D_{\text{O-H}}$ | Compound | $D_{\text{O-H}}$ |
|----------|------------------|----------|------------------|----------|------------------|----------|------------------|
|          | 304.3            |          | 291.2            |          | 286.9            |          | 296.9            |
|          | 300.4            |          | 293.4            |          | 298.6            |          | 294.0            |
|          | 291.0            |          | 293.4            |          | 298.6            |          | 295.7            |
|          | 290.1            |          | 292.7            |          | 300.9            |          | 295.1            |
|          | 289.1            |          | 293.1            |          | 295.4            |          | 294.8            |
|          | 298.7            |          | 292.0            |          | 294.9            |          | 296.1            |
|          | 292.6            |          | 291.2            |          | 295.9            |          | 294.9            |

## VIII. Dissociation energies of N–H bonds in amines and S–H bonds in thiols

The dissociation energies of the N–H bonds in aromatic amines are listed in Table 16. They were calculated using the IP method from experimental rate constants for the reactions of peroxy radicals with amines<sup>62</sup> with diphenylamine ( $D_{\text{N-H}} = 364.7 \text{ kJ mol}^{-1}$ )<sup>21</sup> as the reference amine. The parameters used in calculations are given in Table 5.

The  $D_{\text{N-H}}$  value calculated for 1-naphthylphenylamine using the IP model ( $352.5 \text{ kJ mol}^{-1}$ ) is nearly the same as the value obtained by the chemical equilibrium method ( $352.8 \text{ kJ mol}^{-1}$ , see Table 2).

The dissociation energies of the S–H bonds in aliphatic and aromatic thiols are presented in Table 17. They were calculated in the framework of the IP model using the experimental rate constants for reactions between alkyl radicals and the S–H bonds of the corresponding compounds.<sup>63,64</sup> As can be seen, the structure of the hydrocarbon fragment in thiols has little effect on the  $D_{\text{S-H}}$  value.

## IX. Dissociation energies of Si–H, Ge–H, Sn–H, Se–H and P–H bonds

The Y–H bond dissociation energies in organoelement compounds using the IP model were estimated<sup>77</sup> from the experimen-

tal rate constants for the reactions of hydrogen abstraction by the following radicals (the  $D_{\text{C-H}}$  values in  $\text{kJ mol}^{-1}$  taken from Ref. 12 are given in parentheses):  $\text{RC}\cdot\text{H}_2$  (422),  $\text{Me}_3\text{C}\cdot$  (400),  $\text{PhC}\cdot\text{H}_2$  (375),  $\text{PhC}\cdot\text{HR}$  (364.1), *tert*- $\text{RO}_2\cdot$  (356.8),  $\text{Bu}^t\text{O}\cdot$  (439.4). The parameters used for calculating  $D_{\text{C-H}}$  values are listed in Table 5. The reference compounds with known Y–H bond strengths were  $\text{Et}_3\text{Si-H}$  (398.0),  $\text{Bu}_3^t\text{Ge-H}$  (347.3),  $\text{Bu}_3^t\text{Sn-H}$  (309.6),  $\text{n-C}_8\text{H}_{17}\text{PH}_2$  (375.3) ( $D_{\text{Y-H}}$  in  $\text{kJ mol}^{-1}$  are given in parentheses). The results of calculations are presented in Table 18.

Comparison shows that the weaker the Y–H bond, the longer is this bond and the lower is the corresponding stretching vibration frequency ( $\nu_{\text{Y-H}}$ ).

| Compound                   | $D_{\text{Y-H}}/\text{kJ mol}^{-1}$ | $r_{\text{Y-H}} \times 10^{10}/\text{m}$ | $\nu_{\text{Y-H}}/\text{cm}^{-1}$ |
|----------------------------|-------------------------------------|------------------------------------------|-----------------------------------|
| $\text{H}_3\text{C-H}$     | 440.0                               | 1.093                                    | 2914                              |
| $\text{H}_3\text{Si-H}$    | 384.1                               | 1.480                                    | 2200                              |
| $\text{H}_3\text{Ge-H}$    | 348.9                               | 1.525                                    | 2150                              |
| $\text{H}_3\text{Sn-H}$    | 346.0                               | 1.711                                    | 2067                              |
| $\text{Me}_3\text{C-H}$    | 400                                 | —                                        | —                                 |
| $\text{Et}_3\text{Si-H}$   | 398.0                               | —                                        | —                                 |
| $\text{Bu}_3^t\text{Ge-H}$ | 347.3                               | —                                        | —                                 |
| $\text{Bu}_3^t\text{Sn-H}$ | 309.6                               | —                                        | —                                 |

**Table 16.** Dissociation energies of N–H bonds in aromatic amines calculated from experimental data using the intersecting parabolas model [ $D_{\text{N-H}}(\text{Ph}_2\text{N-H}) = 364.7 \text{ kJ mol}^{-1}$ ].<sup>62</sup>

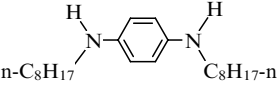
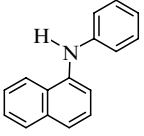
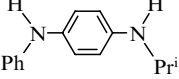
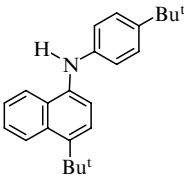
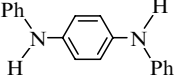
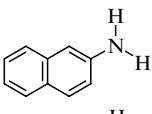
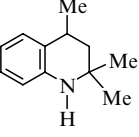
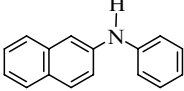
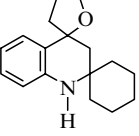
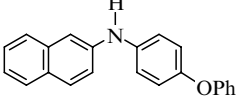
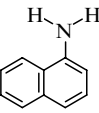
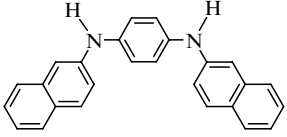
| Amine                                                                              | $D_{\text{N-H}} / \text{kJ mol}^{-1}$ | Amine                                                                               | $D_{\text{N-H}} / \text{kJ mol}^{-1}$ |
|------------------------------------------------------------------------------------|---------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------|
|   | 352.2                                 |    | 352.5                                 |
|   | 340.2                                 |   | 352.1                                 |
|   | 346.9                                 |    | 379.5                                 |
|   | 359.5                                 |   | 353.9                                 |
|   | 360.8                                 |   | 349.5                                 |
|  | 374.7                                 |  | 346.6                                 |

**Table 17.** Dissociation energies of S–H bonds in thiols calculated from experimental data using the intersecting parabolas model.<sup>63, 64</sup>

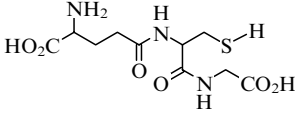
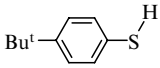
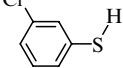
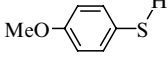
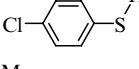
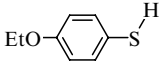
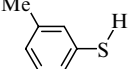
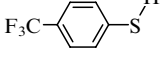
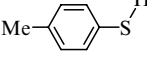
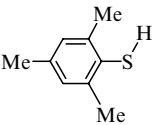
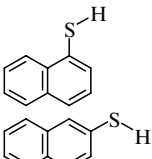
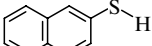
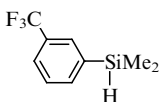
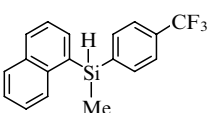
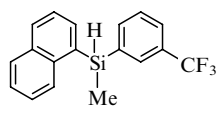
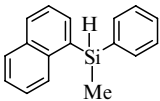
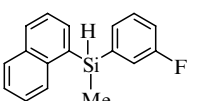
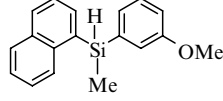
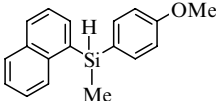
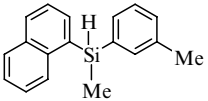
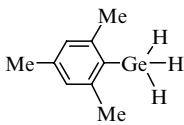
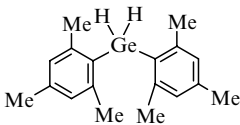
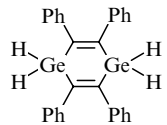
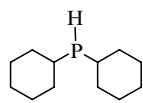
| Thiol                                                                                 | $D_{\text{S-H}} / \text{kJ mol}^{-1}$ | Thiol                                                                                | $D_{\text{S-H}} / \text{kJ mol}^{-1}$ |
|---------------------------------------------------------------------------------------|---------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------|
| HS–H                                                                                  | 382.0 <sup>a</sup>                    | HSS–H                                                                                | 325.0                                 |
| Aliphatic thiols                                                                      |                                       |  | 360.3                                 |
| MeS–H                                                                                 | 366.0 <sup>a</sup>                    | cyclo-[CH(S–H)(CH <sub>2</sub> ) <sub>5</sub> ]                                      | 364.4                                 |
| EtS–H                                                                                 | 366.0                                 | n-C <sub>6</sub> H <sub>11</sub> CHMeS–H                                             | 369.3                                 |
| Pr <sup>n</sup> S–H                                                                   | 367.3                                 | Me <sub>2</sub> C(S–H)CH(NH <sub>2</sub> )CO <sub>2</sub> H                          | 363.1                                 |
| Pr <sup>i</sup> S–H                                                                   | 366.9                                 | H–SCH <sub>2</sub> CH(NH <sub>2</sub> )CO <sub>2</sub> H                             | 360.0                                 |
| Bu <sup>n</sup> S–H                                                                   | 366.0                                 | HOCH <sub>2</sub> C(S)S–H                                                            | 368.2                                 |
| PhC(S)S–H                                                                             | 367.9                                 |                                                                                      |                                       |
| n-C <sub>10</sub> H <sub>21</sub> S–H                                                 | 368.6                                 |                                                                                      |                                       |
| n-C <sub>12</sub> H <sub>25</sub> S–H                                                 | 367.7                                 |                                                                                      |                                       |
| Bu <sup>i</sup> CH <sub>2</sub> CMe <sub>2</sub> CH <sub>2</sub> CMe <sub>2</sub> S–H | 367.9                                 |                                                                                      |                                       |
| Aromatic thiols                                                                       |                                       |                                                                                      |                                       |
| PhS–H                                                                                 | 330.0                                 |   | 329.6                                 |
|    | 327.7                                 |   | 321.2                                 |
|    | 326.0                                 |   | 321.5                                 |
|    | 330.0                                 |   | 330.5                                 |
|    | 326.7                                 |                                                                                      |                                       |

Table 17 (continued).

| Thiol                                                                             | $D_{S-H} / \text{kJ mol}^{-1}$ | Thiol                                                                             | $D_{S-H} / \text{kJ mol}^{-1}$ |
|-----------------------------------------------------------------------------------|--------------------------------|-----------------------------------------------------------------------------------|--------------------------------|
| Aromatic thiols                                                                   |                                |                                                                                   |                                |
|  | 328.5                          |  | 320.3                          |
|                                                                                   |                                |  | 318.7                          |

<sup>a</sup> The bond dissociation energies were taken from Ref. 12.

Table 18. Dissociation energies (in  $\text{kJ mol}^{-1}$ ) of  $X-H$  ( $X = \text{Si, Ge, Sn, P}$ ) bonds calculated from experimental data using the intersecting parabolas model.<sup>65,77</sup>

| Compound                                               | $D$   | Compound                                                                            | $D$   | Compound                                                                             | $D$   | Compound                                                                              | $D$   |
|--------------------------------------------------------|-------|-------------------------------------------------------------------------------------|-------|--------------------------------------------------------------------------------------|-------|---------------------------------------------------------------------------------------|-------|
| Silanes ( $R_3\text{SiH}$ )                            |       |                                                                                     |       |                                                                                      |       |                                                                                       |       |
| $\text{Ph}_3\text{Si}-\text{H}$                        | 371.0 |    | 373.4 |    | 379.9 |    | 378.8 |
| $\text{PhMe}_2\text{Si}-\text{H}$                      | 380.2 |                                                                                     |       |                                                                                      |       |                                                                                       |       |
| $\text{Ph}_2\text{MeSi}-\text{H}$                      | 375.4 |                                                                                     |       |                                                                                      |       |                                                                                       |       |
| $\text{PhMeFSi}-\text{H}$                              | 394.6 |                                                                                     |       |                                                                                      |       |                                                                                       |       |
| $\text{PhMeClSi}-\text{H}$                             | 385.8 |    | 374.2 |    | 378.4 |    | 375.4 |
| $\text{Ph}(\text{C}_6\text{F}_5)\text{MeSi}-\text{H}$  | 384.7 |                                                                                     |       |                                                                                      |       |                                                                                       |       |
| $\text{Ph}(\text{Ph}_3\text{Si})\text{MeSi}-\text{H}$  | 356.9 |                                                                                     |       |                                                                                      |       |                                                                                       |       |
| $(\text{Bu}^t\text{CH}_2)\text{PhMeSi}-\text{H}$       | 375.4 |  | 371.6 |  | 372.8 |                                                                                       |       |
| Germanes ( $R_3\text{GeH}$ )                           |       |                                                                                     |       |                                                                                      |       |                                                                                       |       |
| $\text{Ph}_3\text{Ge}-\text{H}$                        | 322.5 |                                                                                     |       |                                                                                      |       |                                                                                       |       |
| $(\text{PhCH}_2)_3\text{Ge}-\text{H}$                  | 324.9 |  | 337.5 |  | 336.8 |  | 319.9 |
| $\text{Ph}(\text{PhCH}_2)(\text{Ge}-\text{H})\text{H}$ | 324.9 |                                                                                     |       |                                                                                      |       |                                                                                       |       |
| $(\text{Me}_3\text{Si})_3\text{Ge}-\text{H}$           | 305.2 |                                                                                     |       |                                                                                      |       |                                                                                       |       |
| Stannanes ( $R_3\text{SnH}$ )                          |       |                                                                                     |       |                                                                                      |       |                                                                                       |       |
| $\text{Me}_3\text{Sn}-\text{H}$                        | 318.5 | $\text{Ph}_3\text{Sn}-\text{H}$                                                     | 296.9 | $\text{Bu}_3\text{Sn}-\text{H}$                                                      | 309.6 | $\text{H}_3\text{Sn}-\text{H}$                                                        | 346.0 |
| Phosphines ( $R_2\text{PH}$ )                          |       |                                                                                     |       |                                                                                      |       |                                                                                       |       |
| $\text{Et}_2\text{P}-\text{H}$                         | 377.8 | $\text{Bu}_3^t\text{P}-\text{H}$                                                    | 375.0 | $\text{NC}(\text{CH}_2)_3(\text{P}-\text{H})\text{H}$                                | 373.4 |  | 360.6 |
| $(n\text{-C}_8\text{H}_{17})_2\text{P}-\text{H}$       | 375.3 | $[\text{NC}(\text{CH}_2)_3]_2\text{P}-\text{H}$                                     | 369.5 |                                                                                      |       |                                                                                       |       |

## X. Dissociation energies of $\text{C}-\text{Hal}$ bonds

The dissociation energies of the  $\text{C}-\text{halogen}$  ( $\text{Hal}$ ) bonds in halogen-containing compounds were estimated<sup>78</sup> by the IP method from the experimental rate constants for the reactions of halogen abstraction by hydrogen atom and by  $\text{Ph}^\cdot$  and  $\text{Me}^\cdot$  radicals ( $D_{\text{C}-\text{H}} = 474$  and  $440 \text{ kJ mol}^{-1}$ , respectively).<sup>12,13</sup> The  $\text{S}-\text{Cl}$  bond dissociation energy was also estimated for two compounds. The following halides were used as reference compounds with known  $\text{C}-\text{Hal}$  and  $\text{S}-\text{Cl}$  bond strengths (the  $D_{\text{C}-\text{Hal}}$  and  $D_{\text{S}-\text{Cl}} / \text{kJ mol}^{-1}$  values are given in parentheses):  $\text{BrCH}_2\text{CO}_2\text{H}$  (270.9),  $\text{MeBr}$  (290.0),  $\text{MeCl}$  (354.0),  $\text{MeI}$  (240.0),  $\text{PhI}$  (281.0),  $\text{PhCH}_2\text{Cl}$  (309.7),  $\text{PhCH}_2\text{Br}$  (252.9),  $\text{MeSO}_2\text{Cl}$  (292.9).<sup>5</sup> The parameters used for the IP model calculations are given in Table 5. The results of calculations are listed in Table 19.

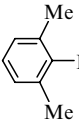
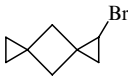
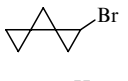
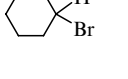
Analysis of the data from Table 19 shows the following (on the average) decreasing order of the bond strengths:  $D_{\text{C}-\text{Cl}} > D_{\text{C}-\text{Br}} > D_{\text{C}-\text{I}}$ .

## XI. Conclusion

Thus, the use of kinetic methods for estimating the  $\text{Y}-\text{H}$  ( $\text{Y} = \text{C, O, N, P, Si, Ge, Sn}$ ) bond strengths makes it possible to considerably extend the range of compounds with known values of this important characteristic. Indeed, earlier only two hydroperoxides, namely,  $\text{H}_2\text{O}_2$  and *tert*- $\text{ROOH}$  were characterised by  $D_{\text{O}-\text{H}}$  values. Carrying out calculations based on experimental data on co-oxidation of organic compounds made it possible to determine the  $\text{O}-\text{H}$  bond strength values for nineteen different hydroperoxides (see Table 12). The number of alcohols and acids for which the  $D_{\text{O}-\text{H}}$  values were calculated (see Tables 4 and 12), and the number of oxygen-containing compounds with known  $D_{\text{C}-\text{H}}$



**Table 19.** Dissociation energies (in kJ mol<sup>-1</sup>) of C–Hal (Hal = Cl, Br, I) and S–Cl bonds calculated from experimental data using the intersecting parabolas model.<sup>78</sup>

| Compound                                                                          | <i>D</i> | Compound                                                                          | <i>D</i> | Compound                                                                          | <i>D</i> | Compound                                                                            | <i>D</i> |
|-----------------------------------------------------------------------------------|----------|-----------------------------------------------------------------------------------|----------|-----------------------------------------------------------------------------------|----------|-------------------------------------------------------------------------------------|----------|
| Hal = Cl                                                                          |          | Hal = I                                                                           |          | Hal = I                                                                           |          | Hal = I                                                                             |          |
| Et–Cl                                                                             | 346.3    | Et–I                                                                              | 231.9    |  | 278.5    |  | 281.8    |
| PhCH <sub>2</sub> CH <sub>2</sub> –Cl                                             | 319.8    | Pr <sup>i</sup> –I                                                                | 230.6    |  | 273.9    |  | 277.4    |
| EtSO <sub>2</sub> –Cl                                                             | 285.6    | Bu <sup>t</sup> –I                                                                | 217.4    |  | 281.6    |  | 278.6    |
| Pr <sup>n</sup> SO <sub>2</sub> –Cl                                               | 285.6    |  | 281.0    |  |          |  | 288.0    |
| Hal = Br                                                                          |          |  | 280.2    |  | 294.3    |  | 287.4    |
| PhCH <sub>2</sub> CH <sub>2</sub> –Br                                             | 268.3    |  | 284.7    |  | 276.8    |  | 280.9    |
| n-C <sub>6</sub> H <sub>13</sub> –Br                                              | 296.6    |  | 284.6    |  |          |  | 279.5    |
| Br–CHMeCO <sub>2</sub> H                                                          | 256.3    |  | 281.9    |                                                                                   |          |                                                                                     |          |
| Br–CH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H                              | 276.3    |                                                                                   |          |                                                                                   |          |                                                                                     |          |
| Br–CH <sub>2</sub> CO <sub>2</sub> H                                              | 269.0    |                                                                                   |          |                                                                                   |          |                                                                                     |          |
|  | 297.9    |                                                                                   |          |                                                                                   |          |                                                                                     |          |
|  | 304.4    |                                                                                   |          |                                                                                   |          |                                                                                     |          |
|  | 292.4    |                                                                                   |          |                                                                                   |          |                                                                                     |          |

values (see Table 9) increased similarly. A salient feature of the methods considered above is that they are applicable to various organic compounds of complex structure. This opens up prospects for estimating the bond dissociation energies in fragments constituting polymers and biopolymers. This review shows that the results obtained using various kinetic methods are in good agreement with one another.

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# Nitric oxide synthase inhibitors containing the carboxamidine group or its isosteres

S Ya Proskuryakov, A G Konoplyannikov, V G Skvortzov, A A Mandrugin, V M Fedoseev

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**Abstract.** The review summarises structures, activities and selectivity of NO-synthase (NOS) inhibitors belonging to various classes of chemical compounds. Linear, cyclic and heterocyclic structures containing guanidine, amidine and/or isothioureia fragments are considered. The structure–activity relationships for these inhibitors were analysed in relation to their action on the inducible NOS isoform. This analysis can provide the basis for the synthesis of new more efficient compounds. The bibliography includes 115 references.

## I. Introduction

The fact that nitrogen(II) oxide is an endothelium-derived relaxing factor (EDRF) and the enzymatic origin of nitric oxide were both established more than 15 years ago.<sup>1,2</sup> Since then, it has been found that the NO<sup>•</sup> radical has unique functions in the functioning of organisms both in normal and various pathophysiological states (ischemic, inflammatory and degenerative processes, cancerogenesis).<sup>3–6</sup> These findings have stimulated a search for and the synthesis of new compounds capable of regulating the activity and NO<sup>•</sup> levels in animal and human organisms with the aim of using these compounds in therapy of many widespread diseases.<sup>7,8</sup>

Since some diseases are characterised by increased NO<sup>•</sup> production (arthritis, diabetes, sepsis, myocardial ischemia), a decrease in NO<sup>•</sup> levels is of importance in the treatment of these diseases. The available inhibitors of nitric oxide synthase (NOS) isoforms (synthase is an enzyme that catalyses the NO<sup>•</sup> synthesis)

are insufficiently active and selective and cannot be localised in various tissues and cell organelles. Hence the search for new chemical NOS inhibitors is a topical problem.<sup>9,10</sup>

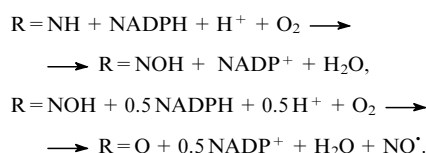
Taking into account that L-arginine is virtually the only endogenous substrate, whose guanidine group provides a nitrogen source for the NO<sup>•</sup> synthesis in enzymatic oxidation, certain analogues of this amino acid would be expected to serve as highly specific substrates for NOS enzymes. Hence, the synthesis of compounds containing groups isosteric to the guanidine group of L-arginine attracts the most attention. In the present review, we analyse the data on the relationships between the chemical structures and biochemical activities of inhibitors that bind specifically to the catalytic site of the enzyme, where L-arginine is accepted and oxidised. The data published in 1997–2003 are summarised. The properties of inhibitors are considered in relation to the inducible NOS (iNOS) isoform, which not only plays a key role in the regulation of nonspecific immunity<sup>4</sup> but also can suppress defence mechanisms in pathogenesis of certain diseases by synthesising excess NO<sup>•</sup>.<sup>8,11,12</sup>

## II. L-Arginine-dependent NO<sup>•</sup> synthesis

In living organisms, NO<sup>•</sup> is produced primarily by enzymatic oxidation of L-arginine,<sup>13,14</sup> although there are other sources of this radical.<sup>15</sup> The following three forms of the enzymes synthesising NO<sup>•</sup> are distinguished: two constitutive forms and one inducible form, which is expressed by anti-inflammatory cytokines and bacterial products. The isoforms are encoded by distinct genes and are named for their predominant localisation: neuronal NOS (NOS-1, nNOS), inducible NOS (NOS-2, iNOS) and endothelial NOS (NOS-3, eNOS).

### 1. Substrates and cofactors

The following three substrates are involved in the NO<sup>•</sup> synthesis performed by the homodimeric enzyme: L-arginine (R = NH), oxygen and nicotinamide adenine dinucleotide phosphate (NADPH) as the electron source. Two-step oxidation of the amino acid occurs through the intermediate formation of N<sup>ω</sup>-hydroxy-L-arginine (R = NOH) followed by the formation of L-citrulline (R = O) and NO<sup>•</sup> in equimolar amounts.<sup>13</sup>



**S Ya Proskuryakov, A G Konoplyannikov, V G Skvortzov** Medical Radiological Research Centre, Russian Academy of Medical Sciences, ul. Koroleva 4, 249036 Obninsk, Russian Federation.

Fax (7-095) 956 14 40, tel. (7-08439) 7 48 63,

e-mail: pros@mrrc.obninsk.ru, noo@mrrc.obninsk.ru

(S Ya Proskuryakov), tel. (7-08439) 7 20 54,

e-mail: konopl@mrrc.obninsk.ru (A G Konoplyannikov),

tel. (7-08439) 7 40 65, e-mail: skvortsov@mrrc.obninsk.ru

(V G Skvortzov)

**A A Mandrugin, V M Fedoseev** Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax (7-095) 939 31 87, tel. (7-095) 939 38 45, e-mail: mandrug@radio.chem.msu.ru (A A Mandrugin), tel. (7-095) 939 31 87,

e-mail: fedoseev@radio.chem.msu.ru (V M Fedoseev)

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The activity of NOS is mediated by several cofactors and prosthetic groups. Some of them, for example, FAD, FMN, a haem with pentacoordinate  $\text{Fe}^{2+}$ , the  $\text{Ca}^{2+}$ -binding protein (calmoduline, CaM) and  $\text{Zn}^{2+}$ , are involved in each subunit. There is certain evidence that cofactors other than (6*R*)-5,6,7,8-tetrahydro-L-biopterin ( $\text{BH}_4$ ) can be absent in the dimer.<sup>14</sup> Flavins involved in the reductase domain transfer electrons from NADPH to the oxidase domain containing the haem (oxidation site),  $\text{BH}_4$ - and L-arginine-binding regions and a zinc ion.<sup>16</sup>

## 2. Dimerisation and proteolysis of NOS

Nitric oxide synthase oxidises L-arginine and synthesises  $\text{NO}'$  only in the form of the homodimeric complex, L-arginine,  $\text{BH}_4$  and the haem being altogether involved in the formation of the active form of the enzyme. Hence, the replacement of the substrate with the inhibitor not only inhibits the  $\text{NO}'$  synthesis but also often hinders the formation of the active tertiary structure of NOS.<sup>14, 16, 17</sup> In intact cells, ~50% of NOS polypeptides exist as dimers.<sup>18</sup> The involvement of the haem in an NOS polypeptide is apparently the first necessary step of dimerisation for all isoforms.<sup>19</sup> However, the role of  $\text{BH}_4$  and L-arginine is more differentiated. In particular, the substrate is more efficient in association of nNOS subunits than  $\text{BH}_4$ . However, this dependence for iNOS is inverse. On the whole, in the presence of the above-mentioned cofactors and the substrate, resistance of the dimer to dissociation and proteolysis decreases in the following series of NOS isoforms: eNOS  $\gg$  nNOS  $>$  iNOS.<sup>20</sup> However, noteworthy is the unexpected fact of the possible binding of L-arginine to the  $\text{BH}_4$ -binding site of eNOS.<sup>21</sup>

## 3. Structure of the oxidase domain of NOS

The oxidase domain of NOS contains four important structure fragments of the enzyme: the oxidation site containing the haem with pentacoordinate iron, the L-arginine-binding region, the  $\text{BH}_4$ -accepting pocket, and the  $\text{Zn}^{2+}$  thiolate complex. Two conservative amino acids play the central role in L-arginine binding. A proton of one of the amino groups (from the guanidine structure) of L-arginine is accepted by the carbonyl group of tryptophan in the haem proximal pocket. In the distal pocket, the carbonyl group of glutamic acid binds the second proton of the same amino group and the proton attached to the N(5) atom.<sup>21</sup> L-Arginine is apparently involved in the accepting pocket of the oxidase domain in the extended *E* conformation.<sup>22</sup> Figure 1 shows the arrangement of one of NOS inhibitors, *viz.*,  $N^{\omega}$ -*n*-propyl-L-arginine (PLA), in the guanidine-binding pocket of NOS<sup>23, 24</sup> and indicates two main amino acids of the accepting pocket, Glu and Trp. Substrate-like inhibitors can interact with the oxidation pocket containing the haem with the penta- or hexacoordinate iron ion, resulting in either the displacement of the sixth ligand (without the bond formation) or the formation of the sixth coordination bond with the haem iron ion (for example, L-thiocitrulline). The carbonyl groups of Trp and Glu are involved in PLA

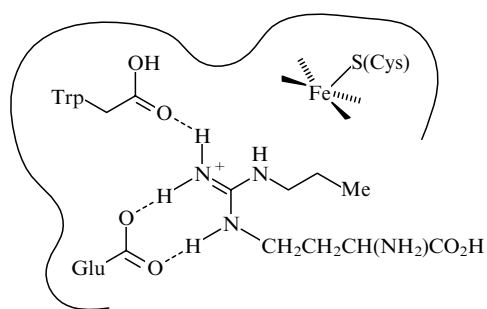


**Figure 1.** Scheme of assumed interactions of  $N^{\omega}$ -*n*-propyl-L-arginine (a substrate-like NOS inhibitor) with the catalytic site of NO synthase, where binding and oxidation of the substrate (L-arginine) occurs.

binding analogously to L-arginine binding. One of the axial bonds of penta- or hexacoordinate  $\text{Fe}^{2+}$  is formed by the cysteine residue from the NOS polypeptide, whereas another bond can be formed with an inhibitor, which substantially affects its efficiency.

Analysis of the relationships between the sizes of the substituents in L-arginine-like inhibitors and stability of inhibitor–NOS complexes (inhibitor analysis) and investigation of the spectroscopic characteristics of nNOS, iNOS and eNOS demonstrated that the size of the substrate pocket of the isoforms increases in the following series: nNOS  $>$  iNOS  $>$  eNOS.<sup>25, 26</sup> In addition, the discriminative topological features of the distal and proximal pockets accepting guanidine amino groups were revealed. The binding region for the amino group (which serves as the nitrogen source for  $\text{NO}'$ ) can interact with fragments substantially bulkier than the  $\text{NH}_2$  or  $=\text{NOH}$  groups. In contrast, the binding site of the distal nitrogen cannot accommodate such groups. These topological features of the substrate-binding pocket are also retained for the isoforms. Thus, iNOS reacts only weakly with *N*-alkyl groups larger than the ethyl group in the vicinity of the haem and cannot accept the SR group in the distal guanidine-binding pocket. At the same time, inhibitors containing larger SAlk or NAlk groups are more strongly bound to the catalytic site of nNOS and, consequently, more strongly and selectively inhibit nNOS than iNOS.<sup>24</sup>

It should be noted that, in spite of the structural features of the catalytic sites of the NOS isoforms, peptide regions located in the haem access channel play apparently a more essential role in selective inhibitor binding to the enzyme. It is these regions that accept  $\text{BH}_4$  and determine dimerisation of monomers, their covalent modification and localisation of the protein in cells. These structural features, which remain unstudied by X-ray diffraction analysis, hold promise for the design of highly selective and active NOS inhibitors.

## III. Structures and activity of nitric oxide synthase inhibitors

Since the discovery of the enzymatic origin of  $\text{NO}'$ , hundreds of compounds have been studied as NOS inhibitors using the isolated enzyme with different degrees of purity. However, these necessary and useful data were obtained in the absence of commonly accepted standards for the analysis of the species origin of the enzymes, procedures for their isolation, reaction conditions, *etc.* In addition, estimates for the inhibiting activity of compounds on isolated enzymes ruled out a number of important mechanisms, which can determine the efficiency of inhibitor at the cell level. Among them are, for example, modifications of the enzyme stability to proteolysis, the metabolism rate of inhibitors, the cell membrane permeability, *etc.*

The activity of nitric oxide synthase inhibitors is generally characterised by the stability of an inhibitor–enzyme complex using the  $K_i$  (see  $\dagger$ ) and  $IC_{50}$  parameters $\ddagger$  determined from the kinetic data. The compounds are classified into four groups according to the activity. For these groups,  $K_i$  ( $IC_{50}$ ) vary in the ranges  $>100$ ,  $10$ – $100$ ,  $<10$  and  $<1$   $\mu\text{M}$ , respectively. For example, the Michaelis–Menten constant of NOS for arginine  $K_M^{\text{Arg}} = 1$ – $10$   $\mu\text{M}$ ,<sup>27</sup> whereas the corresponding constant for L-homoarginine is approximately 10 times larger. The data on selective inhibition of a particular NOS isoform are represented as the  $K_i^{\text{eNOS}}/K_i^{\text{iNOS}}$  (e/i) and  $K_i^{\text{nNOS}}/K_i^{\text{iNOS}}$  (n/i) ratios (or as the corresponding  $IC_{50}$  ratios). The inhibitors are also divided into four groups according to the numerical values of the ‘selectivity’

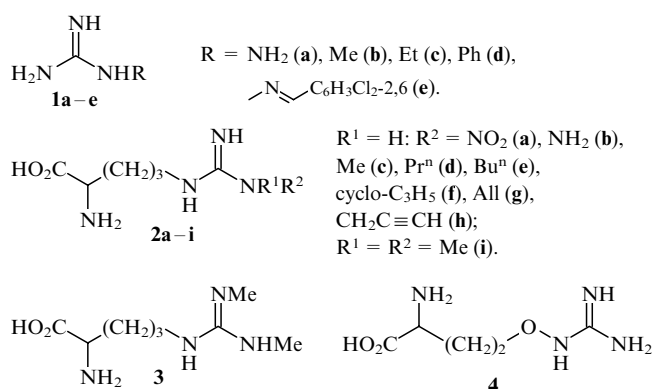
$\dagger$  The inhibition constants  $K_i$  (assuming that the reaction is competitive and stationary) are calculated by the equation  $1/v = 1/V_{\text{max}} + (K_M^{\text{Arg}}/V_{\text{max}}[\text{Arg}]) \times (1 + [I]/K_i)$ , where  $[I]$  and  $[\text{Arg}]$  are the concentrations of the inhibitor and arginine, respectively;  $K_M^{\text{Arg}}$  is the Michaelis–Menten constant.

$\ddagger$   $IC_{50}$  is the inhibitor concentration at which the NOS activity is suppressed by 50% at a given arginine concentration.

parameter:  $e/i$  and  $n/i < 1$  or  $> 1$ ;  $e/i$  and  $n/i < 0.1$  or  $> 10$ ;  $e/i$  and  $n/i < 0.01$  or  $> 100$ ; and  $e/i$  and  $n/i < 0.001$  or  $> 1000$ . Except for the abbreviated names of NOS inhibitors proposed by the International Union of Pharmacology Nomenclature,<sup>28</sup> other abbreviated names and notations correspond to those reported in original works.

### 1. Guanidine and L-arginine derivatives

Aminoguanidine is one of the structurally simple and most well-known NOS inhibitors. This compound inhibits all NOS isoforms and exhibits certain selectivity for iNOS. The *in vivo* action of this inhibitor is difficult to interpret because of the presence of alternative biochemical targets (see comments to the paper<sup>13</sup>). Aminoguanidine (**1a**), like other guanidine derivatives, irreversibly inactivates all NOS isoforms (Table 1).



The replacement of the amino group in compound **1a** with the methyl group noticeably decreases the inhibiting activity of *N*-methylguanidine (**1b**) ( $IC_{50}^{iNOS} \approx 100 \mu M$ ).<sup>31</sup> Of 1-substituted

guanidines, *N*-ethylguanidine (**1c**) proved to be the strongest iNOS inhibitor. Compound **1c**, unlike compound **1a**, appeared to be more selective for this isoform.

The known pharmaceutical vasorelaxant agent, an  $\alpha_2$ -adrenoreceptor agonist, *viz.*, 1-(2,6-dichlorobenzylideneamino)guanidine (**1e**), was found to inhibit NOS.<sup>35</sup> In the initial period, this agent reversibly inhibits the enzyme in HEK 293 cell cytosol ( $K_i^{nNOS} = 1 \mu M$ ), but later on, irreversible inactivation of nNOS occurs. In the presence of compound **1e**, the lifetime of nNOS in the cell culture decreased from 20 to 10 h.<sup>36</sup>

L-Arginine derivatives (**2a–i**) containing the substituted guanidine group were the first, which proved to be NOS inhibitors. It should be emphasised that their D isomers have no effect on the enzymatic activity of NOS.<sup>24</sup> According to the iNOS-inhibiting activity of *N*<sup>ω</sup>-nitro-L-arginine (**2a**), the latter can be assigned to strong inhibitors ( $K_i < 10 \mu M$ , see Table 1). The activity of nNOS and eNOS is suppressed to a greater degree compared to iNOS due to the difference in the mechanisms of binding to the enzyme isoforms. Binding to iNOS, as well as the replacement with L-arginine, occur rapidly. Binding of the inhibitor to constitutive NOS occurs slowly, and the inhibitor is even more slowly separated from the enzymes in the presence of a substrate.<sup>37, 38</sup> The amino derivative of arginine **2b** also inhibits NOS both *in vitro* and *in vivo* through either irreversible removal of the haem from the polypeptide or covalent binding of the haem to the polypeptide.<sup>39</sup>

Active compounds were also found among monoalkyl-arginines. *N*<sup>ω</sup>-Methyl-L-arginine (**2c**), like nitro derivative **2a**, serves as an efficient inhibitor of all NOS isoforms without pronounced selectivity. The mechanism of action of compound **2c** as an inhibitor involves inactivation of the enzyme, compound **2** being hydroxylated as a pseudosubstrate with NOS analogously to L-arginine. However, products formed in the next step ( $MeNO^+$ ,  $CH_2O$ , *etc.*), covalently modify the enzyme, which is apparently accompanied by removal of the haem.<sup>40–42</sup> It should be noted that *N*<sup>ω</sup>-methyl-L-arginine (**2c**) and *N*<sup>ω</sup>,*N*<sup>ω</sup>-dimethyl-L-arginine (**2i**) (asymmetric dimethylarginine) are endogenous NOS inhibitors formed in living organisms. Derivatives **2c,i** have approximately equal activity ( $K_i^{nNOS} \approx 0.5$  and  $0.7 \mu M$ , respectively),<sup>43</sup> which is attributed to the fact that one of the amino groups of the guanidine fragment of L-arginine is not bound to the substrate-binding region (see Fig. 1). By contrast, symmetric *N*<sup>ω</sup>,*N*<sup>ω</sup>-dimethyl-L-arginine (**3**) is a very weak inhibitor.

In a series of L-arginine derivatives containing aliphatic substituents in the *N*<sup>ω</sup> position, the iNOS-inhibiting activity of the compounds decreases substantially as the substituent size increases [ $> 4000 \mu M$  for *N*<sup>ω</sup>-*n*-butyl-L-arginine (**2e**)], but the nNOS-inhibiting activity increases.<sup>24</sup> For example, *N*<sup>ω</sup>-*n*-propyl-arginine (**2d**), being a weak iNOS inhibitor ( $IC_{50}^{iNOS} \approx 950 \mu M$ ), exhibited high selectivity for nNOS ( $n/i < 0.001$ )<sup>31</sup> and moderate selectivity for eNOS ( $e/i < 0.1$ ). *N*<sup>ω</sup>-Cyclopropyl-L-arginine (**2f**) appeared to be a strong m-iNOS inhibitor ( $K_i^{iNOS} \approx 8 \mu M$ ).<sup>42</sup>

The appearance of a multiple bond in the alkyl substituent of arginine [in *N*<sup>ω</sup>-allyl-L-arginine (**2g**) and *N*<sup>ω</sup>-propargyl-L-arginine (**2h**)] is accompanied by a decrease in their nNOS-inhibiting activity and an increase in the iNOS- and eNOS-inhibiting activity. Apparently, this is associated with inactivation of iNOS under the action of inhibitors with a multiple bond.<sup>44</sup>

The amino acid of plant origin, L-canavanine (**4**), in which the  $\delta$ -methylene group of L-arginine is replaced with the oxygen atom, weakly and non-selectively inhibits the  $NO^{\bullet}$  synthesis ( $IC_{50}^{nNOS} \approx 130 \mu M$ ). This is apparently attributed to the fact that a hydrogen bond involving the hydrogen atom at the N(5) atom cannot exist, because the labile hydrogen is absent in the favourable tautomeric form of L-canavanine.<sup>24</sup> However, physiological experiments provided evidence for specific activity of this amino acid against iNOS. In particular, the hypertensive effect of the inhibitor on animals treated with lipopolysaccharide (with the iNOS inducer) was substantially higher than that on the intact

**Table 1.** Inhibiting activity of guanidine and L-arginine derivatives.

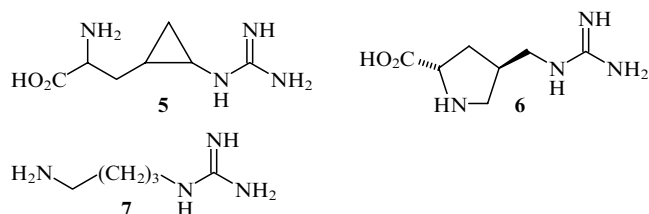
| Compound  | $K_i^{iNOS}$ / $\mu M$<br>(see <sup>a</sup> ) | Selectivity (see <sup>b</sup> ) |         | Ref. |
|-----------|-----------------------------------------------|---------------------------------|---------|------|
|           |                                               | $n/i$                           | $e/i$   |      |
| <b>1a</b> | 30 <sup>c</sup>                               | 6                               | 10      | 14   |
|           | 30 <sup>d</sup>                               | 12                              | 9       | 28   |
|           | 5 <sup>e</sup>                                | $> 1$                           | $> 1$   | 31   |
| <b>1c</b> | 1 <sup>e</sup>                                | $> 10$                          | $> 10$  | 31   |
| <b>2a</b> | 3 <sup>e</sup>                                | 0.09                            | $< 0.1$ | 14   |
|           | 2 <sup>c,d</sup>                              | 0.02                            | 0.05    | 28   |
|           | 13 <sup>e</sup>                               | 0.2                             | 0.09    | 31   |
|           | 0.7 <sup>f</sup>                              | 0.02                            | 0.04    | 32   |
| <b>2c</b> | 7                                             | 0.7                             | 0.5     | 14   |
|           | 5 <sup>d</sup>                                | 0.2                             | 0.2     | 24   |
|           | 1.3 <sup>d</sup>                              | 1                               | 0.3     | 29   |
|           | 1 <sup>f</sup>                                | 1                               | 0.5     | 33   |
| <b>2e</b> | 100 <sup>d</sup>                              | 0.004                           | 0.05    | 24   |
|           | 25 <sup>d</sup>                               | 0.02                            | 0.08    | 34   |
| <b>2h</b> | 0.6 <sup>g</sup>                              | $> 1$                           | $> 1$   | 34   |

**Note.** Hereinafter, the averaged data are given, which can be used for comparative analysis only within the scope of the present review.

<sup>a</sup> In the cases noted, the constants  $K_i$  were calculated from the data reported in the corresponding studies according to the equation  $IC_{50} = K_i(1 + [Arg])/K_M^{Arg}$ . <sup>b</sup> The selectivity (predominant inhibition of one NOS isoform compared to another isoform) is expressed as the ratio of the values characterising the activity of the inhibitor,  $IC_{50}$  or  $K_i$  ( $n/i = IC_{50}^{nNOS}/IC_{50}^{iNOS}$ ,  $e/i = IC_{50}^{eNOS}/IC_{50}^{iNOS}$ ). <sup>c</sup> h-NOS,  $IK_{50}$ ;  $[Arg] = 30 \mu M$  (the species origin of NOS: m, r, b, h are mouse, rat, bovine and human, respectively). <sup>d</sup>  $K_i$  was calculated from the data published in the study.<sup>24, 29, 30</sup> <sup>e</sup> m-i NOS, r-nNOS, b-eNOS. <sup>f</sup> h-NOS. <sup>g</sup> m-i NOS, b-nNOS, b-eNOS,  $IK_{50}$ ;  $[Arg] = 120 \mu M$ .

animals, in which the vascular tone is regulated by NO<sup>•</sup> produced by eNOS.<sup>45</sup>

The NO-inhibiting properties of derivatives **5–7**, which are structurally similar to L-arginine, contain a substituent in the amino acid moiety and are characterised by the same structure of the guanidine group, were studied.<sup>46</sup>



It appeared that, of the conformational isomers of (±)-*trans*-3(2-guanidino)cyclopropylalanine (**5**), *syn,trans*-guanidinocyclopropylalanine is a poor substrate, whereas the *anti* isomer is a weak NOS inhibitor. Amino acid **6**, in which the ornithine fragment of L-arginine is replaced with L-proline, is also a weak NOS inhibitor.<sup>47</sup> The absence of the amino acid moiety does not hinder the formation of a complex of the inhibitor with the guanidine-binding region, as evidenced by abundant data. However, the amino acid fragment limits the number of isomers (generally, of the L form), which can bind to the catalytic site of the enzyme.

Studies of 1-amino-4-guanidinobutane [agmatine (**7**)], which is one of the products of L-arginine metabolism, revealed new NOS-inhibiting properties. Agmatine (**7**) enhances oxidation of NADPH and facilitates the formation of H<sub>2</sub>O<sub>2</sub> by the isomer of nNOS, the latter being inactivated. In the reversible initial inhibition step, the affinity of agmatine (**7**) for nNOS was characterised by  $K_i^{\text{nNOS}} \approx 30 \mu\text{M}$ .<sup>48</sup>

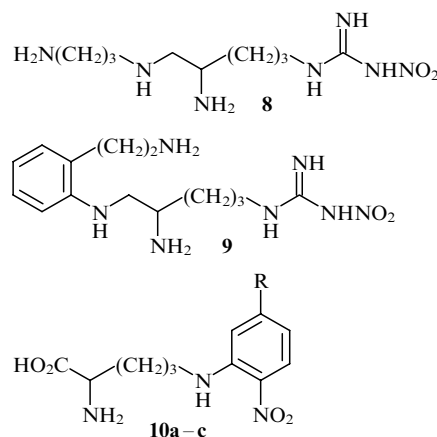
Considering the satisfactory inhibiting activity of compound **2a**, *N*<sup>ω</sup>-nitro-L(D)-arginine derivatives as dipeptides containing D and L isomers of phenylalanine were synthesised and characterised. The inhibition constants ( $K_i^{\text{iNOS}} > 10 \mu\text{M}$ ) show that these compounds can be considered as weak inhibitors. Of these compounds, *N*<sup>ω</sup>-nitro-L-arginyl-L-phenylalanine benzyl ester, which is conditionally selective for iNOS, is most active against iNOS ( $K_i^{\text{iNOS}} = 18 \mu\text{M}$ , *n/i* and *e/i* > 1).

At the same time, compounds with unique selectivity for nNOS and eNOS were found among inefficient iNOS inhibitors ( $K_i^{\text{iNOS}} > 1000 \mu\text{M}$ ) belonging to this series. In particular, D-phenylalanyl-*N*<sup>ω</sup>-nitro-D-arginine methyl ester selectively inhibits nNOS and eNOS compared to iNOS ( $K_i^{\text{iNOS}} = 3600 \mu\text{M}$ , *n/i* < 0.001, *e/i* < 0.01). It should be noted that dipeptides containing the nitro-D-arginine (D-NA) and D/L-phenylalanine (D/L-Phe) fragments proved to be iNOS inhibitors uncompetitive with L-arginine, but they are competitive nNOS and eNOS inhibitors.<sup>49, 50</sup> These data suggest that there are specific binding sites in iNOS outside the guanidine-binding pocket, which can accept amino acid fragments with an unnatural geometry.

More active and selective inhibitors were prepared by the replacement of the carboxy group with the amide group in dipeptides. Amides of *N*<sup>ω</sup>-nitro-L-arginyl-D-asparagine ( $K_i^{\text{iNOS}} = 9 \mu\text{M}$ , *n/i* < 0.1, *e/i* > 10) and *N*<sup>ω</sup>-nitro-L-arginyl-D-2,4-diaminobutanoic acid ( $K_i^{\text{iNOS}} = 25 \mu\text{M}$ , *n/i* < 0.01, *e/i* > 1) exhibited exclusive selectivity for nNOS compared to eNOS. One of the least active iNOS inhibitors, *viz.*, L-lysyl-*N*<sup>ω</sup>-nitro-D-arginine amide, exhibited selectivity for all three isoforms ( $K_i^{\text{iNOS}} = 4700 \mu\text{M}$ , *n/i* < 0.001, *e/i* > 0.1).

Reduction of the amide group to the amine group in this class of stereoselective compounds afforded peptidomimetic agent **8**, which has moderate iNOS-inhibiting activity ( $K_i^{\text{iNOS}} > 10 \mu\text{M}$ ) and exhibits even higher selectivity for nNOS (*n/i* < 0.01 and *n/e* < 0.001).<sup>51</sup> With the aim of increasing the lipophilicity of such compounds, their analogues were synthesised. One of them (compound **9**) also has exclusive activity and selectivity for nNOS ( $K_i^{\text{iNOS}} = 3.5 \mu\text{M}$ , *n/i* ≈ 0.01 and *n/e* < 0.001).<sup>52</sup>

Yet another class of NOS inhibitors, which contain no carboxamide groups and are structurally similar to arginine **2a**, was found among compounds **10a–c**. 5-Methylphenyl-2-nitro-*N*(5)-L-ornithine (**10b**) appeared to be the most active of these compounds and exhibited moderate selectivity for nNOS ( $K_i^{\text{nNOS}} = 1.4 \mu\text{M}$ , *n/i* < 1, *e/i* < 1). Stereoselectivity of this compound, unlike that of arginine derivatives, was not pronounced. The stereoisomer of D-ornithine **10c** inhibited nNOS 30 times weaker compared to the L form of **10b**.<sup>53</sup>



R = H (**a**), Me (L-form) (**b**); Me (D-form) (**c**).

Therefore, efficient NOS inhibitors were found among compounds containing the high-basicity guanidine group. However, the degree of binding to the enzymes is substantially affected by another fragment of the inhibitor molecule, which is responsible for its selectivity for NOS isoforms.

## 2. Inhibitors containing the carboxamidine group

The theoretical model<sup>24</sup> of the L-arginine-binding pocket of NOS suggests that the oxidised amino group of the guanidine fragment is not involved in complexation of L-arginine (or a substrate-like inhibitor) with the corresponding amino acids of the catalytic site. Hence, modifications or the complete replacement of the amino group oxidised to NO<sup>•</sup> should not influence substantially the interaction of a substrate-like inhibitor with the enzyme (see Fig. 1).

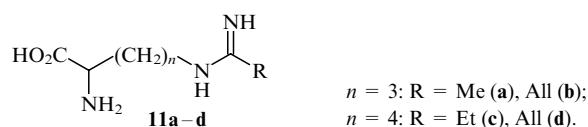
In a series of *N*<sup>ω</sup>-(1-iminoalkyl)-L-ornithines **11a,b** and L-lysines (**11c,d**), *N*(5)-(1-iminoethyl)-L-ornithine (**11a**) is the most active iNOS inhibitor, which exhibits low selectivity for nNOS and eNOS (Table 2). An increase in the length of the alkyl substituent leads to a decrease in the activity of inhibitors of all NOS isoforms, unlike *N*<sup>ω</sup>-alkyl-L-arginines **2**, whose affinity for nNOS increases.<sup>24</sup>

**Table 2.** Inhibiting activity of amino acid derivatives containing the amidine fragment.

| Compound   | $K_i^{\text{iNOS}} / \mu\text{M}$ | Selectivity |            | Ref. |
|------------|-----------------------------------|-------------|------------|------|
|            |                                   | <i>n/i</i>  | <i>e/i</i> |      |
| <b>11a</b> | 5 <sup>a</sup>                    | < 1         | < 1        | 24   |
| <b>11b</b> | 60                                | 0.002       | < 1        | 54   |
| <b>11c</b> | 2 <sup>b</sup>                    | > 0.1       | > 10       | 50   |
|            | 1 <sup>b</sup>                    | 10          | 16         | 55   |
| <b>12a</b> | 2 <sup>b</sup>                    | 500         | ≈ 10       | 56   |
| <b>12b</b> | 8 <sup>b,c</sup>                  | 80          | 100        | 57   |
| <b>12c</b> | 1.4 <sup>b</sup>                  | 300         | 100        | 57   |
| <b>12d</b> | 1 <sup>a</sup>                    | 60          | 130        | 58   |

<sup>a</sup> IC<sub>50</sub>. <sup>b</sup>  $K_i$  was calculated from the data published in the study<sup>31</sup>.

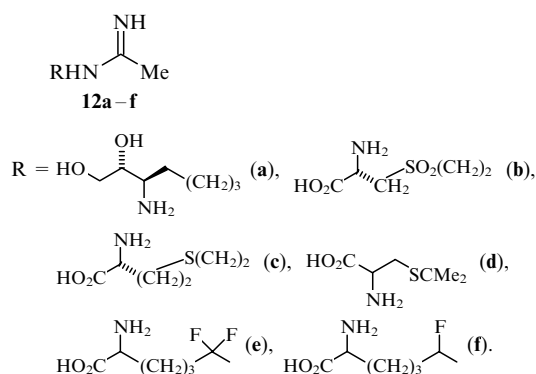
<sup>c</sup> h-NOS [Arg] = 30 μM.



The influence of the allyl substituent on the behaviour of the L-ornithine molecule was demonstrated using *N*(5)-(1-iminobut-3-enyl)-L-ornithine (**11b**) as an example. The latter also exhibited high selectivity for nNOS. Apparently (as in the above-described cases), this is associated with an inactivation mechanism of the reaction of compound **11b** with the enzyme.

The replacement of ornithine with lysine gives rise to *N*(6)-(1-iminioethyl)-L-lysine (**11c**) having the highest iNOS-inhibiting activity. Unlike L-ornithine derivatives, the lysine derivative exhibits moderate selectivity for iNOS (see Table 2). The replacement of the ethyl substituent with the allyl group in *N*(6)-(1-iminobut-3-enyl)-L-lysine has virtually no effect on the activity and selectivity. Therefore, the aliphatic substituent at the carboxamidine group has the same effect on the iNOS-inhibiting activity of compounds **11a–d** as the aliphatic substituent at the guanidine group. However, the selectivity of inhibitors belonging to the amino-acid class depends substantially on the modification of such substituents (the insertion of an unsaturated bond) and the nature of the amino acid residue (lysine instead of ornithine).

An original series of stereospecific NOS inhibitors **12a–f** analogous to compounds **11c** was designed (see Table 2).



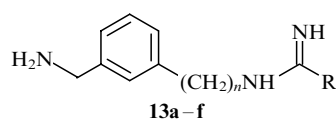
The influence of the carboxy group on the efficiency of inhibition was studied for compound **11c** and *N*-[(5*S*)-amino-(6*R*),7-dihydroxyheptyl]acetamidine (**12a**), which, although being less active against iNOS, appeared to be highly selective for this isoform (compared to eNOS).

In a series of derivatives in which the carbon atom is replaced with the S atom and the SO<sub>2</sub> group (**12b,c**), the iNOS-inhibiting activity of the L isomers is higher (*IC*<sub>50</sub> = 0.7–1.6 μM) than that of the corresponding D isomers. Three compounds of this series, viz., *S*-{2-[(1-iminioethyl)amino]ethyl}-4,4-dioxo-L-cysteine (**12b**), *S*-{2-[(1-iminioethyl)amino]ethyl}-L-homocysteine (**12c**) and *S*-{2-[(1-iminioethyl)amino]isopropyl}-L-cysteine (**12d**), exhibited high selectivity for iNOS.

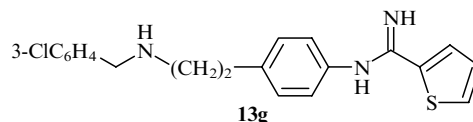
Fluorination of lysine at position 4 afforded the following iNOS inhibitors: *N*(5)-(1-iminioethyl)-4,4-difluoro-L-lysine (**12e**) and *N*(5)-(1-iminioethyl)-4-fluoro-L-lysine (**12f**).<sup>59</sup>

The presence of an amino acid residue is not necessary for inhibitors containing the carboxamidine group,<sup>60</sup> as well as for compounds containing the guanidine group.

Of non-amino acid inhibitors containing the amidine group, *N*-[3-(aminomethyl)benzyl]acetamidine (**13a**) proved to be iNOS-selective. Apparently, the activity and specificity are governed by the two-step chemical reaction of the inhibitor with the inducible enzyme. Unlike the fast and reversible reaction of arylamidine **13a** with constitutive NOS, the second step of the reaction of this inhibitor with iNOS occurs slowly and virtually irreversibly<sup>61</sup> (Table 3).

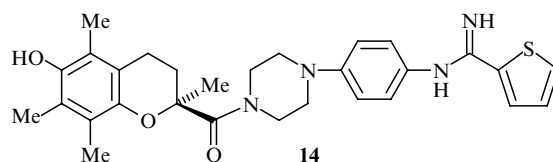


| Compound <b>13</b> | R                  | <i>n</i> | Compound <b>13</b> | R                 | <i>n</i> |
|--------------------|--------------------|----------|--------------------|-------------------|----------|
| <b>a</b>           | Me                 | 1        | <b>d</b>           | CH <sub>2</sub> F | 0        |
| <b>b</b>           | Me                 | 0        | <b>e</b>           | 2-thienyl         | 0        |
| <b>c</b>           | MeSCH <sub>2</sub> | 0        | <b>f</b>           | 2-furyl           | 0        |



Of other analogues of structure **13a**, nNOS-selective inhibitors, in particular, *N*-[3-(aminomethyl)phenyl]acetamidine (**13b**), were found. These inhibitors differ from compound **13a** by one methylene group. In this class of compounds, the inclusion of the thiomethyl group into the acetamidine fragment in *N*-[3-(aminomethyl)phenyl]methylthioacetamidine (**13c**) gives rise to the most active inhibitor of both iNOS and nNOS. Compound **13d** containing the fluoromethyl substituent in the acetamidine group is also a highly efficient nNOS inhibitor. Analogously, the replacement of the acetamidine group with the hetarylamidine group (**13e,f**) increases the nNOS-inhibiting activity of the resulting compounds (*K*<sub>i</sub><sup>nNOS</sup> = 6 and 9 nM, respectively). Of other thiophene-2-carboxamidines, *N*-{4-[2-[(3-chlorophenyl)methyl]-amino]ethyl]phenyl}thiophene-2-carboxamidine **13g** is a highly efficient iNOS inhibitor (see Table 3), in which the thiophene fragment proved itself as a promising pharmacophore.<sup>15</sup>

The presence of the thiophenecarboxamidine group and the active site of the vitamin E in one molecule made it possible to prepare highly selective nNOS inhibitor **14** (*K*<sub>i</sub><sup>r-nNOS</sup> ≈ 0.9, *K*<sub>i</sub><sup>b-eNOS</sup> ≈ 110, *K*<sub>i</sub><sup>m-iNOS</sup> > 300 μM) and the antioxidant BN80933 exhibiting the anti-ischemic activity.<sup>31, 62</sup>



Among syntheses of compounds biologically active *in vivo*, noteworthy is the synthesis of drugs, i.e., substances with useful pharmacological properties (necessary lipophilicity, solubility, etc.), which undergo metabolism with elimination of an NOS inhibitor in living organisms. For example, *N*(6)-(1-iminioethyl)-L-lysine *N*-tetrazol-5-ylamide **11c** showed efficiency comparable with that of compound **11a** in a model of endotoxin shock and arthritis.<sup>63</sup>

**Table 3.** Inhibiting activity of non-amino acid compounds containing the amidine group.

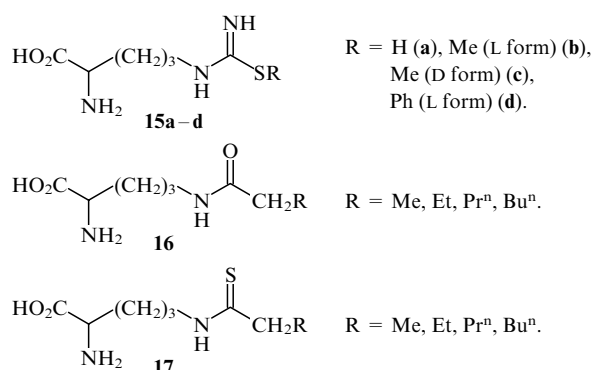
| Compound <b>13</b> | <i>K</i> <sub>i</sub> <sup>iNOS</sup> /μM | Selectivity |        | Ref. |
|--------------------|-------------------------------------------|-------------|--------|------|
|                    |                                           | n/i         | e/i    |      |
| <b>a</b>           | 0.14                                      | > 10        | ≈ 500  | 29   |
|                    | 0.2 <sup>a, b</sup>                       | > 10        | > 1000 | 14   |
| <b>b</b>           | 2 <sup>c</sup>                            | 0.02        | > 1    | 29   |
| <b>c</b>           | 0.02 <sup>c</sup>                         | < 1         | > 10   | 29   |
| <b>g</b>           | 5 <sup>a, b</sup>                         | 0.004       | < 1    | 12   |
|                    | 0.3 <sup>a</sup>                          | < 1         | > 1    | 14   |

<sup>a</sup> *IC*<sub>50</sub>. <sup>b</sup> h-NOS, [Arg] = 30 μM. <sup>c</sup> h-NOS. <sup>d</sup> m-iNOS, r-nNOS, h-eNOS.

The above data demonstrate that a decrease in the basicity of the guanidine-like group (which determines binding of the inhibitor to the enzyme) as a result of the complete replacement of one amino group does not decrease the inhibiting activity. Moreover, more active compounds **13a,c,g** were prepared by modifications of the carboxamidine residue with aryl and hetaryl fragments.

### 3. L-Thiocitrulline and its isothiocarbamide analogues

L-Citrulline and its analogues **15–17** belong to a vast class of compounds in which one nitrogen atom of the guanidine group is replaced by the oxygen or sulfur atom. L-Citrulline, which is one of the products of enzymatic oxidation of L-arginine, is a very weak NOS inhibitor.<sup>24</sup> However, L-thiocitrulline (**15a**) proved to be a strong inhibitor, nNOS being inhibited ~50 times stronger than iNOS (Table 4).



One of the mechanisms determining the strength of affinity of compound **15a** to the neuronal isoform of the enzyme involves binding between the Fe atom of the haem and the thiol group of the inhibitor. This fact was observed spectrophotometrically (a type-II differential spectrum of the haem recorded upon binding of compounds as the sixth ligand of the hexacoordinate Fe atom).

The introduction of the methyl substituent into the thiol group of L-thiocitrulline **15a** giving rise to S-methyl-L-thiocitrulline (**15b**) substantially strengthens binding to the enzyme and simultaneously decreases selectivity. A further increase in the size of the aliphatic substituent leads to a decrease in the inhibiting activity by a factor of *ca.* 50. Unlike binding of L-thiocitrulline **15a**, binding of its aliphatic derivatives to the enzyme was characterised by a type I spectral shift (*i.e.*, by the differential spectrum analogous to the spectrum of the haem upon the formation of the L-arginine–enzyme complex). This reflects the displacement of the sixth ligand from the hexacoordinate haem iron without bonding with the latter.<sup>64</sup> By contrast to *N*<sup>ω</sup>-alkyl-L-arginines, stereoselectivity was not absolutely necessary for binding this

group of inhibitors to the enzyme. S-Methyl-D-thiocitrulline (**15c**) inhibits, although weakly, iNOS and nNOS ( $IC_{50} \approx 470$  and  $160 \mu\text{M}$ , respectively). S-Methyl-L-thiocitrullinyl-L-phenylalanine appeared to be a strong and selective iNOS inhibitor ( $IC_{50} = 0.65 \mu\text{M}$ ,  $n/i \approx 60$ ).<sup>67</sup>

The replacement of the second amino group in L-citrulline or L-thiocitrulline with the alkyl group leads to a virtually complete loss (a decrease by two orders of magnitude) of the inhibiting activity of these compounds. For *N*(5)-acyl-L-ornithines **16** and *N*(5)-thioacyl-L-ornithines **17**,  $IC_{50} \geq 1000 \mu\text{M}$ . This is indicative of a weak affinity of the sulfur and oxygen heteroatoms for the catalytic site, if the alkyl group is at position 6 of the molecule. Therefore, for a strong complex with the enzyme to be formed, it is necessary that the inhibitor should contain the second NH group that forms the carboxamidine fragment.<sup>24</sup>

In compounds containing the isothiocarbamide group, as in guanidines and carboxamides, the amino acid moiety is not a necessary component for the design of efficient inhibitors. Exceptions are thiocarbamide, in which the nitrogen atom bears the terminal L-thiocitrulline residue ( $K_i > 2500 \mu\text{M}$ ), and its N-methyl derivatives. Their inhibiting activity is substantially lower (by > 500 times) than that of the corresponding S-alkyl derivatives. Ethyl- (**18b**) and isopropylisothiocarbamides (**18c**) are weakly selective for this isoform and proved to be the most active iNOS inhibitors (see Table 4).

|              | Compound <b>18</b> | R <sup>1</sup>                                                      | R <sup>2</sup> |
|--------------|--------------------|---------------------------------------------------------------------|----------------|
| <b>18a–e</b> |                    |                                                                     |                |
| <b>a</b>     |                    | (CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub>                     | H              |
| <b>b</b>     |                    | Et                                                                  | H              |
| <b>c</b>     |                    | Pr <sup>i</sup>                                                     | H              |
| <b>d</b>     |                    | (CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> OMe-3 | H              |
| <b>e</b>     |                    | H                                                                   | Ph             |

All S-alkylisothiocarbamides are competitive reversible inhibitors; they are simultaneously substrates for the haem.<sup>34,65,66</sup> S-Ethylisothiocarbamide promotes dimerisation of iNOS to a greater degree even compared to L-arginine.<sup>68</sup> S-(2-Aminoethyl)-isothiocarbamide (**18a**), like aminoguanidine **1a**, inhibits expression of iNOS in mouse macrophages and rat lungs.<sup>69</sup> In aqueous solutions (pH 7), S-aminoalkylisothiocarbamides are rearranged into the corresponding mercaptoalkylguanidines,<sup>70</sup> which are also iNOS inhibitors.<sup>71</sup>

Among S-phenylalkyl derivatives of isothiocarbamides, only compound **18d** exhibited selectivity, which was manifested in weaker inhibition (by a factor of 20) of b-eNOS compared to m-iNOS.<sup>72</sup>

N-Phenyl derivatives more actively inhibit nNOS. At the same time, N-phenylisothiocarbamide (**18e**) exhibited weak selectivity ( $K_i^{\text{iNOS}} \approx 0.9 \mu\text{M}$ ,  $n/i \approx 0.1$  and  $e/i \approx 0.5$ ). It should be noted that S-ethyl-N-phenylisothiocarbamide derivatives are less active against iNOS compared to nNOS. The values of  $K_i$ ,  $n/i$  and  $e/i$  for 2- and 4-trifluoromethylphenyl derivatives **19a,b** are, respectively,  $K_i \approx 20$  and  $40 \mu\text{M}$ ;  $n/i \approx 0.06$  and  $0.01$ ;  $e/i \approx 1$  and  $0.3$ .

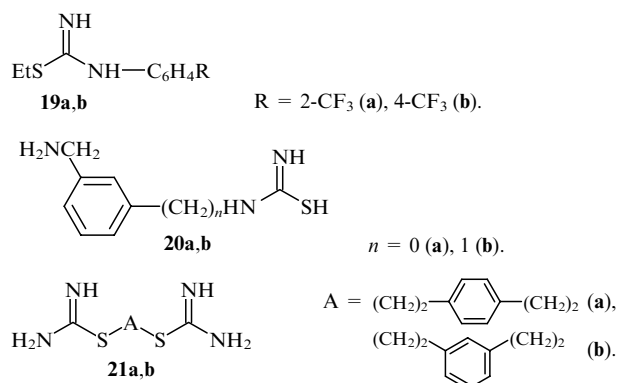


**Table 4.** Inhibiting activity of S-substituted derivatives of citrulline and thiourea.

| Compound   | $K_i^{\text{iNOS}}/\mu\text{M}$ | Selectivity |      | Ref. |
|------------|---------------------------------|-------------|------|------|
|            |                                 | n/i         | e/i  |      |
| <b>15a</b> | 4 <sup>a</sup>                  | 0.02        | —    | 64   |
| <b>15b</b> | 0.8 <sup>b</sup>                | < 0.1       | —    | 33   |
| <b>18a</b> | 6 <sup>c</sup>                  | > 1         | > 1  | 28   |
| <b>18b</b> | 0.1                             | > 1         | 1    | 28   |
|            | 0.02 <sup>d</sup>               | > 1         | > 1  | 65   |
|            | 0.02 <sup>e</sup>               | > 10        | > 10 | 66   |
| <b>18c</b> | 0.01                            | > 10        | > 10 | 66   |
| <b>18d</b> | 0.2                             | > 1         | > 10 | 66   |
| <b>21a</b> | 0.007                           | > 1         | > 10 | 66   |

<sup>a</sup> r-NOS. <sup>b</sup> r-NOS. <sup>c</sup>  $K_i$  was calculated from the data published in the study.<sup>31</sup> <sup>d</sup> h-NOS. <sup>e</sup> m-iNOS, r-nNOS, b-eNOS.



Compound **19b** did not inhibit nNOS in a tissue culture (see Table 4).<sup>73</sup>

Amidine **13a** and its analogue **13b** are known as unique inhibitors. Hence, isothiocarbamide derivatives were constructed on the basis of the above compounds.<sup>74</sup> However, compounds **20a,b** did not exhibit the expected inhibiting activity. *N*-(3-Amino-methylphenyl)isothiocarbamide (**20a**) was the most active inhibitor ( $IC_{50}^{iNOS} = 23 \mu M$  without pronounced selectivity). However, it appeared that the benzyl derivatives of isothiocarbamides (in particular, compound **20b**) serve as h-iNOS stimulators when added simultaneously with <sup>14</sup>C-arginine without preincubation with the enzyme.

The introduction of the *N*-amino group into isothiocarbamides (by analogy with aminoguanidine) did not give rise to strong and selective inhibitors. These compounds were many times (> 100) less active than the corresponding *S*-alkylisothiocarbamides. Like aminoguanidine, these compounds inactivate NOS and accelerate autoinactivation of nNOS in the absence of a substrate.<sup>31</sup>

Compounds **21a,b** containing two isothiocarbamide groups proved to be active. *S,S'*-[1,4-Phenylene(bisethyle)diisothiocarbamide (**21a**) inhibited iNOS even at a nanomolar concentration. A change in the position of the substituents from *para* to *meta* led to the appearance of selectivity, because a substantial decrease in activity of *S,S'*-[1,3-phenylene(bisethyle)diisothiocarbamide (**21b**) toward eNOS was observed ( $IC_{50}^{iNOS} \approx 0.05 \mu M$ , *n/i*  $\approx 5$ , *e/i*  $\approx 200$ ).

Crystallographic study of complexes of *S*-alkylisothiocarbamides (and their selenium analogues) with eNOS demonstrated that not only hydrogen bonds of the conservative amino acids Trp and Glu, which are acceptors of substrates for all isoforms, but also nonpolar interactions in the catalytic pocket of the enzyme play a role in binding to the substrate pocket of the enzyme.<sup>75</sup> Study of the eNOS-inhibiting activity of compounds **19** and **21a,b** revealed the topological factors responsible for the affinity of the inhibitors for this constitutive enzyme, which are partially determined by interaction of the second ureide group with the propionate of the pyrrole ring D of the haem.

An increase in the length of the hydrocarbon fragment, which binds two isothiocarbamide residues, to C<sub>12–14</sub> results in the formation of active NOS inhibitors. Apparently, this is associated with the involvement of new peptide bonds outside the catalytic site and the substrate access channel in a contact with the inhibitor, because bis(isothiocarbamides) (unlike simple *S*-alkylisothiocarbamides) inhibit electron transfer in the reduction domain of NOS.<sup>62</sup> Unfortunately, this class of compounds is of limited pharmacological utility because of toxicity and poor cell membrane permeability.<sup>66</sup>

On the whole, both the inhibiting activity of the above-described compounds and their selectivity are determined by the mechanism of the enzyme–inhibitor interaction. The strongest and most selective inhibitors are characterised by either a slow rate of binding to the enzyme or the ability to inactivate the enzyme (suicide inhibitors). The latter (arginine **2b**, ornithine **11a** and isothiocarbamide **18a**) enhance proteolysis of NOS, whereas reversible inhibitors, such as compounds **2a** and **18b**, promote stability of the NOS dimer.<sup>36, 76</sup>

#### IV. Cyclic analogues of substrate-like inhibitors

The involvement of a guanidine-like group in a cyclic structure opens considerable possibilities for the chemical design of NOS inhibitors recognised by a target enzyme on the principle of similarity with L-arginine. These compounds containing one or two amidine nitrogen atoms in the ring differ somewhat in the mechanism of action.

##### 1. 1*H*-Pyrazole-1-carboxamidines

1*H*-Pyrazole-1-carboxamidines represent a small group of competitive NOS inhibitors containing one of the nitrogen atoms of

the guanidine fragment in the heterocycle.<sup>77, 78</sup> 1*H*-Pyrazole-1-carboxamidine (**22a**), which is a very strong but nonselective NOS inhibitor, is a parent compound (Table 5).



R = H (**a**), CH(NH<sub>2</sub>)CH<sub>2</sub>NH<sub>2</sub> (**b**),  
HNC<sub>6</sub>H<sub>4</sub>(CH<sub>2</sub>)<sub>2</sub>NH<sub>2</sub>-3 (**c**).

Table 5. Inhibiting activity of pyrazoles and pyrrolidines.

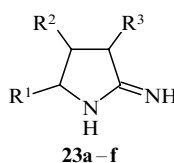
| Compound   | $K_i^{iNOS} / \mu M$ | Selectivity |            | Ref. |
|------------|----------------------|-------------|------------|------|
|            |                      | <i>n/i</i>  | <i>e/i</i> |      |
| <b>22a</b> | 0.7 <sup>a</sup>     | ~ 1         | ~ 1        | 78   |
| <b>22b</b> | 12                   | < 1         | > 10       | 78   |
| <b>23a</b> | 5 <sup>b</sup>       | < 1         | > 1        | 56   |
| <b>23b</b> | 0.3 <sup>b</sup>     | > 1         | > 1        | 79   |
| <b>23c</b> | 0.03                 | ~ 1         | > 1        | 79   |
| <b>23d</b> | 0.07                 | 10          | 400        | 79   |
| <b>23f</b> | 0.15 <sup>b</sup>    | > 10        | > 1000     | 80   |

<sup>a</sup> m-iNOS, r-nNOS, b-eNOS. <sup>b</sup>  $K_i$  was calculated from the data published in the study<sup>31</sup>.

The introduction of the methyl group at position 3 or 4 of the pyrazole ring decreases the inhibiting activity by an order of magnitude. On the whole, this class of compounds inhibit nNOS to a greater degree and inhibit eNOS to a smaller degree. *N*<sup>G</sup>-Substituted derivatives, viz., *N*-(1,2-diaminoethyl)-1*H*-pyrazole-1-carboxamidine (**22b**) and *N*-(3-aminoethylamino)-1*H*-pyrazole-1-carboxamidine (**22c**), were found to exhibit high selectivity (*n/i*  $\approx 0.1$ , *e/i*  $\approx 10$ ).

##### 2. Cyclic amidines

Amidine-containing compounds, primarily, heterocyclic imines and imidazoles, belong to the most well-studied class of cyclic NOS inhibitors. The introduction of aliphatic substituents at positions 4 and 5 of the pyrrolidine ring leads to a substantial increase in the activity and selectivity of new compounds, particularly, of 4-methyl-2-iminopyrrolidine (**23b**) and *trans*-5-ethyl-4-methyl-2-iminopyrrolidine **23c** (see Table 5).



R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = H (**a**);  
R<sup>1</sup> = R<sup>3</sup> = H, R<sup>2</sup> = Me (**b**);  
R<sup>1</sup> = *trans*-Et, R<sup>2</sup> = Me, R<sup>3</sup> = H (**c**);  
R<sup>1</sup> = *cis*-n-C<sub>5</sub>H<sub>11</sub>, R<sup>2</sup> = (+)-Me, R<sup>3</sup> = H (**d**);  
R<sup>1</sup> = *cis*-n-C<sub>5</sub>H<sub>11</sub>, R<sup>2</sup> = (+)-CF<sub>3</sub>, R<sup>3</sup> = H (**e**);  
R<sup>1</sup> = (*R*)-n-C<sub>5</sub>H<sub>11</sub>, R<sup>2</sup> = (*S*)-Me,  
R<sup>3</sup> = (*S*)-OH (**f**).

The iNOS-inhibiting activity of pyrrolidine derivatives **23b** and **23c** is two orders of magnitude higher than that of the starting compound **23a** ( $K_i^{iNOS} < 1 \mu M$ ). The resolution of racemic mixtures of (+)-4-methyl-*cis*-5-n-pentyl-2-iminopyrrolidine (**23d**) and 4-trifluoromethyl-*cis*-5-n-pentyl-2-iminopyrrolidine (**23e**) into stereoisomers demonstrated that the (+)-*cis* isomers are almost an order of magnitude more selective for iNOS than for eNOS ( $K_i \approx 0.1 \mu M$ , *n/i*  $\approx 10$ , *e/i* > 100).<sup>79</sup> This is evidence that new stereospecific acceptors were revealed in iNOS. The recently characterised iNOS inhibitor, viz., (3*S*,4*S*,5*R*)-3-hydroxy-4-methyl-5-n-pentyl-2-iminopyrrolidine (**23f**), exhibited selectivity (*e/i*) three times higher than that of compound **23d**. This fact confirmed once again that a search for stereoselective iNOS inhibitors in the class of iminopyrrolidines holds promise.

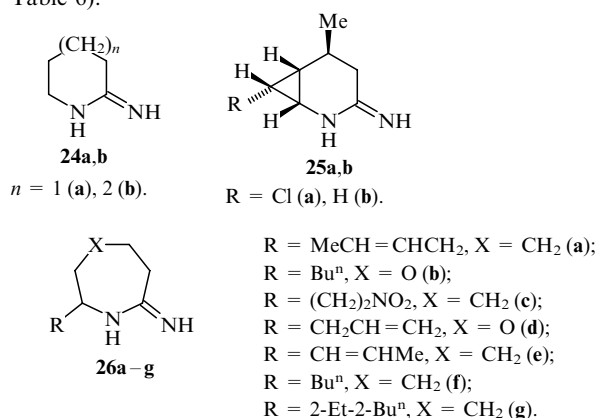
Highly active competitive iNOS inhibitors with  $K_i < 1 \mu M$  were found in a series of heterocyclic imines containing from five to nine carbon atoms in the ring (Table 6). However, these

**Table 6.** Inhibiting activity of 2-imino-N-containing heterocyclic derivatives.

| Compound   | $K_i^{\text{iNOS}}/\mu\text{M}$ | Selectivity |     | Ref. |
|------------|---------------------------------|-------------|-----|------|
|            |                                 | n/i         | e/i |      |
| <b>24a</b> | 0.2 <sup>a</sup>                | ~1          | >1  | 56   |
| <b>24b</b> | 0.4                             | ~1          | >1  | 56   |
| <b>25a</b> | 0.002 <sup>b</sup>              | —           | 10  | 81   |
| <b>26a</b> | 0.2 <sup>a</sup>                | >1          | 150 | 82   |
| <b>26b</b> | 0.5                             | 10          | 300 | 82   |
| <b>26c</b> | 0.03                            | >1          | 10  | 82   |
| <b>26d</b> | 0.04 <sup>a</sup>               | >1          | >10 | 83   |
| <b>26e</b> | 0.03 <sup>c</sup>               | >1          | >10 | 83   |
| <b>26f</b> | 0.1                             | ~2          | 130 | 83   |
| <b>26g</b> | 0.4                             | >1          | 200 | 83   |

<sup>a</sup>  $K_i$  was calculated from the data published in the study<sup>31</sup>. <sup>b</sup> h-iNOS. <sup>c</sup> The experimental value of  $K_i$  = 0.09  $\mu\text{M}$ .

inhibitors do not exhibit pronounced selectivity. The activity of 2-iminopyrrolidine (**23a**) is *ca.* 25 times lower than that of the six-membered amidine 2-iminopiperidine **24a**. A further increase in the size of the inhibitor molecule leads to a decrease in activity (see Table 6).



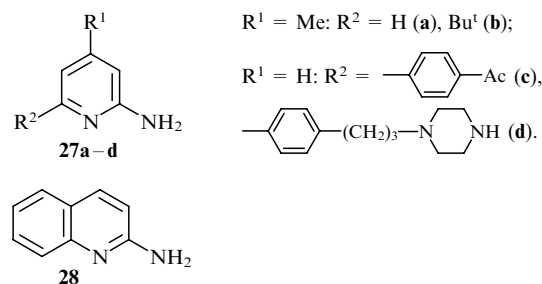
Fused six-membered amidines were found to have the unique inhibiting properties. In this series, the bicyclic amidine (1*S*,5*S*,6*R*,7*R*)-7-chloro-3-imino-5-methyl-2-azabicyclo[4.1.0]heptane (**25a**) proved to be most active against h-iNOS (see Table 6). Certain fused and spirocyclic derivatives of 2-iminopiperidine were found to be highly active iNOS inhibitors ( $IC_{50} < 0.1 \mu\text{M}$ ,  $e/i > 1$ ).<sup>84</sup> DL-(1*R*,5*S*,6*R*)-3-Imino-5-methyl-2-azabicyclo[4.1.0]heptane hydrochloride (**25b**) has *in vitro* and *in vivo* very high inhibiting activity ( $IC_{50}^{\text{h-iNOS}} = 0.09$ ,  $IC_{50}^{\text{m-iNOS}} = 0.007 \mu\text{M}$ , respectively). In experiments on mice treated with lipopolysaccharides, the dose of the agent necessary to decrease the concentration of nitrite anions (the product of  $\text{NO}^*$  metabolism) in blood plasma was  $0.013 \text{ mg kg}^{-1}$ , which is almost 1500 times lower than the maximum tolerable level for animals.

The introduction of side substituents and modifications of the ring in hexahydro-2-iminoazepine (**24b**) gave rise to iNOS-selective inhibitors. For example, hexahydro-7-(but-2-enyl)-2-iminoazepine (**26a**) containing the alkenyl substituent at position 7 inhibits iNOS *ca.* 100 times more strongly than eNOS. Due to the presence of the oxygen atom at position 5, the selectivity of hexahydro-7-n-butyl-2-imino-5-oxazepine (**26b**) for iNOS is almost two times higher than that for eNOS, the nNOS-inhibiting activity varying only slightly.<sup>56</sup> The iNOS-inhibiting activity of hexahydro-2-imino-7-(2-nitroethyl)azepine (**26c**) containing the polar nitroethyl group is almost an order of magnitude higher, although the selectivity of this compound is low.

Alkylation at position 7 in hexahydro-2-iminoazepines (see Table 6) results in an increase in activity and selectivity of such

inhibitors as hexahydro-7-n-butyl-2-imino-5-oxazepine (**26d**), hexahydro-2-imino-7-propenylazepine (**26e**), hexahydro-7-n-butyl-2-iminoazepine (**26f**) and hexahydro-7-(2-ethyl-2-n-butyl)-2-iminoazepine (**26g**) ( $K_i < 1 \mu\text{M}$ ,  $e/i > 100$ ).<sup>83</sup>

The synthesis of analogues of iminopiperidines, *viz.*, aminopyridines **27a–d**, is a natural continuation of a search for NOS inhibitors among heterocyclic imines.

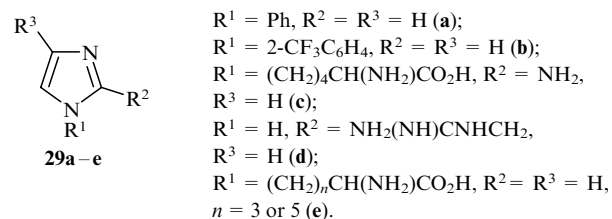


Later on, one of the first inhibitors belonging to this class, *viz.*, 2-amino-4-methylpyridine (**27a**)<sup>85</sup> ( $K_i$  are 55, 65 and  $98 \mu\text{M}$  for h-iNOS, h-nNOS and h-eNOS, respectively), has been used as a competitive radioligand to estimate the affinity and selectivity of other NOS inhibitors.<sup>31</sup> However, neither compound **27a** nor other mono- and disubstituted alkyl derivatives of 2-aminopyridine exhibited pronounced selectivity for the inducible enzyme ( $n/i > 1$ ,  $e/i > 1$ ). Of these compounds, 2-amino-6-*tert*-butyl-4-methylpyridine (**27b**) is the strongest iNOS inhibitor ( $IC_{50} < 1 \mu\text{M}$ ). 2-Amino-6-(4-substituted)phenylpyridines (for example, **27c**) did not have iNOS-inhibiting activity. However, arylidenepiperazine-bridged compound **27d** appeared to be an h-nNOS strong inhibitor ( $IC_{50} < 1 \mu\text{M}$ ), the selectivity being low ( $e/n > 1$ ). Compound **27d** exhibited the highest selectivity and inhibited h-nNOS six times more strongly than h-eNOS ( $IC_{50}^{\text{h-nNOS}} = 0.14 \mu\text{M}$ ).<sup>86</sup> 2-Aminopyridines fused with five- or six-membered saturated and unsaturated rings are active iNOS inhibitors ( $IC_{50} < 10 \mu\text{M}$ ) without pronounced selectivity, compounds containing unsaturated rings being more active. 2-Aminoquinoline **28** is the most active iNOS inhibitor ( $IC_{50} \approx 2 \mu\text{M}$ ).<sup>87</sup>

### 3. Imidazoles and nitroindazoles

Imidazole derivatives can be considered as cyclic analogues of carboxamidines containing both amidine nitrogen atoms in the heterocycle. Their reactions with the enzyme are targeted primarily to the haem. Imidazoles bind to the enzyme as the sixth ligand of the hexacoordinate iron atom in the haem, *i.e.*, analogously to  $\text{CO}$ ,  $\text{NO}^*$ ,  $\text{O}_2$  and  $\text{CN}^-$ . This property was well studied for cytochrome P-450, which is closely similar to NOS.<sup>88</sup>

Inhibition of NOS by imidazoles occurs reversibly. However, depending on the nature of the substituents and the NOS source, imidazoles compete with  $\text{BH}_4$  and/or L-arginine for binding to the catalytic site. For example, 1-phenylimidazole (**29a**) ( $IC_{50}^{\text{h-iNOS}} \approx 40 \mu\text{M}$ ), which is one of the strongest iNOS inhibitors, noncompetitively (with respect to L-arginine) binds to m-iNOS and competitively binds to b-eNOS (Table 7).



These differences in the inhibition mechanisms makes it difficult to interpret the inhibition constants determined by spectroscopic or kinetic methods.

Modifications of the substituent at the nitrogen atom afford inhibitors active against nNOS. However, frequently used 1-(2-

**Table 7.** Inhibiting activity of imidazole and 7-nitroindazole derivatives.

| Compound   | $K_i^{\text{iNOS}}/\mu\text{M}$ | Selectivity |      | Ref.   |
|------------|---------------------------------|-------------|------|--------|
|            |                                 | n/i         | e/i  |        |
| <b>29a</b> | 35 <sup>a</sup>                 | ~10         | ~20  | 10     |
| <b>29b</b> | 30 <sup>a, b</sup>              | 1           | >10  | 89, 90 |
| <b>29c</b> | 30 <sup>a, d</sup>              | <1          | <1   | 91     |
| <b>29d</b> | 10                              | <1          | >1   | 92     |
| <b>31b</b> | 0.03 <sup>a, e</sup>            | >1          | 1000 | 93     |
| <b>33</b>  | 1.6 <sup>a, f</sup>             | 0.1         | 0.5  | 94     |

<sup>a</sup>  $IK_{50}$ . <sup>b</sup> r-iNOS, m-nNOS, b-eNOS. <sup>c</sup> r-nNOS, e-hNOS. <sup>d</sup> r-iNOS, r-nNOS, h-eNOS. <sup>e</sup> h-iNOS, crude cell lysate. <sup>f</sup> m-iNOS, b-nNOS, b-eNOS.

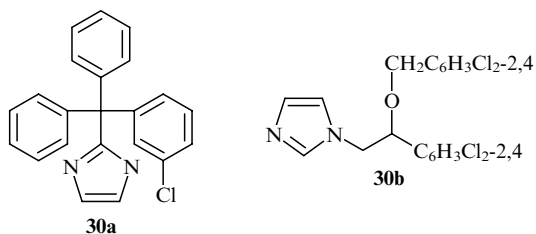
trifluoromethylphenyl)imidazole (**29b**) did not exhibit considerable activity and selectivity in *in vitro* experiments (see Table 7), although it caused a decrease in pain sensitivity of animals to formalin, which reflects its nNOS-inhibiting ability. Since imidazole derivatives containing substituents at positions 2 and 4 have lower inhibiting activity ( $IC_{50} > 1000 \mu\text{M}$ ),<sup>95</sup> attempts to design highly efficient inhibitors belonging to the class of 1,2-disubstituted imidazoles failed. It is believed that compounds with this structure may be useful tools for revealing the characteristic features of the guanidine–oxygen- and  $\text{BH}_4$ -binding regions of NOS.<sup>96</sup>

An increase in the length of the aliphatic bridge between the imidazole and the amino acid group made it possible to prepare active compounds.<sup>92</sup> Inhibitors **29e** containing an odd number of methylene groups are more selective for nNOS ( $K_i^{\text{nNOS}} = 2 \mu\text{M}$  for both compounds). Compounds containing an even number of methylene groups are less active.

Crystallographic studies demonstrated that two imidazole molecules can simultaneously bind to the oxidative domain of the m-iNOS monomer: one molecule is located in the catalytic site as the sixth ligand of the haem iron atom, and another molecule is located in the guanidine-binding pocket with Glu371.<sup>22</sup> In this connection, guanidine-substituted imidazoles were synthesised. However, most agents appeared to be poorly active, if at all. Among these compounds, imidazole derivative **29d** is the strongest inhibitor (against iNOS;  $IC_{50} \approx 140 \mu\text{M}$ ).<sup>97</sup>

Attempts were made to enhance the inhibiting activity of imidazoles by including an amino acid residue into molecules of these inhibitors. 2-Amino-5-(imidazol-1-yl)pentanoic acid (**29c**) has the highest activity (see Table 7).

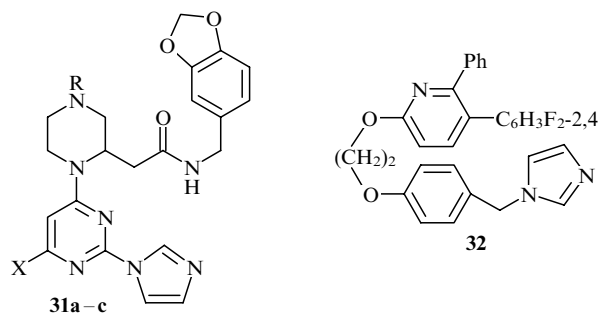
Antifungal clotrimazole (**30a**) and miconazole (**30b**), which inhibit nNOS competitively with CaM, belong to imidazoles containing bulky substituents.<sup>98</sup>



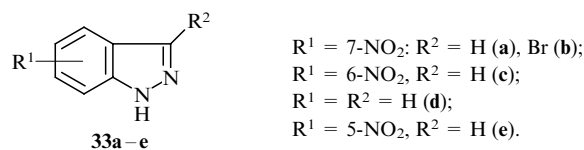
In addition, these drugs *in vitro* inhibit dimerisation of the oxidative domain of iNOS. In RAW264.7 cells, clotrimazole (50  $\mu\text{M}$ ) also blocks the formation of dimeric iNOS,<sup>99</sup> unlike substrate-like inhibitors, in the presence of which the fraction of dimeric iNOS increases from 50% to 90%.<sup>18, 69</sup>

Powerful inhibitors with bulky substituents were found by screening 8649 compounds prepared by combinatorial chemistry based on nitrogen-containing heterocycles.<sup>93</sup> Of 53 compounds

inhibiting iNOS by 60% at 200  $\mu\text{M}$ , three compounds, **31a–c**, which have  $IC_{50}^{\text{iNOS}} < 1 \mu\text{M}$  in a cell test system, were chosen.



R = H, X = Cl (**a**); R =  $\text{CO}_2\text{Me}$ , X = H (**b**);  
R =  $\text{CO}_2\text{Et}$ , X = H (**c**).



R<sup>1</sup> = 7- $\text{NO}_2$ ; R<sup>2</sup> = H (**a**), Br (**b**);  
R<sup>1</sup> = 6- $\text{NO}_2$ , R<sup>2</sup> = H (**c**);  
R<sup>1</sup> = R<sup>2</sup> = H (**d**);  
R<sup>1</sup> = 5- $\text{NO}_2$ , R<sup>2</sup> = H (**e**).

Compound **31b** was a highly efficient nNOS inhibitor not only in a cell culture,<sup>100</sup> but also in animals treated with a lipopolysaccharide ( $ID_{50} = 1.2 \text{ mg kg}^{-1}$ )<sup>8</sup> (based on the criterion of a decrease in the nitrite level in rat blood plasma). Crystallographic analysis of the complex of the oxidative domain of iNOS with compound **31b** demonstrated that free nitrogen of the imidazole group is coordinated to the haem iron atom in the sixth axial position, and the structure of the guanidine-binding sequence involving Glu371 is destroyed under the action of the adjacent imidazole, pyrimidine and piperazine rings. Inhibitors belonging to this series of compounds do not suppress activity of dimeric NOS. However, inhibitors were found among imidazole-containing compounds.

3-(2,4-Difluorophenyl)-6-{2-[4-(1*H*-imidazol-1-ylmethyl)phenoxy]ethoxy}-2-phenylpyridine (**32**) inhibits the  $\text{NO}^{\bullet}$  synthesis in activated macrophages with  $IC_{50} = 0.08 \mu\text{M}$  and have the therapeutic effect in experimental arthritis models.<sup>101</sup>

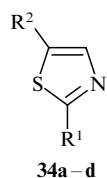
The inhibition mechanism involving the interaction with the haem was observed for compounds of the nitroindazole series. The most well-known agent, *viz.*, 7-nitroindazole **33a**, is a competitive inhibitor of iNOS (against L-arginine and  $\text{BH}_4$ ) and eNOS (against  $\text{BH}_4$ ). This is associated with the fact that compound **33a**, like its analogue, *viz.*, 3-bromo-7-nitroindazole (**33b**) ( $IC_{50}^{\text{r-iNOS}} = 0.29 \mu\text{M}$ , n/I < 1, e/I > 1),<sup>102</sup> contacts with one of the propionate groups of the haem, thus suppressing its interaction with  $\text{BH}_4$ .<sup>62</sup>

Nitroindazoles **33c** ( $K_i^{\text{b-nNOS}} = 40 \mu\text{M}$ ) and **33a** were the strongest b-nNOS inhibitors, whereas the inhibiting activities of indazole (**33d**) and 5-nitroindazole (**33e**) were very weak ( $IC_{50} > 1000 \mu\text{M}$ ).<sup>103</sup> However, according to the results of the study,<sup>104</sup> compounds **33c,e** are virtually identical in the r-nNOS-inhibiting activity. The selectivity of 7-nitroindazole **33a** for nNOS, which is manifested *in vivo*, is apparently associated with its cell membrane permeability and metabolism.<sup>14</sup>

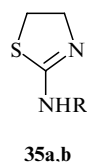
#### 4. Cyclic analogues of isothioureas

Cyclisation of *S*-aminoalkylisothioureas affords the corresponding *S,N*-heterocycles with structures isosteric with the guanidine group of L-arginine.<sup>105, 106</sup> Although thiazole **34a** is a very weak inhibitor of all NOS isoforms ( $K_i > 200 \mu\text{M}$ ), the introduction of an amino group giving rise to 2-aminothiazole (**34b**) increases the inhibiting activity against iNOS by a factor of *ca.* 5 (Table 8).

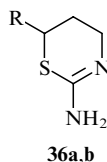
$\%ID_{50}$  is the dose at which the rate of the  $\text{NO}^{\bullet}$  synthesis is half that observed for an intact sample.



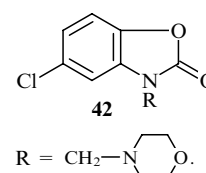
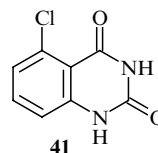
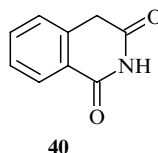
$R^1 = R^2 = H$  (**a**);  
 $R^1 = NH_2$ ,  $R^2 = H$  (**b**), Me (**c**);  
 $R^1 = NH(CH_2)_3Cl$ ,  $R^2 = H$  (**d**).



$R = H$  (**a**);  
 $(CH_2)_3Ala$  (**b**).



$R = H$  (**a**);  
 Me (**b**).



$R = CH_2-N$  (morpholine ring).

**Table 8.** Inhibiting activity of cyclic analogues of isothioureas.

| Compound   | $K_i^{iNOS}$ / $\mu M$ | Selectivity |      | Ref. |
|------------|------------------------|-------------|------|------|
|            |                        | n/i         | e/i  |      |
| <b>34b</b> | 50 <sup>a</sup>        | < 1         | < 1  | 61   |
| <b>35a</b> | 0.3                    | 2           | 1    | 61   |
| <b>35b</b> | 8 <sup>b,c</sup>       | < 1         | < 1  | 107  |
| <b>36a</b> | 0.6 <sup>d</sup>       | 1           | 2    | 56   |
| <b>36b</b> | 0.004 <sup>c</sup>     | > 10        | > 10 | 65   |
| <b>39</b>  | 9 <sup>f</sup>         | 1           | 0.3  | 108  |
| <b>40</b>  | 2                      | 20          | 4    | 108  |
| <b>41</b>  | 2                      | 25          | 1    | 108  |
| <b>42</b>  | 0.8 <sup>g</sup>       | > 1         | > 1  | 109  |

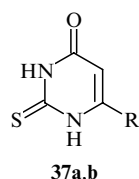
<sup>a</sup> h-NOS. <sup>b</sup>  $IC_{50}$ . <sup>c</sup> r-iNOS, r-nNOS, h-eNOS. <sup>d</sup>  $K_i$  was calculated from the data published in the study.<sup>31</sup> <sup>e</sup> m-iNOS, r-nNOS, b-eNOS. <sup>f</sup> [Arg] = 5  $\mu M$ , m-iNOS, m-nNOS, b-eNOS. <sup>g</sup> h-NOS.

2-Amino-5-methylthiazole (**34c**) ( $IC_{50} \approx 12 \mu M$ ) is even more active.<sup>61</sup> However, these inhibitors exhibited selectivity for none of the NOS isoforms. *N*(5)-(Thiazolin-2-yl)-L-ornithine (**35b**) prepared by modifying the amino group in 2-amino-2-thiazoline (**35a**) is an active eNOS inhibitor ( $IC_{50} \approx 1 \mu M$ ). At the same time, *N*(5)-(thiazol-2-yl)-L-ornithine (**34d**) is a weak inhibitor.<sup>107</sup>

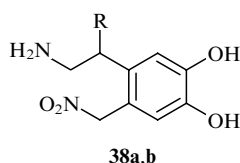
The activity and selectivity of 2-amino-5,6-dihydro-4*H*-1,3-thiazine (**36a**) synthesised by cyclisation of *S*-aminopropylisothiourea exhibits are similar to those of compound **35a** (see Table 8). The replacement at position 6 leads to a substantial increase in activity and selectivity of the derivatives (as in the case of N-containing heterocyclic imines) (see Table 6). For example, 2-amino-6-methyl-5,6-dihydro-4*H*-1,3-thiazine (**36b**) inhibits iNOS almost 150 times more strongly than thiazine **36a**.

## 5. Other inhibitors

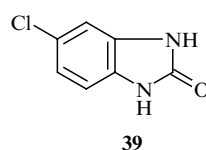
The NOS-inhibiting activity was found in a series of antithyroid agents belonging to thiouracils. 6-Methyl- (**37a**) and 6-*n*-propyl-2-thiouracils (**37b**) exhibited selectivity for r-nNOS inhibition. At a concentration of 500  $\mu M$ , compound **37a** inhibited the synthesis of L-citrulline by the enzyme isoforms m-iNOS, r-nNOS and b-eNOS by  $\approx 20\%$ , 80% and 40%, respectively.<sup>110</sup> The inhibition occurred competitively and reversibly, suppression of  $BH_4$ -dependent dimerisation of nNOS playing a certain role in this effect.<sup>111</sup>



$R = Me$  (**a**),  $Pr^n$  (**b**).



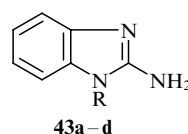
$R = H$  (**a**), OH (**b**).



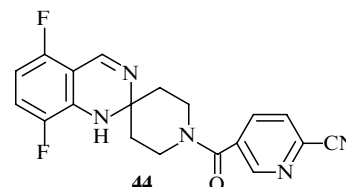
The introduction of the nitro group in dopamine and nor-adrenaline gave rise to the corresponding nitro derivatives, *viz.*, 4-(2-aminoethyl)-5-nitromethylpyrocatechol (**38a**) and 4-(2-aminoethyl-1-hydroxy)-5-nitromethylpyrocatechol (**38b**). These compounds inhibited NOS two orders of magnitude more strongly ( $K_i \approx 50 \mu M$ ) than the starting catecholamines. The inhibition occurred reversibly and competitively with L-arginine and  $BH_4$ ; in addition, slight selectivity for r-nNOS, was observed, which may be attributed to suppression of enzyme dimerisation.<sup>112</sup> These results suggest that the nitro group plays a great role in inhibitor–NOS complexation.

Screening of a chemical library revealed a series of promising bicyclic NOS inhibitors. Thus,  $IC_{50}^{m-iNOS}$  for 5-chloro-1,3-dihydro-2*H*-benzimidazol-2-one (**39**), (2*H*,4*H*)-isoquinoline-1,3-dione (**40**) and 5-chloro-(1*H*,3*H*)-quinazolin-2,4-dione (**41**) were < 10  $\mu M$ . The selectivity of compounds **39** and **41** for r-nNOS and b-eNOS (n/i) is > 10 and > 1, respectively. In a series of benzoxazolones, 6-chloro-*N*-morpholinomethylbenzoxazolone (**42**) appeared to be an active h-iNOS inhibitor, which, however, did not exhibit noticeable selectivity (see Table 8).

It is known<sup>113</sup> that substituted 2-aminobenzimidazoles **43a–d** have NOS-inhibiting activity. 2-Aminobenzimidazole (**43a**) competitively inhibited iNOS, the selectivity for eNOS being very low ( $IC_{50}^{h-iNOS} = 25 \mu M$ , n/i  $\approx 3$ , e/i > 5). 2-Amino-1-aminomethylbenzimidazole (**43b**) is more selective for h-nNOS ( $IC_{50}^{h-nNOS} \approx 6 \mu M$ , n/i < 0.1, n/e < 0.1). 1-Ethyl- (**43d**) and 2-amino-1-isopropylaminobenzimidazoles (**43c**) are inactive.<sup>113</sup>



$R = H$  (**a**),  $CH_2NH_2$  (**b**),  
 $Pr^iNH$  (**c**), Et (**d**).

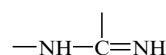


Recently, compounds belonging to the class of 1,2-dihydroquinazolineamines and their spirocyclic derivatives were found to have inhibiting activity against iNOS.<sup>114</sup> For example, 1-(6-cyano-3-pyridylcarbonyl)-5',8'-difluorospiro[piperidine-4,2'(1'*H*)-quinazoline]-4'-amine hydrochloride (**44**) showed high efficiency both *in vitro* and *in vivo* ( $IC_{50}^{h-iNOS} = 0.04 \mu M$ , n/i > 10, e/i > 1000).

## V. Conclusion

Based on the above data, the following physicochemical features responsible for the efficiency of NOS inhibitors, which interact with the catalytic site of the enzyme, can be noted.

1. The guanidine, carboxamide or isothiocarbamide groups in linear or cyclic structures



provide hydrogen bonding with Glu and/or the formation of a coordination bond with the haem Fe atom.

2. Small hydrophobic substituents at the guanidine-like group (alkyl, phenyl or thienyl), which can form additional bonds with haem-proximal peptide regions, should be present.

3. The chemical activity of a guanidine-like group as a pseudosubstrate can have a determining effect on both the selectivity and inhibiting activity of substrate-like compounds.

4. In addition to these factors, such properties of compounds as suppression of superoxide synthase activity of the enzyme, regulation of NOS dimerisation and inactivation of active oxygen forms produced by NOS can facilitate efficiency of *in vivo* NOS inhibition.<sup>115</sup>

One would expect that the next step in the chemical synthesis and design of pharmacological agents modifying the enzymatic NO<sup>•</sup> production will be aimed at preparing compounds that combine the following functions: specificity for NOS isoforms, antioxidant activity and specificity for accumulation in subcellular targets (caveoles, synapses, mitochondria, *etc.*).

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# Phosphapalladacycles: forms of existence and reactions<sup>†</sup>

V V Dunina, O N Gorunova

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**Abstract.** Some aspects of the reactivity of cyclopalladated complexes with phosphorus donor atoms are discussed, in particular, the routes of modification of the metal coordination environment in phosphapalladacycles by means of diverse auxiliary ligands; the transformations of phosphapalladacycles involving the Pd–C bond; the modification of phosphapalladacycles with retention of the Pd–C bond; and dechelation and destruction of phosphapalladacycles. The regiochemistry of ligand coordination to PC-palladacycles is considered from the standpoint of the *trans*-effect of the P- and C-donor atoms of the palladacycle. The bibliography includes 359 references.

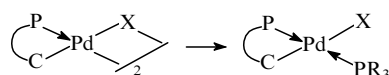
## I. Introduction

The development of modern chemistry of phosphapalladacycles is mainly determined by the increased demands of the homogeneous metal complex catalysis for compounds of this class, as they proved to be remarkably efficient and practically convenient catalysts or precatalysts.<sup>1–11</sup> There are two approaches to the optimisation of the structures of phosphapalladacycles to meet the requirements of a particular chemical process and a particular substrate: (1) modification of electronic and steric characteristics of the phosphapalladacycle and (2) variation of the nature of auxiliary ligands in the coordination environment of palladium.

The first approach (usually, fairly labour consuming) involves targeted design of P-donor ligands and the selection of optimal methods for their cyclopalladation. The relevant information can be found in a review,<sup>12</sup> which gives a detailed analysis of the known methods for the synthesis of the PC- and PCP-type cyclopalladated complexes (CPCs). An alternative solution to this problem is chemical modification of the phosphapalladacycle prepared beforehand. The influence of the structure of phosphapalladacycles on their catalytic activity can be followed from a

series of reviews on homogeneous catalysis, which are devoted to either particular types of reactions<sup>2, 3, 6, 13</sup> or particular classes of cyclopalladated (pre)catalysts of the PC<sup>5, 7, 8</sup> or PCP type.<sup>4, 5, 7, 9–11</sup>

The second approach appears less labour consuming, as it implies only the variation of the coordination environment of the metal in the pre-formed phosphapalladacycles. Its efficiency can be illustrated by the substantial increase in the activity of the PC-type (pre)catalysts in the Suzuki and Stille reactions and in amination attained on passing from standard dimeric complexes to monomeric analogues (mononuclear palladium complexes) with monodentate phosphines.<sup>14–18</sup>



Conversely, in other processes (for example, in the Heck reaction), the activity of the monomeric phosphine derivatives proved to be lower than the activity of the dimers.<sup>19, 20</sup> The activity of the cyclopalladated catalysts can be substantially enhanced by selecting an appropriate bridging anion in the CPC dimers ( $\text{Cl}^- < \text{AcO}^- < \text{CF}_3\text{COO}^-$ )<sup>21</sup> or by converting dimers into monomeric  $\beta$ -diketonate derivatives.<sup>22</sup> Similar effects have been found for the use of CN-palladacycles whose catalytic activity in various processes can either increase<sup>23–28</sup> or, conversely, decrease<sup>29</sup> on passing from dimers to monomers. For example, the cationic mononuclear adducts of the CN-palladacycles efficiently catalyse CO copolymerisation with ethylene,<sup>30</sup> while in the Heck reaction they show no activity.<sup>29</sup> These facts demonstrate the necessity of individual approach to the coordination environment of palladium in the palladacycle chosen for catalysis.

The implementation of the second approach requires the knowledge of synthetic routes to various derivatives of a palladacycle and of their behaviour in chemical transformations. The only published review on the cyclometallation of phosphorus-containing ligands (separately<sup>31</sup> and in the monograph<sup>32</sup>) covers the literature only up to 1985 and does not describe the behaviour of phosphapalladacycles in various reactions or the modification routes of the coordination environment of palladium.

The purpose of this review is to analyse the properties and the reactivity of phosphapalladacyclic compounds based on publica-

V V Dunina Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax (7-495) 932 88 46, tel. (7-495) 939 53 76, e-mail: dunina@org.chem.msu.ru

O N Gorunova Institute of Physiologically Active Compounds, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation. Fax (7-495) 913 21 13, tel. (7-495) 939 53 76, e-mail: o.gorunova@org.chem.msu.ru

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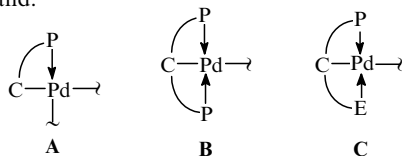
<sup>†</sup> This review naturally continues the review by the same authors 'Phosphapalladacycles: preparation routes' published previously [Russ. Chem. Rev. 73 309 (2004)].

tions that appeared up to 2003. Two different types of reactions are considered:

1. Modification of the coordination environment of the metal in phosphapalladacycles by introducing auxiliary ligands without affecting the proper metallacyclic fragment (Section II).

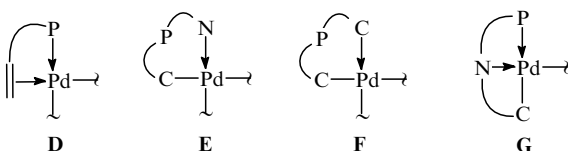
2. Transformations of phosphapalladacycles (Section III): reactions involving the Pd–C bond and processes resulting in palladacycle modification with retention of the cyclic structure. This Section also covers dechelation and destruction of palladacycles.

The investigation objects include mono- (**A**) and bicyclic (**B**, **C**) compounds in which palladium is directly linked to one or two atoms of trivalent phosphorus and to, at least, one carbanionic centre incorporated in the same anionic bi- or tridentate chelated ligand.



E is heteroatom.

The structures of type **D–G**



are beyond the scope of this review as their properties differ significantly from the properties of phosphapalladacycles **A–C**.<sup>‡</sup>

However, PC-chelated derivatives of phosphino-phosphorus ylides are included in the consideration, despite the formally neutral nature of ligands of this class (really, the zwitterionic nature), because the C-donor atom in them exhibits pronounced carbanion properties.

An idea of the diversity of derivatives possible for CPC bearing P-donor atoms can be gained from Supplements 1–3, which present data on the methods of synthesis of phosphapalladacycle derivatives classified according to structural features: PC-type compounds (**A**, Supplement 1), their bicyclic (pincer) PCP-analogues (**B**, Supplement 3) and PC-coordinated phosphino-phosphorus ylides (Supplement 2). Within each Table, phosphapalladacycles are grouped according to the type of hybridisation of the metal-bonded carbon atom ( $sp^3$  or  $sp^2$ ) and the size of the chelate ring (six-, five-, four-, and three-membered). In addition, derivatives of each palladacycle are classified according to types of complexes, either neutral or cationic, with either mono- or bidentate auxiliary ligands. The complexes whose structures were reliably confirmed by X-ray diffraction are asterisked.

## II. Forms of existence of phosphapalladacycles

This Section describes phosphapalladacycle derivatives of PC- and PCP types and their interconversion routes.

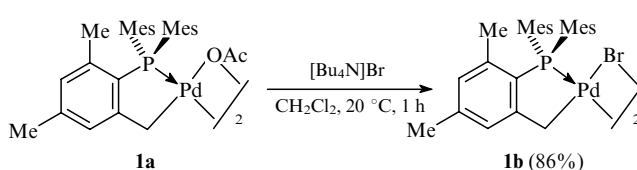
### 1. Monocyclic PC-complexes

#### a. Dimers

The direct intramolecular cyclopalladation of monodentate P-donor ligands usually gives, as the primary products, dimeric complexes with halide or carboxylate bridges, most often, chloride or acetate ones (depending on the nature of the palladating agent used).<sup>12</sup> Modification of bridging anions is required in those cases where it is necessary (1) to increase the dimer solubility (most

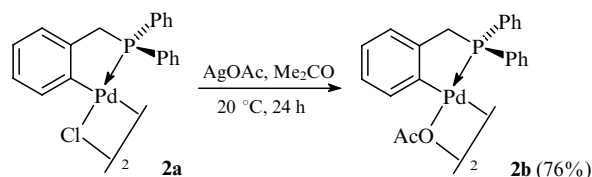
often, the solubility of  $\mu$ -halide dimers is lower than that of  $\mu$ -carboxylate analogues); (2) to remove the complications caused by the dynamic behaviour of complexes (most typical of  $\mu$ -carboxylate dimers<sup>2, 22, 51</sup>); (3) to increase the thermal stability of complexes;<sup>8</sup> (4) to optimise the structure of a dimeric PC-type (pre)catalyst.<sup>21</sup>

The transformation of  $\mu$ -acetate PC-dimers into  $\mu$ -chloride or  $\mu$ -bromide analogues is easily accomplished by simple replacement of  $\mu$ -OAc by a 'softer' halide at room temperature (see Supplement 1). The reactions with LiCl are carried out in a mixture of methanol with dichloromethane<sup>53</sup> or in aqueous acetone,<sup>54</sup> while those with ammonium salts (for example, with  $[Bu_4N]Cl$  or  $[Bu_4N]Br$ ) are carried out in dichloromethane. An example of anion exchange in dimer **1a** is presented below<sup>¶</sup> (see Ref. 51).

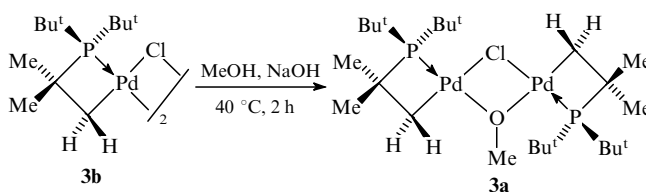


The  $\mu$ -chloride PC-dimers are usually transformed into  $\mu$ -bromide or  $\mu$ -iodide analogues (with softer anions) by means of simple metal halide salts KBr,<sup>55, 56</sup> LiBr,<sup>57</sup> KI<sup>55, 57</sup> and NaI.<sup>58, 59</sup> The reactions are carried out in acetone at room temperature.

However, the reverse replacement of relatively soft bridging halide anions in dimers by harder anions (for example, the **2a**  $\rightarrow$  **2b** transition) requires dehalogenation of the substrate with an appropriate  $RCO_2Ag$  salt ( $R = Me, Ph$ ).<sup>54, 60</sup>



Of the few non-standard forms of dimeric CPC with monoatomic bridges, we would like to mention the non-symmetrical  $\mu$ -methoxy- $\mu$ -chloride complex **3a**, which is prepared by methoxylation of  $\mu$ -chloride dimer **3b** with methanol in an alkaline medium.<sup>61</sup>



As was to be expected, the reaction of non-symmetrical dimer **3a** with phosphine affords a mixture of two mononuclear derivatives with different anions.

One more type of dimeric CPCs with diatomic bridges includes phosphapalladacycles with azolate bridges, namely, pyrazolate (pz),<sup>62–64</sup> 4-methyl- (4-mpz) and 3,5-dimethyl-substituted (3,5-dmpz) pyrazolate bridges.<sup>63, 64</sup> These binuclear com-

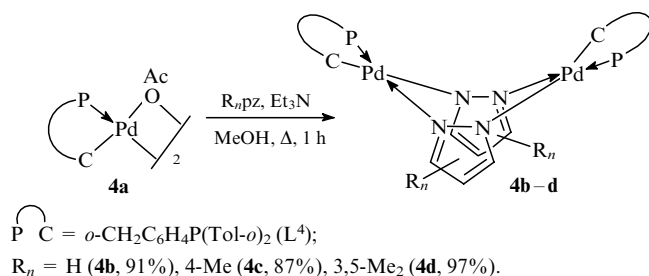
<sup>‡</sup> Examples of structures **D–G** have been reported.<sup>33–50</sup>

<sup>§</sup> For PC-palladacycles, these studies have not been carried out, but the stability of benzylamine CN-dimers is known<sup>52</sup> to increase, depending on the nature of the bridging anions, in the series  $CN^- < NCO^- < Cl^- < SCN^-$ .

<sup>¶</sup> In the designations of complexes, the Arabic numeral corresponds to the superscript in the designation of the cyclopalladated ligand  $HL^n$ , while the letters are used to number particular derivatives of a particular phosphapalladacycle (see the designations in the previous review<sup>12</sup>).

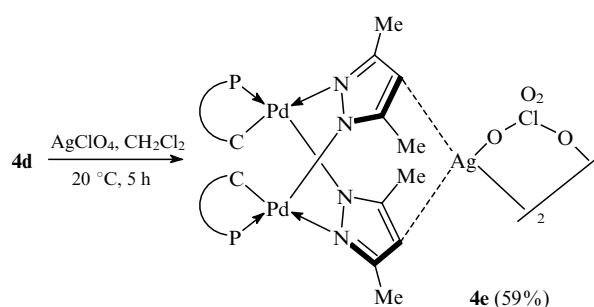


plexes are prepared by treatment of the  $\mu$ -acetate<sup>63,64</sup> or  $\mu$ -chloride<sup>62</sup> dimer with pyrazole. In the former case, the reaction is carried out in the presence of  $\text{Et}_3\text{N}$  in methanol on heating, while in the latter case, in the presence of  $\text{NaOH}$  at room temperature. In both cases, the yields are relatively high (80%–97%). The scheme of transformation of dimer **4a** into pyrazolate analogues **4b–d** is shown below.



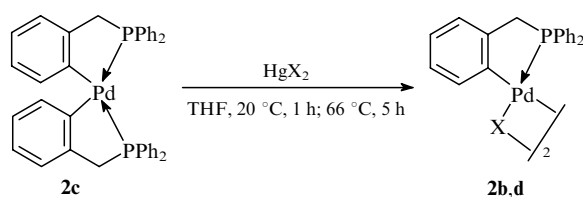
In the  $\mu$ -pyrazolate dimers, the central six-membered ring  $\{\text{Pd}_2\text{N}_4\}$  involves two nitrogen atoms from each bridging ligand. This determines the structural diversity of dimers **4b–d**. Since the tetraazadipalladacycle exists as the boat conformation, the complexes acquire the shape of a ‘half-open book’ (a typical shape of  $\mu$ -carboxylate dimers). The same conformation is typical of simple coordination compounds of palladium with bridging pyrazolate ligands.<sup>65,66</sup>

With this orientation of two flat pyrazolate ligands, a  $\pi$ -electron-enriched gap convenient for incorporation of a cation of another metal is formed between them. The reaction of bridging 3,5-dimethylpyrazolate ligands in dimer **4d** with  $\text{AgClO}_4$  provides an example of secondary complexation.<sup>63,64</sup>



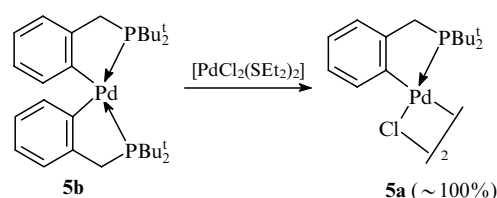
The structure of hexanuclear complex **4e** was confirmed by X-ray diffraction analysis.<sup>63</sup> The structural parameters of this complex were interpreted as being indicative of  $\eta^1$ -binding of the silver ion to the unsubstituted carbon atoms of the two bridging pyrazolate ligands, which are arranged at a  $44.8^\circ$  angle with respect to each other.

The synthesis of dimeric CPCs from *spiro*-complexes is important from the practical standpoint. The easy cleavage of the bridges, which allows one to modify the coordination environment of the metal by introducing auxiliary ligands (see Section II.1.b) is a valuable advantage of dimers with bridging anions compared to *spiro*-PC-structures. The *spiro*-complex can be converted into the dimer in two ways: on treatment with mercury(II) bromide or acetate or on treatment with an appropriate palladium(II) halide.<sup>67</sup>

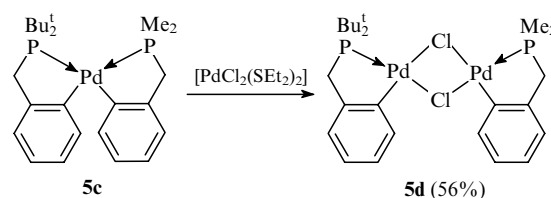


The drawbacks of the former method include the formation of mercury metal in the reaction and the requirement to strictly maintain the 1 : 1 reactant ratio, as an excess of a mercury salt (for example,  $\text{HgBr}_2$ ) promotes full cleavage of the  $\text{Pd} - \text{C}$  bond to give a coordination complex of palladium(II) bromide with *ortho*-mercured phosphine<sup>67</sup> (see Section III.3.a).

The latter method based on the use of a stoichiometric amount of the  $[\text{PdCl}_2(\text{SEt}_2)_2]$  complex is more convenient and usually gives binuclear  $\mu$ -halide compounds in high yields. For example,  $\mu$ -chloride dimer **5a** was synthesised from *spiro*-complex **5b** in a quantitative yield.<sup>67</sup>



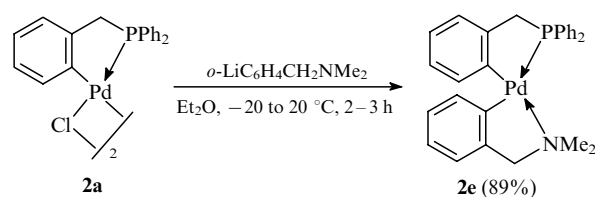
At first glance, it seems attractive to prepare  $\mu$ -chloride dimers by this method using two different phosphapalladacycles. An attempt to implement this idea has been reported.<sup>67</sup>



However, due to the relatively low yield of product **5d** and the known dynamic behaviour of dimeric complexes,<sup>51,68,69</sup> which opens the way for easy migration of palladacycles between mixed-ligand dimer molecules, one can hardly expect reactions of this type to be selective.

Polymeric palladium chloride can also be used for this purpose instead of  $[\text{PdCl}_2(\text{SEt}_2)_2]$ , but this is less efficient and requires more drastic conditions (refluxing in xylene for many hours). In addition, the process can be complicated by the side formation of the palladium(II) complex with *ortho*-chlorinated phosphine.<sup>67</sup> The possibility of using hydrogen chloride in ether for converting the *spiro*-complex into the corresponding  $\mu$ -chloride dimer was shown for the platinum analogues. Under these conditions, the formation of the  $[\{\text{Pt}(\eta^2\text{-L}^5)(\mu\text{-Cl})\}_2]$  dimer from the mononuclear *cis*- $[\text{Pt}(\eta^2\text{-L}^5)_2]$  complex has been detected by spectroscopy.<sup>70</sup>

The transformation of  $\mu$ -halide dimers into *spiro*-complexes is possible only when *ortho*-lithiated derivatives, for example, *o*- $\text{LiC}_6\text{H}_4\text{CH}_2\text{XR}_2$  ( $\text{X} = \text{N}, \text{P}, \text{As}$ ;  $\text{R} = \text{Alk}, \text{Ar}$ ) (see Supplement 1), are used as auxiliary ligands.<sup>71–73</sup> The reactions of this type proceed under mild conditions ( $\text{Et}_2\text{O}$ ,  $-20^\circ\text{C}$ ) usually giving the corresponding *spiro*-complexes in high yields (61%–89%). This method allows the preparation of mixed-ligand (heteroleptic) complexes including those with different heterodonor atoms in two palladacycles (for example, complex **2e**).



Note that other routes for the transformation of  $\mu$ -halide dimers into *spiro*-complexes are also known in the chemistry of the CN analogues. For example, one can use organotin derivatives of

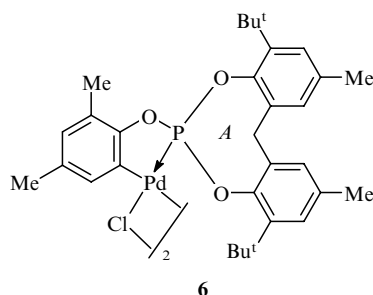
the incoming ligand.<sup>74,75</sup> This type of transformation has been observed during the CPC carbonylation.<sup>76</sup> Using cycloplatinated complexes as examples, it was demonstrated that a non-functionalised ligand (azobenzene) can be involved in this process with assistance by silver ions.<sup>77</sup> However, it remains obscure whether these methods can be adapted to PC-systems.

$\mu$ -Halide dimeric CPCs usually exist as mixtures of geometric isomers (*syn*- and *anti*-isomers). When the molecule contains stereocentres or other chirality elements, the number of isomers increases to at least six (four of these are spectrally discernible) due to the existence of *syn*- and *anti*-isomers as the *meso*-form (*R,S*-D) and the racemate (*S,S*-D and *R,R*-D).<sup>78,79</sup>

The *syn*:*anti* isomer ratio depends on the structure of the phosphapalladacycle<sup>12,17,69</sup> and on the nature of the solvent, but usually the *anti*-isomer is thermodynamically more favourable.<sup>80</sup> The fact that the dimeric cyclopalladated derivatives of trimesitylphosphine (HL<sup>1</sup>) exist only as the *anti*-isomers<sup>55</sup> is attributable to the tendency for avoiding unfavourable through-space interactions between two bulky PMes<sub>2</sub> groups in the *syn*-isomer.

The drawbacks of the dimeric CPCs include also their dynamic behaviour, which often hampers recording the <sup>1</sup>H NMR spectra at room temperature. The  $\mu$ -acetate PC-dimers having a half-open book conformation are the most fluxional.<sup>2,22,51,59,68</sup> The spectroscopic studies of the CN analogues have shown that the dynamic behaviour of these structures stems from the inversion of acetate bridges.<sup>81,82</sup> In the  $\mu$ -halide PC-dimers, the central four-membered ring {Pd<sub>2</sub>Hal<sub>2</sub>} is usually planar (according to X-ray diffraction);<sup>83–85</sup> some folding of the ring is observed only in sterically hindered complexes.<sup>79,86</sup> Nevertheless, in these dimers, too, exchange processes may take place due to the lability of the halide bridges. The fluxional behaviour of the  $\mu$ -chloride CN-analogues was confirmed unambiguously using stereochemical criteria.<sup>87</sup>

The complications arising in the measurement of the NMR spectra of dimeric complexes caused by isomerism can be illustrated in relation to complex **6**. The pronounced signal broadening in its <sup>1</sup>H and <sup>31</sup>P NMR spectra recorded at 25 °C has been suggested<sup>69</sup> to be due to the interconversions of *syn*/*anti*-isomers and the atropoisomers of the eight-membered ring **A**.



This is confirmed by splitting of the <sup>31</sup>P NMR signals into eight peaks on lowering the temperature to –90 °C due to freezing out of the exchange processes. Previously, it has been suggested<sup>58</sup> that *syn* to *anti* transitions of the dimeric complexes are intramolecular. The presence of a signal close in position to that of the free HL<sup>6</sup> ligand in the low-temperature spectrum of dimer **6** may imply decoordination of the P-donor atom of one palladacycle, which opens up the way for the subsequent rotation around the Pd–C bond.<sup>69</sup>

In the case of dimeric complexes **4b–d** with pyrazolate bridges, *anti*-isomers also tend to predominate in solutions.<sup>64</sup> However, the isomeric composition of these complexes depends on the degree of substitution of the bridging azolate heterocycle. Dimer **4d** with disubstituted 3,5-dmpz ligands exists as the *anti*-isomer both at room temperature and in the cold (–60 °C), whereas its analogues with unsubstituted (pz) and monosubstituted (4-mpz) pyrazolate bridges (**4b** and **4c**) exist as mixtures of *syn*- and *anti*-isomers in solutions at low temperature (<sup>31</sup>P NMR data). The redistribution of isomers in favour of the latter (which

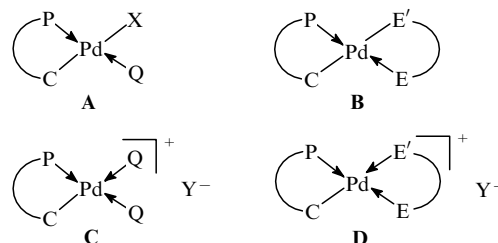
is the only form at 20 °C) attests to the dynamic behaviour of the dimers. Presumably, the interconversion of geometric isomers in these structures takes place through the formation of mononuclear species with monodentate N-bonded pyrazolate.<sup>64</sup>

The combination of the properties of dimeric PC-complexes including poor solubility, isomerism and dynamic mobility makes them inconvenient for practical use and structural studies. The corresponding mononuclear derivatives are free from these drawbacks.

## b. Mononuclear derivatives of PC-palladacycles

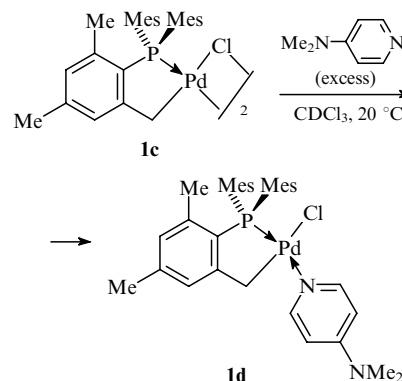
The mononuclear CPCs are used first of all for obtaining spectroscopic evidence for the structures of phosphapalladacycles. In addition, they are used in catalysis; some of them proved to be more efficient catalysts than the corresponding dimers.<sup>14–18</sup>

The structures of mononuclear PC-palladacycles are diverse: they depend on the nature of the auxiliary ligands incorporated in the molecule (the denticity, the charge and the nature of the heterodonor atoms) and on the steric crowding of this ligand and the PC-palladacycle. Depending on the charge of the auxiliary ligand, either neutral (**A**, **B**) or cationic (**C**, **D**) complexes containing monodentate (**A**, **C**) or bidentate (**B**, **D**) auxiliary ligands are formed.



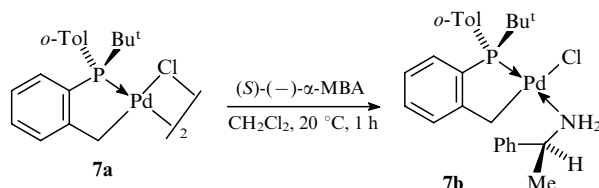
The mononuclear complexes of type **A** are the simplest derivatives of phosphapalladacycles; under certain conditions, they can even be the primary cyclopalladation products.<sup>12</sup> In the general case, these complexes are produced by cleavage of halide bridges in the dimers by monodentate auxiliary ligands. The possibility of such dimer monomerisation is largely determined by the steric requirements of the PC-palladacycle and the incoming ligand, the basicity of this ligand and the preferred geometric configuration of the resulting mononuclear adduct. Type **A** complexes are synthesised most often using phosphines and pyridine or its derivatives as auxiliary ligands. The reactions of PC-dimers with pyridine are usually carried out at room temperature.<sup>54,60,88,89</sup> The complete *in situ* conversion of the dimer into the monomer on treatment with a moderate excess of pyridine-d<sub>5</sub> in CDCl<sub>3</sub> opens up an easy way for obtaining spectroscopic (<sup>1</sup>H NMR) characteristics of phosphapalladacycles.<sup>90</sup>

The influence of the basicity of the auxiliary ligand on the monomerisation of the PC-dimers has been elucidated in a spectroscopic study of the reaction of  $\mu$ -chloride dimer **1c**<sup>55,91</sup> with pyridine derivatives. It was shown that this dimer readily reacts with highly basic 4-dimethylaminopyridine (pK<sub>a</sub> = 9.61) to give mononuclear adduct **1d** but does not react (even on heating)



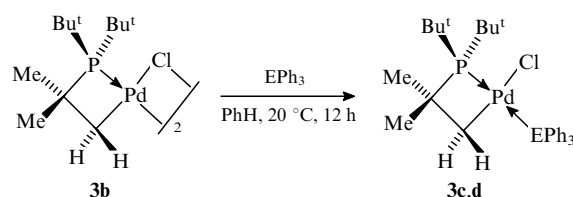
with analogous compounds containing electron-withdrawing 3-CN or 4-CO<sub>2</sub>Me groups ( $pK_a = 1.35$  and  $3.51$ , respectively).<sup>92</sup>

For the same reason, only the primary highly basic  $\alpha$ -methylbenzylamine ( $\alpha$ -MBA) was able to cleave the chloride bridges of dimer **7a** under mild conditions to give mononuclear derivative **7b**.<sup>60</sup>



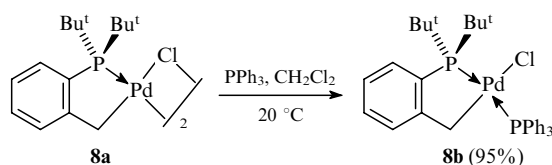
No adducts of PC-palladacycles with less basic monodentate tertiary amines are known. Attempts to introduce an amine of this type into the coordination sphere of a CN-palladacycle have failed.<sup>93</sup>

The nature of the donor atom of the auxiliary ligand is an important factor governing its affinity to palladium. This determines not only the ease but the mere possibility of its coordination to the PC-palladacycle. Thus a study of monomerisation of dimer **3b** under the action of related ligands like  $\text{EPh}_3$  ( $\text{E} = \text{P}, \text{As}, \text{Sb}$ ) has shown that only with triphenylphosphine does the reaction proceed readily under mild conditions to give mononuclear complex **3c**, whereas with  $\text{AsPh}_3$  the reaction does not go to completion (complex **3d** largely dissociates in solutions due to the weaker  $\text{Pd} \leftarrow \text{As}$  bond), and in the case of  $\text{SbPh}_3$ , no reaction takes place for **3b**.<sup>88, 94</sup>



$\text{E} = \text{P}$  (**3c**),  $\text{As}$  (**3d**).

The transformation of dimeric CPCs into monomers for structural studies is often accomplished using phosphines, the most popular of which is triphenylphosphine, a ligand with moderate steric requirements (the Tolman cone angle  $\theta = 145^\circ$ ).<sup>†</sup> The reactions of the PC-dimers (for example, dimer **8a**) with  $\text{PPh}_3$  are usually carried out at room temperature in benzene<sup>78, 79, 88, 90</sup> or dichloromethane,<sup>58, 69, 96</sup> or more rarely, acetone.<sup>56</sup> In some cases, due to the low solubility of the starting dimers or steric hindrance,<sup>94</sup> heating is required.<sup>60, 94, 97–99</sup>



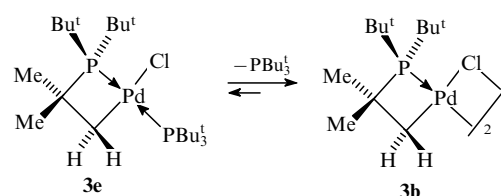
A similar procedure is used to prepare adducts with other phosphines with relatively small molecules, for instance,  $\text{PPh}_2\text{Me}$ <sup>88</sup> and  $\text{PMe}_2\text{Ph}$ ,<sup>96</sup> ( $\theta = 127$  and  $136^\circ$ , respectively), with phosphites  $\text{P}(\text{OMe})_3$ ,<sup>58, 69, 74</sup>  $\text{P}(\text{OEt})_3$ ,<sup>69</sup> and  $\text{P}(\text{OPh})_3$ ,<sup>58, 69, 74, 94</sup> ( $\theta = 107$ ,  $109$  and  $128^\circ$ , respectively)<sup>95, 100</sup> and with 5-phenyldibenzophosphole (DBP)<sup>94</sup> (see Supplement 1).

In the reactions of dimeric CPCs with P-donor substrates, the steric factors become crucial, while the basicity of the auxiliary ligand is less significant. As a consequence, even in the reaction with phosphines containing a donor phosphorus atom optimal for

the coordination to palladium, the formation of mononuclear adducts can be prevented by steric restrictions. For example, a spectroscopic study ( $^1\text{H}$  and  $^{31}\text{P}$  NMR) of the complexation of dimer **3b** with monodentate phosphines has shown that the strength of their binding with the PC-palladacycle decreases in the sequence given below:<sup>88</sup>

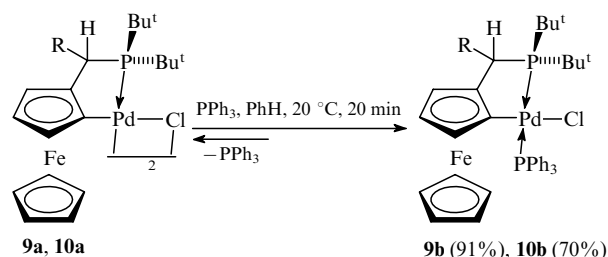
|               |                |                              |                     |                    |                  |                                |                    |
|---------------|----------------|------------------------------|---------------------|--------------------|------------------|--------------------------------|--------------------|
| $\text{ER}_3$ | $\text{PEt}_3$ | $\sim \text{PPh}_2\text{Me}$ | $\sim \text{PPh}_3$ | $> \text{PPR}_3^i$ | $> \text{PCy}_3$ | $\sim \text{PBu}_2^i\text{Me}$ | $> \text{PBu}_3^i$ |
| $\theta$      | 132            | 127                          | 145                 | 160                | 170              | 161                            | 182                |
| $pK_a$        | 8.69           | 4.57                         | 2.73                | —                  | 9.70             | —                              | 11.40              |

A comparison of the Tolman cone angles  $\theta$  and the  $pK_a$  constants<sup>101</sup> demonstrates that this sequence is correlated with the increase in the ligand bulk but by no means with the basicity. The adducts with  $\text{PEt}_3$ ,  $\text{PPh}_2\text{Me}$ ,  $\text{PPh}_3$  and  $\text{PPR}_3^i$  ( $\theta = 127–160^\circ$ ) are stable in the solid state and in solutions; complexes with more bulky phosphines,  $\text{PCy}_3$  and  $\text{PBu}_2^i\text{Me}$  ( $\theta = 170$  and  $161^\circ$ , respectively), were prepared but they partly dissociate in solutions to give the starting dimer. In the case of sterically overcrowded adduct **3e** with the  $\text{PBu}_3^i$  phosphine ligand ( $\theta = 182^\circ$ ), the monomer  $\rightleftharpoons$  dimer equilibrium is shifted to the right almost completely, as indicated by the lack of spin–spin coupling between the two  $^{31}\text{P}$  nuclei.<sup>88, 102</sup>



Moreover, an attempted recrystallisation of the isolated complex **3e** gave the starting dimer **3b**.<sup>88, 102, 103</sup> When bulky phosphines such as  $\text{PBu}_2^i\text{Tol-}o$  ( $\theta = 186^\circ$ ) and  $\text{PBu}^i(\text{Tol-}o)_2$  ( $\theta = 190^\circ$ ) are made to react with PC-palladacycles, for example, with dimer **5a**, mononuclear derivatives are not formed for steric reasons.<sup>57</sup>

It is reasonable to assume that the steric crowding of the PC-palladacycle should also influence the efficiency of the reaction with phosphines. For example, the transformation of dimeric CPCs **9a** and **10a** with an unwieldy ferrocenyl core into the mononuclear derivatives **9b**, **10b**, containing even a small auxiliary ligand,  $\text{PPh}_3$  ( $\theta = 145^\circ$ ), does not proceed to completion when a strictly stoichiometric amount of the phosphine is used.<sup>78, 79</sup> According to the  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectra, the reaction mixture contains mononuclear adducts **9b**, **10b** together with the starting dimers **9a**, **10a** and the unreacted phosphine  $\text{PPh}_3$ .

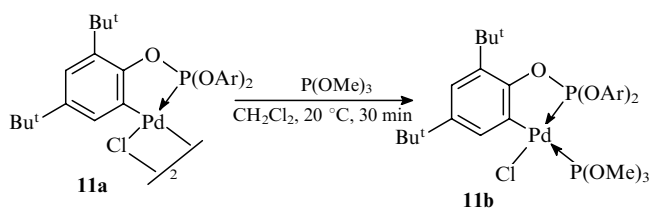


$\text{R} = \text{H}$  (**9a,b**),  $\text{Me}$  (**10a,b**).

The equilibrium between the dimeric and monomeric complexes can be shifted towards the latter by using a slight (10%–15%) excess of the auxiliary ligand.<sup>78, 79</sup> This method is also used in synthetic work<sup>60, 97, 98</sup> (see Supplement 1).

The steric obstacles are especially obvious in the monomerisation of cyclopalladated bulky phosphites. An attempt to monomerise the sterically overcrowded dimer **11a** by treating it with bulky tris(*o*-tolyl)phosphine ( $\theta = 194^\circ$ ) has not met with success, whereas the small-size phosphite  $\text{P}(\text{OMe})_3$  ( $\theta = 107^\circ$ ) readily reacts with dimer **11a** at room temperature to give adduct **11b**.<sup>69</sup>

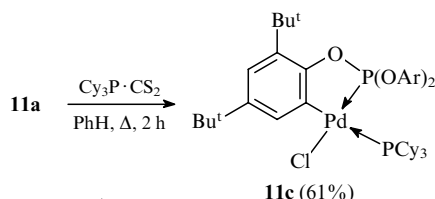
<sup>†</sup> Here and below, the Tolman cone angles  $\theta$  were taken from Ref. 95



Ar = C<sub>6</sub>H<sub>3</sub>Bu<sup>t</sup><sub>2</sub>-2,4.

Extra complications arise in the monomerisation of dimeric CPCs based on phosphites due to the forced (electronic requirements, see Section II.2.b) *cis*(P,P)-configuration of the resulting adduct. In this case, a bulky auxiliary ligand should be inserted into the Pd coordination sphere near the bulky P(OC<sub>6</sub>H<sub>3</sub>Bu<sup>t</sup><sub>2</sub>-2,4)<sub>2</sub> fragment of the phosphite palladacycle. Note for comparison that dimeric CPCs based on phosphines (for example, dimer **3b**) react with bulky phosphines such as PBu<sub>2</sub>Me, PCy<sub>3</sub> and P(Tol-*o*)<sub>3</sub> under mild conditions (20 °C) to give the *trans*(P,P)-complex.<sup>88</sup> In this case, the auxiliary ligand is inserted into the Pd coordination sphere near the methylene group (the least steric requirements) of the phosphine palladacycle.

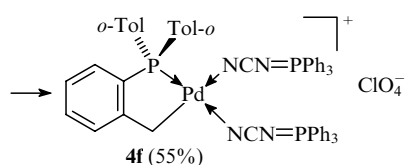
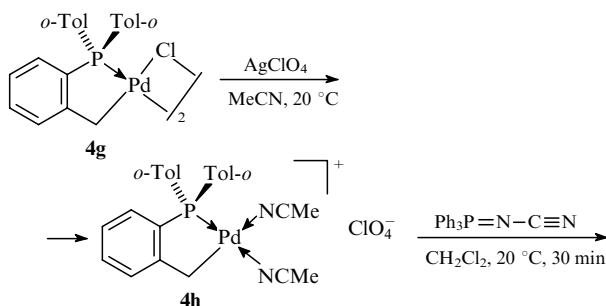
It is pertinent to mention a modified method for the synthesis of mononuclear phosphine derivatives of PC-palladacycles consisting of the use of the phosphine adduct with carbon disulfide instead of the free phosphine. Since the electron-enriched aliphatic phosphines (unlike aromatic phosphines) form rather stable adducts of the Alk<sub>3</sub>P·CS<sub>2</sub> type,<sup>104</sup> these adducts are destroyed only on heating. Only using this technique, was dimer **11a** completely converted into mononuclear adduct **11c** (this reaction with free phosphine does not proceed to completion).<sup>69</sup>



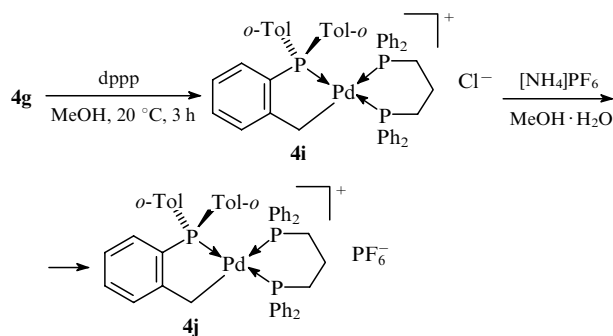
Ar = C<sub>6</sub>H<sub>3</sub>Bu<sup>t</sup><sub>2</sub>-2,4.

Although the true role of carbon disulfide in this reaction is not discussed in the study cited,<sup>69</sup> one cannot rule out the intermediate formation of species with the ylide phosphonium-dithiocarboxylate ligand R<sub>3</sub>P<sup>+</sup>—CSS<sup>−</sup> (see Ref. 104).

The cationic complexes of type **C** belong to the least studied class of phosphapalladacycle derivatives. The introduction of two monodentate neutral ligands into the reaction with the PC-palladacycle requires the preliminary removal of chloride ions from the dimeric precursor on treatment with silver salts. The reaction is carried out in a solvent capable of coordination, for example, in acetonitrile. A cationic bis(acetonitrile) adduct is formed intermediately and can be used for the subsequent introduction of other auxiliary ligands, including those with low coordinating capacity. The synthesis of bis(iminophosphorane) derivative **4f** from cyclopalladated tris(*o*-tolyl)phosphine **4g** through acetonitrile intermediate **4h** can serve as an example of using this approach.<sup>105</sup>



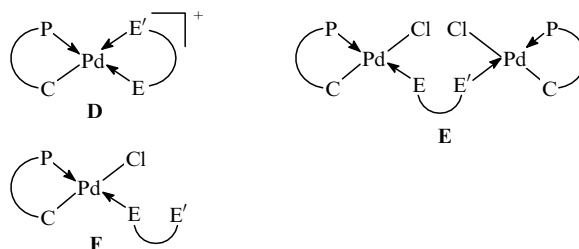
Cationic complexes of type **D** are formed upon coordination of non-charged bidentate ligands to a phosphapalladacycle. Under the optimal conditions, these derivatives can be obtained directly from μ-chloride dimeric CPCs. In most cases, the reaction is carried out at room temperature. The direct reaction of the μ-chloride dimer with a neutral chelating reagent gives rise to ionic complex **D** with the outer-sphere chloride.<sup>58, 60, 69</sup> The introduction of the [NH<sub>4</sub>]PF<sub>6</sub>, KPF<sub>6</sub> or NaClO<sub>4</sub> salts either directly or in the second stage of the reaction (after chelation of the auxiliary ligand) allows these adducts to be isolated as hexafluoro-phosphates<sup>90</sup> or perchlorates<sup>56</sup> (see Supplement 1). This technique was used to prepare ionic complexes **4i** or then **4j** from dimer **4g**.<sup>30</sup>



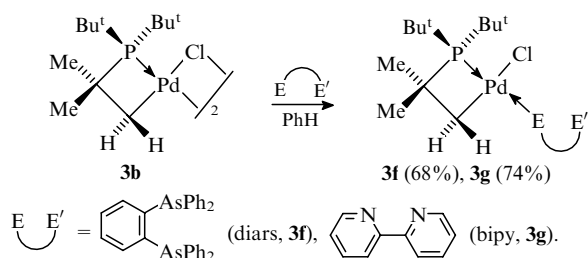
dppp is Ph<sub>2</sub>P(CH<sub>2</sub>)<sub>3</sub>PPh<sub>2</sub>.

The obvious gain in entropy caused by binding of bidentate ligands compared to monodentate ligands is partially counterbalanced by the necessity of replacement of two halide ligands in the initial dimer (instead of mere cleavage of halide bridges). As a consequence, the rules for complexation of phosphapalladacycles with mono- and bidentate ligands become similar in many respects.

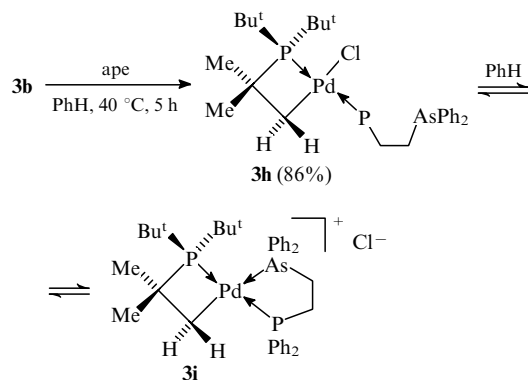
Detailed studies of the complexation of μ-chloride dimer **3b** with a number of potentially bidentate ligands<sup>106</sup> have shown that the ligand structure has a pronounced effect on the course of the reaction. Under unfavourable conditions, type **E** and **F** complexes with bridging or monodentate ligands, respectively, are formed instead of the expected κ<sup>2</sup>-chelation (complex **D**).



As was to be expected, the chelating properties of the ligand depend, first of all, on the nature of the donor atoms (P > As > N); this is most important for their reactions with μ-halide dimers. As opposed to the easy chelation attained with diphosphines, dppe [bis(diphenylphosphino)ethane]<sup>58, 69</sup> and dppp,<sup>30</sup> the As,As- (diars) and N,N-donor (bipy) ligands behave as monodentate in the reaction with dimer **3b**. Even with a twofold excess of the ligand (for diars) or on raising the temperature (for bipy), only neutral adducts **3f**, **3g** are formed.<sup>106</sup>

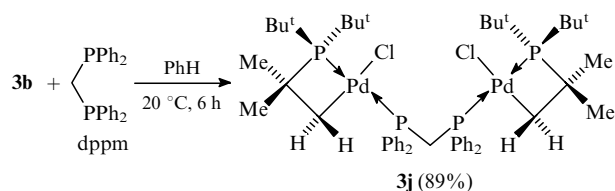


A similar reaction of complex **3b** with a P,As-donor ligand (ape) also gave mononuclear derivative **3h** of type **F**; however, according to  $^{31}\text{P}$  NMR spectroscopy, it is equilibrated in solutions with cationic complex **3i** of type **D**:



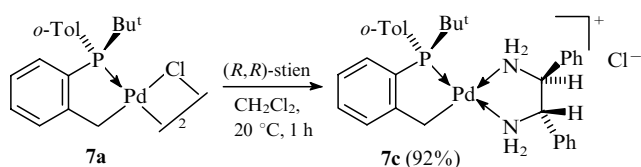
ape is  $\text{Ph}_2\text{P}(\text{CH}_2)_2\text{AsPh}_2$ .

The coordination mode of the potentially bidentate ligands also depends on the length of the fragment that separates the donor atoms and determines the size of the chelate ring. Methylene-diphosphines are known<sup>107–109</sup> to possess low susceptibility for chelation (in particular, in the reactions with palladacycles<sup>110–113</sup>) due to the strain in the four-membered  $\{\text{MP}_2\text{C}\}$  ring thus formed. Therefore, it is not surprising that bis(diphenylphosphino)methane (dppm) reacts with  $\mu$ -chloride dimer **3b** as a bridging ligand to give non-charged dimer **3j** of type **E**, despite the presence of two optimal donor atoms of phosphorus:<sup>106</sup>



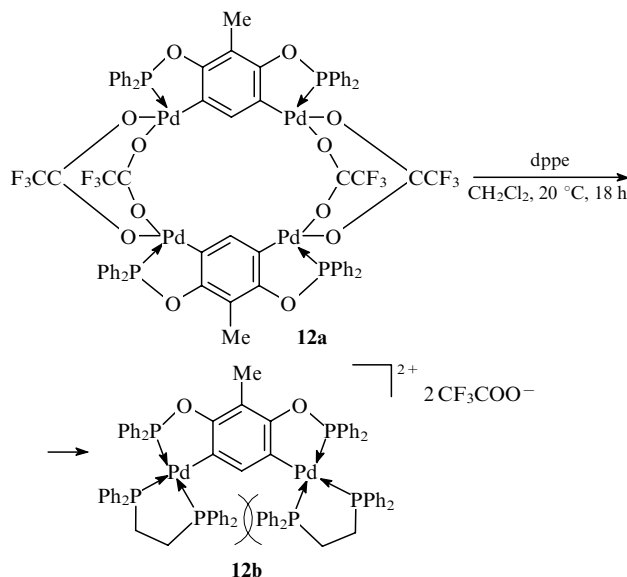
Probably, the chelation of dppm with PC-palladacycles could be accomplished by dehalogenating the starting  $\mu$ -Cl-dimers, because the efficiency of this approach for CN-analogues is well known.<sup>110, 111, 113, 114</sup>

The chelation properties of N,N-donor ligands are enhanced with an increase in their basicity and a decrease in the steric requirements. Thus  $(R,R)$ -1,2-diamino-1,2-diphenylethane (stien), containing two primary amino groups, directly reacts with  $\mu$ -chloride dimer **7a** under mild conditions to give cationic complex **7c** in a high yield, despite the steric crowding of the phosphine ligand.<sup>60</sup>



This reaction can be carried out *in situ*, which is especially important for solving some stereochemical problems.<sup>90</sup>

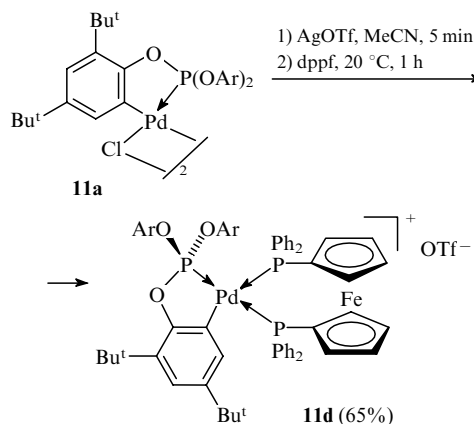
The success of chelation using potentially bidentate ligands with dimeric PC-palladacycles is also determined by the ability of bridging anions to compete for the metal. The situation is simplified upon the replacement of bridging halide ligands by harder anions. For example, binuclear derivative **12b** is formed as the major product when tetranuclear complex **12a**, containing trifluoroacetate bridges, reacts with diphosphine dppe.<sup>115</sup>



The researchers noted the formation of a minor amount of a compound with bridging diphosphine ligands, probably having a tetranuclear structure similar to the structure established by X-ray diffraction for the starting complex **12a**.<sup>‡</sup>

This side process might be due to steric restrictions between the neighbouring  $\text{PPh}_2$  groups of two diphosphines dppe chelated to the metal atoms of the doubly cyclopalladated bis(phosphinite)  $\text{H}_2\text{L}$ <sup>12</sup>.

An efficient solution to the problem of anion competition in the formation of type **D** complexes is the removal of chloride ions from the metal coordination sphere in the starting dimer on treatment with an appropriate silver salt, for example, triflate<sup>69</sup> or hexafluorophosphate.<sup>106</sup> The reaction with  $\text{AgOTf}$  is usually carried out in acetonitrile in two steps with intermediate generation of the reactive bis(acetonitrile) adduct of the PC-palladacycle, which is then made to react with an auxiliary ligand. Using this method, successful chelation of 1,1'-bis(diphenylphosphino)-ferrocene (dppf) with the phosphite palladacycle of dimer **11a** was accomplished.<sup>69</sup>

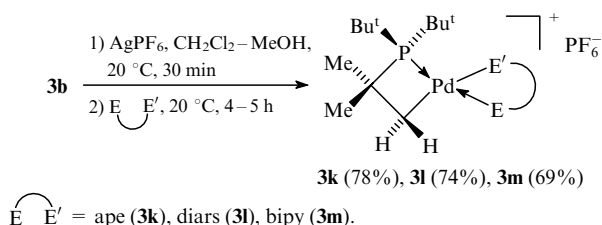


Ar =  $\text{C}_6\text{H}_3\text{Bu}^t\text{-2,4}$ .

‡ The synthesis of the complex **12a** is the first example of double cyclopalladation of P-donor substrates at the same benzene ring.

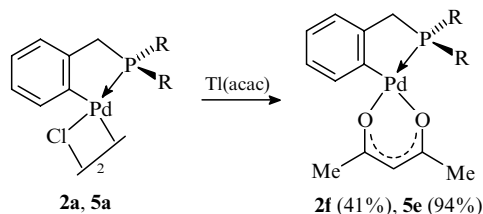
It should be noted that an attempt to prepare complex **11d** by direct reaction of  $\mu$ -chloride dimer **11a** with diphosphine dpfp ( $\text{CH}_2\text{Cl}_2$ , 20 °C, 30 min) has not met with success, a complex mixture of products being formed under these conditions.<sup>69</sup>

The dehalogenation of  $\mu$ -chloride dimers under the action of  $\text{AgPF}_6$  is carried out in a mixture of dichloromethane with methanol;  $\text{AgCl}$  is removed before the addition of the auxiliary ligand to the solution of the intermediate solvated PC-palladacycle. The cationic complexes **3k**, **3l** and **3m** with the ape, diars and bipy ligands having low coordinating abilities have been obtained by this method in quite acceptable yields.<sup>106</sup>



The neutral complexes of type **B** are formed upon chelation of PC-palladacycles by anionic ligands. Although the ionic type of these ligands (which are used as Na, K or Tl salts) essentially eliminates the possibility of competition of the bridging halides of the starting CPC dimer for the metal, some synthetic problems still remain. As auxiliary ligands in the synthesis of type **B** complexes,  $\beta$ -diketonates,<sup>54, 57, 60, 97</sup> dithiocarboxylates,<sup>53, 69</sup> pyrazolylborates,<sup>116</sup> prolinates<sup>79, 117</sup> and 2-acylphenolates<sup>118</sup> have been used (see Supplement 1).

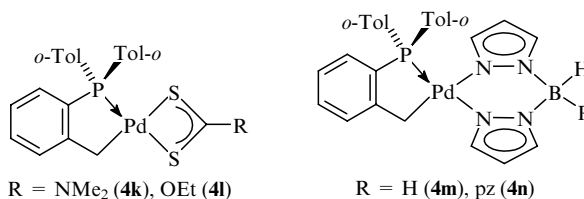
For the spectral investigations of PC-palladacycles, complexes with the symmetric acetylacetonate (acac) ligand are most convenient. The acetylacetonate complexes possess a number of advantages: first, the  $^1\text{H}$  NMR spectrum of the acetylacetonate ligand is 'transparent' (the ligand gives rise to only three additional singlets); second, the volatility of the neutral complexes allows the use of mass spectrometry in the studies of PC-palladacycles.<sup>54, 119</sup> For the synthesis of acetylacetonate complexes from  $\mu$ -chloride dimers, fairly toxic thallium salt  $\text{Tl}(\text{acac})$  is normally used; with rare exceptions,<sup>57</sup> the yields are relatively low (40%–70%)



$\text{R} = \text{Ph (2a,f), Bu}^t \text{ (5a,e)}.$

The replacement of  $\text{Tl}(\text{acac})$  by  $\text{K}(\text{acac})$  was of low utility. Acetylacetonate derivative **10c** has been prepared from dimer **10a** in only a 28% yield,<sup>90</sup> although the yields of the corresponding complexes in the reactions of  $\text{K}(\text{acac})$  with CN-palladacycles reach 97%.<sup>120</sup> It is worth noting that transition from dimeric PC-complexes to the mononuclear type **B**  $\beta$ -diketonate derivatives and the subsequent modification of auxiliary ligands (for example, the replacement of the methyl groups in the acetylacetonate ligand by trifluoromethyl groups) may markedly enhance the catalytic activity of phosphapalladacycles.<sup>22</sup>

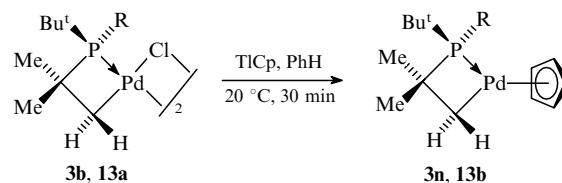
The dithiocarboxylate and bis(pyrazolyl)borate ligands are also symmetric. The dithiocarbamate (**4k**) and xanthate (**4l**) derivatives of the PC-palladacycles have found application in the synthesis of bi- and polynuclear heterometallic compounds.



Thus the reactions of dithiocarboxylate complexes with Lewis acids such as  $\text{HgX}_2$ ,<sup>53, 121, 122</sup>  $\text{AgClO}_4$  and  $[\text{M}(\text{OClO}_3)(\text{PPh}_3)]$  ( $\text{M} = \text{Ag, Au}$ ),<sup>123</sup> have resulted in bimetallic Pd,M complexes in which the metal atoms are connected by bridging sulfur atoms.

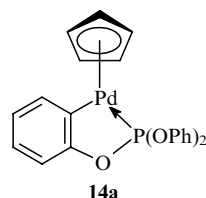
The modification of dimer **4a** with poly(pyrazol-1-yl)boronates to give complexes **4m,n** has been designed to facilitate the oxidative addition of electrophiles ( $\text{MeI}$ ,  $\text{ArBr}$ , etc.) to the metal and to stabilise the Pd(IV) centre in the resulting cyclopalladated complex through increasing the nucleophilicity of the Pd(II) centre.<sup>116</sup> Unfortunately, these attempts have failed.

Cyclopentadienyl derivatives of phosphapalladacycles occupy a special position among mononuclear complexes of type **B**, because the auxiliary ligand is  $\eta^5$ -coordinated instead of being  $\kappa^2$ -bound through two heteroatoms. These complexes are synthesised by treatment of the corresponding  $\mu$ -chloride dimers (for example, **3b** or **13a**) with  $\text{TiCp}$  or  $\text{LiCp}^*$  ( $\text{Cp}^*$  is pentamethylcyclopentadienyl) in benzene<sup>124</sup> or THF<sup>58, 59</sup> at room temperature. Complexes with the  $\text{Cp}^-$  ligand have been obtained in quite satisfactory yields (67% for  $\text{R} = \text{Ph}$  and 77% for  $\text{R} = \text{Bu}^t$ ), whereas the yields of complexes with the bulky  $\text{Cp}^*$ - ligand are much lower (39% for  $\text{R} = \text{Ph}$  and 60% for  $\text{R} = \text{Bu}^t$ ).<sup>124</sup>



$\text{R} = \text{Bu}^t \text{ (3b,n), Ph (13a,b)}.$

The number of complexes in which the PC-palladacycle is bound to the  $\eta^5$ - $\text{Cp}$ <sup>58, 59, 124</sup> or  $\eta^5$ - $\text{Cp}^*$  ligand<sup>124</sup> is limited to derivatives of two cyclopalladated phosphines ( $\text{P}(\text{Bu}^t)_3$  and  $\text{P}(\text{PhBu}^t)_2$ )<sup>124</sup> and two phosphites,  $[\text{P}(\text{OPh})_3]$ <sup>58</sup> and  $[\text{P}(\text{OTol-}o)_3]$ <sup>59</sup> (see Supplement 1). The  $\eta^5$ -coordination of the auxiliary ligand in complex **14a** was confirmed by X-ray diffraction; however, the ligand is bound to the metal non-symmetrically, the  $\text{Pd}-\text{C}(\text{Cp})$  bond lengths varying in the range of 2.284(7)–2.347(9) Å.<sup>58</sup>

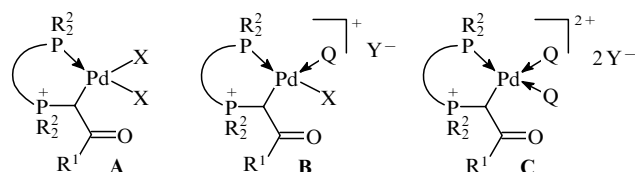


To conclude this Section, let us consider the possibility of back monomer  $\rightarrow$  dimer transformation. The success of this transformation is determined, first of all, by the nature of the donor atoms of the auxiliary ligand and its denticity. The removal of the mono- or bidentate ligands with relatively rigid N- and O-donor atoms from the coordination sphere of the palladacycle is attained by mere protonation of the auxiliary ligand (for example, with dilute  $\text{HCl}$ ).<sup>79, 90, 117, 125</sup> The situation becomes much more complicated on passing to adducts with phosphine ligands due to stronger binding of the soft P-donor atom with the soft Pd(II) centre. Nevertheless, the monodentate phosphines can be

removed using a method elaborated for CN systems,<sup>126</sup> namely, by treatment of the adduct with an excess of a cheap bidentate ligand, ethylenediamine (en), in a biphasic system (for example, in the dichloromethane–water system).<sup>90, 127, 128</sup>

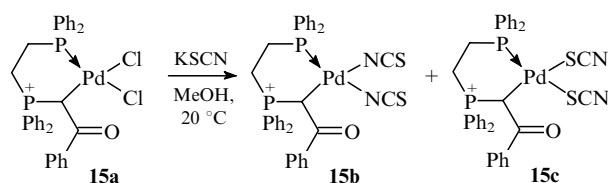
### c. Phosphino-P-ylide complexes

Due to the formal neutrality of zwitter-ionic phosphino-P-ylide ligands, the forms of existence of the metallacycles they form (A–C) differ from those for classical PC-systems. Chelation with these ligands yields mononuclear compounds of type **A** with five-<sup>129–133</sup> or six-membered<sup>129–137</sup> PC-palladacycles or bis(chelate) *spiro*-complexes.<sup>138</sup> Binuclear compounds with phosphino-P-ylide ligands have not been reported as yet. The ways for modification of the metal coordination environment in these systems are reduced to variation of the nature of the anions in type **A** complexes and the introduction of one or two neutral monodentate ligands, resulting in mono- (**B**) or dication (**C**) derivatives, respectively. In both cases, halide replacement takes place.

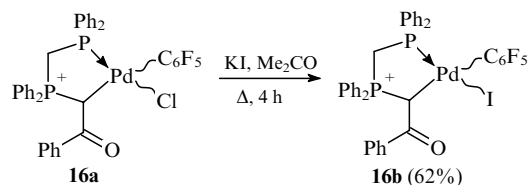


This constitutes the key difference between the reactions of phosphino-P-ylide PC-complexes and those typical of classical dimeric PC-systems in which labile halide bridges are cleaved.

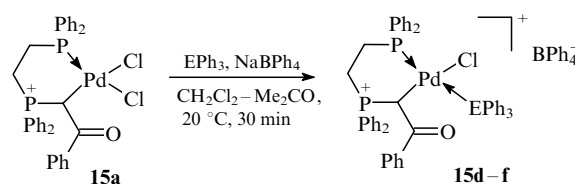
Perhaps, for this reason, the replacement of two chloride ions in type **A** complexes by softer halides ( $\text{Br}^-$ ,  $\text{I}^-$ ) or by a pseudohalide ( $\text{SCN}^-$ ) on treatment with simple salts, NaBr, NaI or KSCN, under mild conditions ( $\text{MeOH}-\text{CH}_2\text{Cl}_2$ , 20 °C) gives the target products in moderate yields (24%–59%).<sup>130, 131</sup> This can be illustrated by the transformation of dichloride **15a** into isothiocyanate derivative **15b** in 26% yield. It is worth noting that two isomers, **15b** and **15c** (1 : 2) containing N- and S-bound anions, respectively, exist in solutions (IR data).<sup>130</sup>



The metathesis of anions in monoarylated complexes  $[\text{ArPd}(\eta^2\text{-L})\text{Cl}]$  requires long-term heating of the chloride precursor with KBr, KI or KSCN in acetone, but the yields of modified complexes (for example, **16b**) increase in this case to 62%–73%.<sup>133</sup>

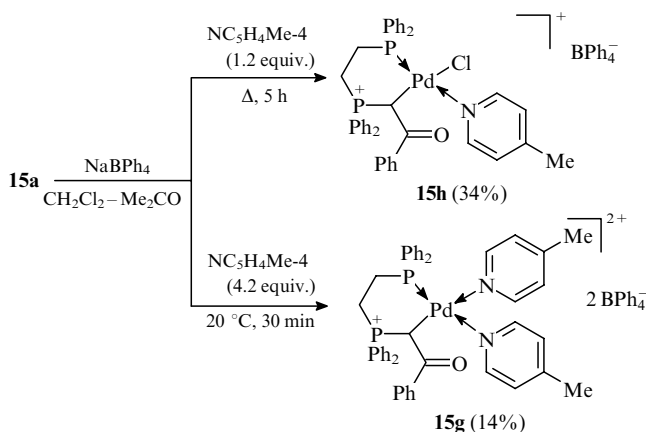


A monodentate neutral auxiliary ligand can be attached to a phosphino-P-ylide palladacycle only after dehalogenation of the dichloride precursor, for example, on treatment with sodium tetraphenylborate.<sup>131, 132, 136</sup> Reactions of this type are usually carried out under mild conditions, irrespective of the coordinating ability of the incoming ligand, which can be represented by phosphines, phosphites, arsines, or stibines or N-donor ligands (see Supplement 2).



E = P (**15d**, 39%), As (**15e**, 41%), Sb (**15f**, 37%).

Using this method, it is even possible to introduce two auxiliary neutral ligands into the coordination to a phosphino-P-ylide palladacycle, which is indicative of the efficiency of this approach. The substitution of N-donor ligands for the two halides in the dichloride precursor **15a** (bis-adducts **15g**) can be attained by using a four-fold excess of 4-methylpyridine; the reaction with an equimolar amount of the auxiliary ligand yields monoadduct **15h**.<sup>132</sup>



Although dicationic complex **15g** has been isolated in a low yield, this reaction is of interest, because structures of this type are rather seldom encountered among both classical PC-palladacycle derivatives<sup>105</sup> and their CN-analogues.<sup>5, 47, 111</sup>

The cationic phosphino-P-ylide complexes, formed in the reactions with neutral monodentate ligands (see Supplement 2), are less stable<sup>132, 136</sup> than neutral dichloride precursors such as  $[\text{Pd}(\eta^2\text{-L})\text{Cl}_2]$ , which are resistant against oxidants and heating.

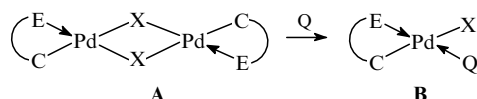
Apparently, attempts at direct substitution of monodentate ligands for the chloride in type **A** precursor are impracticable due to the lower stability of phosphino-P-ylide palladacycles compared to the classical PC-analogues. For example, partial decomposition of dichloride complexes of type **A** with evolution of free ligands  $\text{L}''$  has been detected by IR spectroscopy on refluxing in pyridine.<sup>130</sup> Analysis of the dependence of the degree of destruction on the structure of the complexes showed that the stability of phosphapalladacycles of this type depends on their size (five-membered rings are more stable than six-membered rings) and on the electronic effects of substituents at the carbonyl group ( $\text{Ph} > \text{Me} > \text{MeO}$ ).<sup>130</sup>

## 2. Regioselectivity of ligand coordination to phosphapalladacycles

The problem of determining the geometric configuration of complexes formed upon the coordination of additional ligands to palladacycles arises necessarily in relation to structural studies or practical use. For example, when palladacycles are used as catalysts, it is pertinent to have an idea of the regiochemistry of particular stages of the catalytic cycle. The regiochemistry of the coordination of additional ligands to palladacycles is one more feature which distinguishes PC-palladacycles from their CN-analogues.

### a. General views on the regiochemistry of coordination to palladacycles

Palladium complexes are usually classified as labile. It is known that their reactions in solutions are many orders of magnitude faster than the reactions of platinum analogues.<sup>139</sup> Therefore, it is natural to assume that the regiochemistry of the reactions of palladacycles with auxiliary ligands is determined by thermodynamics rather than the kinetics of these processes. This accounts for the fact, surprising at first glance, that the monodentate auxiliary ligand is inserted predominantly (in some cases, exclusively) into the *trans*-position to the heterodonor atom of the palladacycle in the dimeric CPC rather than to the carbon atom, which has a higher capacity for labilisation of the *trans*-located Pd–Hal bond.



A distinctive feature of CN-systems is the high regioselectivity of monomerisation of the dimeric complexes by auxiliary ligands. In the vast majority of cases, the monodentate N- and P-donor ligands are inserted into the coordination sphere of the CN-palladacycle in the *trans*-position to nitrogen.<sup>140–144</sup> Exceptions to this rule are few<sup>145–147</sup> and refer only to pyridine adducts, whereas the formation of monophosphine derivatives with the *trans*(P,C)-geometry is either impossible,<sup>111</sup> or these complexes are highly unstable and highly reactive.<sup>148</sup> The introduction of phosphine into the *trans*-position to the carbon atom becomes possible only after removal of the halide and blocking of the *cis*-position. For example, bis(phosphine) derivatives [Pd(C<sup>⋈</sup>N)(PAr<sub>3</sub>)<sub>2</sub>]<sup>+</sup> have been prepared in this way.<sup>149</sup>

This high selectivity is usually attributable to the anti-symbiosis phenomenon according to which the *trans*-coordination of two soft ligands to a transition metal destabilises the system.<sup>150,151</sup> Recently, more expressive terms, ‘transphobia’<sup>111,113,152,153</sup> and ‘*trans* choice’,<sup>154</sup> have been proposed for interpreting the regioselectivity of reactions of CPC with Lewis bases within the framework of the same antisymbiosis concept. All three concepts can be substantiated in terms of the Maximum Hardness Principle (MHP) proposed by Pearson.<sup>155,156</sup> According to this principle, structures (or systems) with the maximum energy difference between the occupied and vacant orbitals possess the highest thermodynamic stability. A softer molecule has a more diffuse electron shell and is more reactive.

The ‘*trans* choice’ principle is underlain by the concept of stabilisation of square planar complexes with *trans*-arrangement of the ‘softest’ and the ‘hardest’ ligands in the coordination sphere.<sup>154</sup> To predict the regiochemistry of the reactions of palladacycles using this concept, one needs quantitative characteristics of the ‘softness’ or ‘hardness’ of the donor atoms in the palladacycle and the additional ligands present in the coordination sphere. Since such information is unavailable without calculations, the use of this concept is limited to qualitative analysis.

The ‘transphobia’ concept<sup>113,152</sup> appears more attractive, as it opens the way for some quantitative considerations. In this case, analysis of the differences in the stability of different geometric configurations is based on comparison of the *trans*-effects of two pairs of ligands on the diagonals of the square planar complex. The essence of this concept is the assumption that the degree of destabilisation of complexes increases with an increase in the *trans*-effect of both partners. If only donor atoms (X, Y, C) of the ligands bound to the metal are taken into account, then, in the most general form, the transphobia (which has been proposed to be designated by the letter T<sup>152</sup>) sequence for pairs of donors located on one diagonal is as follows:<sup>111,113,152</sup>

$$X/Y \text{ (X, Y = Hal, N, P)} \approx C/X \text{ (X = Hal, N)} < C/P < C/C.$$

Among the rules found for the coordination properties of CN-palladacycles, the following deserves attention: (1) greater *trans*-

effect of  $\sigma$ -bonded aryl groups compared to phosphines entails an increase in the transphobia in ligand pairs in the sequence  $PR_3/PR_3 < Ar/PR_3 < Ar/Ar$ ;<sup>111</sup> (2) the antisymbiotic effect for triarylphosphines is higher<sup>§</sup> than for trialkylphosphines ( $PAlk_3 < PAr_3$ );<sup>111,113</sup> (3) the transphobia for any ligand pair increases on passing from platinum to palladium.<sup>111,113,152</sup> The transphobia concept predicts high reactivity for the complexes in which ligands with high *trans*-effects are located on the same diagonal.<sup>113,148,149,152</sup>

The applicability of the transphobia concept to CN-systems has been confirmed by vast experimental data.<sup>111,113,148,149,152,153,161,162</sup> However, in the general case, this concept does not fully explain the significant difference between the PC-palladacycles and CN-systems, namely, the lower (in some cases, inverted) regioselectivity of binding of monodentate and non-symmetrical bidentate ligands. Apart from the expected dependence on the behaviour of the incoming ligand, the regioselectivity of the phosphapalladacycle coordination with additional ligands depends, to a considerable extent, on the features of the PC-palladacycle. The nature of the P-donor atom (phosphine, phosphinite or phosphite) is most important, first of all, due to different relationships between the  $\sigma$ -donor and  $\pi$ -acceptor properties. The hybridisation of the C-donor atom ( $sp^2$  or  $sp^3$ ) and steric effects may also be significant. Depending on the combination of these factors, mononuclear derivatives of PC-palladacycles can form as *cis*- or *trans*-isomers or an isomer mixture.

### b. The *trans*-effect in palladacycles

The ligand *trans*-effect discovered by Chernyaev in the beginning of the 20th century has been studied in detail both experimentally and theoretically.<sup>158,163–166</sup> The terminology used in this field has been markedly changed through the years. Originally, the terms ‘*trans*-influence’ and ‘*trans*-effect’ have been used in the literature to refer to the static (ground state) and dynamic (kinetic, transition state) aspects of the phenomenon. In our opinion, these terms do not reflect the key difference between these two variables. The terms ‘structural *trans*-effect’ (STE) and ‘kinetic *trans*-effect’ (KTE) used more recently are much more informative.<sup>166</sup>

Due to the known lability of palladium compounds,<sup>139</sup> consideration of the regiochemistry of reactions of palladacycles may be limited to the use of static (thermodynamic) parameters describing the structural *trans*-effect (STE). Unfortunately, despite the long-standing history of development of the views on the *trans*-effect, the main bulk of studies concerning the quantitative *trans*-effect refers to platinum compounds.<sup>158,163–166</sup> The information on palladium complexes,<sup>160,167</sup> the more so, organopalladium compounds,<sup>168,169</sup> in particular, cyclometallated ones,<sup>161,170</sup> is extremely scarce. Although it is believed<sup>159</sup> that derivatives of metals with similar electron configurations do not differ much in properties, the transfer of general rules from one metal to another may bring about distortions.

The few known data on the *trans*-effect of ligands in organopalladium compounds demonstrate that only general trends are retained on passing from platinum to palladium. For instance, on the basis of comparison of the chemical shifts of metallated  $sp^2$ -hybridised carbon atoms in the <sup>13</sup>C NMR spectra of a series of CPCs of the type [PdX(C<sup>⋈</sup>N)(PPh<sub>3</sub>)], the following STE sequence for the X<sup>–</sup> anions was established:  $CN^- < SCN^- < Cl^- < Br^- < I^-$ .<sup>170</sup> This sequence is consistent with the general views on the halide STE in platinum coordination compounds ( $F^- < Cl^- < Br^- < I^-$ ).<sup>139,159,165</sup> A similar (but not identical) order of variation of the halide STE has been found by analysis of

§ This conclusion contradicts the results of quantitative estimates of the *trans*-effect of various phosphines in platinum complexes obtained by X-ray diffraction<sup>157</sup> and IR<sup>158,159</sup> and NMR spectroscopy,<sup>157,159,160</sup> according to which it decreases in the sequence  $PEt_3 \approx PBu_3 > PMe_2Ph > PPh_3$ .



X-ray diffraction data for the *trans*-[PhPdX(PPh<sub>3</sub>)<sub>2</sub>] complexes (X = F, Cl, Br, I): F<sup>−</sup> < Cl<sup>−</sup>; Br<sup>−</sup> < I<sup>−</sup>; but Cl<sup>−</sup> ≥ Br<sup>−</sup>.<sup>169</sup> However, the positions of the cyanide and the thiocyanate ions in the series of STE found for CPCs<sup>170</sup> differ from those typical of coordination compounds of platinum (Cl<sup>−</sup> < I<sup>−</sup> ≈ SCN<sup>−</sup> < CN<sup>−</sup>;<sup>139, 158, 159</sup>). These deviations may be due to different contributions of the σ- and π-constituents of the M–L bond (L is the ligand) located in the *trans*-position. In the case of platinum, the order of anions changes on passing from σ-STE (SCN<sup>−</sup> < CN<sup>−</sup> > Br<sup>−</sup> ≈ Cl<sup>−</sup><sup>164</sup>) to π-STE (CN<sup>−</sup> < SCN<sup>−</sup><sup>164</sup>). The STE for carboxylate anions in palladium compounds has not been estimated; however, it can be assumed (by analogy with platinum compounds<sup>159, 160, 163</sup>) that the effect of these O-donor anions should be least pronounced. For example, according to IR data (ν<sub>Pt–H</sub>), the STE of anions increases in the sequence NO<sub>3</sub><sup>−</sup> < CF<sub>3</sub>COO<sup>−</sup> < ArCOO<sup>−</sup> < NCO<sup>−</sup> ≈ NCS<sup>−</sup> ≈ Cl<sup>−</sup> ≈ Br<sup>−</sup> < I<sup>−</sup> ≈ SCN<sup>−</sup> < CN<sup>−</sup>.<sup>158, 159</sup>

X-Ray diffraction data for a large series of iminoacyl palladium complexes including CO-type CPCs were used to determine the relative STE values for C- and N-donor ligands and for iodide in these complexes: bipy < I<sup>−</sup> < σ-C(sp<sup>2</sup>)<sup>−</sup> (see Ref. 161). This sequence is consistent with the STE series for platinum complexes derived from IR spectroscopy data (ν<sub>Pt–H</sub>): Py ≈ MeNH<sub>2</sub> < I<sup>−</sup> < PhC≡C<sup>−</sup>.<sup>58, 159</sup> However, the NMR spectra (J<sub>Pt–P</sub>) give a somewhat different sequence: I<sup>−</sup> < Py < Et<sub>2</sub>NH < Me<sup>−</sup> < Ph<sup>−</sup>.<sup>158–160</sup>

The results of studies of the STE of heterodonor ligands in palladium compounds<sup>168</sup> imply that this effect is most pronounced in P-containing ligands. For example, it was found that in the palladium coordination complexes [Pd(X<sup>∧</sup>Y)Cl<sub>2</sub>] with the bidentate ligands X<sup>∧</sup>Y, the STE decreases in the sequence Ph<sub>2</sub>P<sup>∧</sup>PPh<sub>2</sub> > Ph<sub>2</sub>P<sup>∧</sup>SMe > Ph<sub>2</sub>As<sup>∧</sup>SMe.<sup>167</sup> For the allyl complexes [Pd(η<sup>3</sup>-All\*)(O<sup>∧</sup>X)]BF<sub>4</sub> (All\* = 2-methylallyl; O<sup>∧</sup>X = XCH<sub>2</sub>COOEt, where X = PPh<sub>2</sub>, NPh<sub>2</sub>, OPh, SPh, NC<sub>5</sub>H<sub>5</sub>), a similar dependence has been found: PPh<sub>2</sub> ≫ NPh<sub>2</sub> ≈ OPh > SPh > NC<sub>5</sub>H<sub>5</sub>.<sup>168</sup> These sequences are mainly in line with the STE scale established for platinum coordination complexes using X-ray diffraction data (from comparison of the Pt–Cl bond lengths): PPh<sub>3</sub> > AsPh<sub>3</sub> > Me<sub>2</sub>S ≈ Ph<sub>2</sub>S > NH<sub>3</sub>.<sup>157</sup>

### c. Estimation of the *trans*-effect of P- and C-donor atoms in phosphapalladacycles

It can be seen from the foregoing that the studies on the structural *trans*-effect of ligands in palladium(II) complexes and, the more so, in organometallic types of complexes are few. The total lack of any information on the STE in phosphapalladacyclic structures and the inconsistency of some conclusions, drawn using different criteria, concerning the ligand *trans*-effect in platinum(II) coordination compounds promote the search for more legitimate ways for estimating the STE in PC-palladacycles of various types. To interpret and/or predict the regiochemistry of the coordination of palladacycles with an additional ligand, it is necessary first to compare the STEs of a carbon and a heterodonor atom of the palladacycle.

Since a large number of publications deal with the X-ray diffraction analysis of the PC- (Table 1) and especially CN-palladacycles (Table 2), we used X-ray diffraction data to tackle this problem. The PC-palladacycles in which the metal is bound either to two identical anions [dimeric CPCs with chloride (**1c**, **3b**, **6**, **9a**, **11a**, **17–21**), bromide (**3o**, **22**), iodide (**4o**) and carboxylate (**4a**, **7d**, **12b**) bridges] or with bidentate symmetrical auxiliary ligands [mononuclear derivatives of PC-palladacycles (**11e**, **23a**), their phosphino-P-ylide analogues (**16c**) and the dichlorides of the latter (**15a**, **24**)] were used as models. Comparison of the lengths of bonds formed by the metal with two identical atoms that occupy *trans*-positions relative to the carbanionic and heterodonor centres, provides the most correct view on the relative STEs of the two 'ends' of the ligand enclosed in a palladacycle.

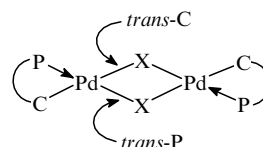


Table 1 presents the lengths of two Pd–X bonds (X = Cl, Br, I, O, S or P) that occupy the *trans*-positions with respect to C- and P-donor atoms of phosphapalladacycles and the difference

**Table 1.** *trans*-Effect of P- and C-donor atoms in PC-palladacycles.

| Structure | Number of the compound | C-Donor            | P-Donor                       | $\frac{l(\text{Pd}-\text{X})/\text{\AA}}{\frac{\text{trans-P}}{\text{trans-C}}}$ |                | $\Delta l/\text{\AA}$ | Code <sup>a</sup> | Ref.     |
|-----------|------------------------|--------------------|-------------------------------|----------------------------------------------------------------------------------|----------------|-----------------------|-------------------|----------|
| X = Cl    |                        |                    |                               |                                                                                  |                |                       |                   |          |
|           | 3b                     | CH <sub>2</sub>    | PBu <sub>2</sub> <sup>t</sup> | 2.429                                                                            | 2.474          | 0.045                 | BIHLOT01          | 171, 172 |
|           | 17                     | AllCH <sub>2</sub> | PBu <sub>2</sub> <sup>t</sup> | 2.416                                                                            | 2.455          | 0.039                 | CAFFOE            | 83       |
|           | 1c                     | ArCH <sub>2</sub>  | PMes <sub>2</sub>             | 2.400<br>2.415                                                                   | 2.487<br>2.472 | 0.087<br>0.057        | VANHEX            | 85       |
|           | 9a                     | Fc                 | PBu <sub>2</sub> <sup>t</sup> | 2.426<br>2.404                                                                   | 2.446<br>2.445 | 0.020<br>0.041        | QALNUM            | 79       |

Table 1 (continued).

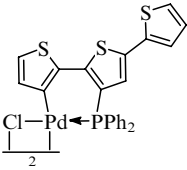
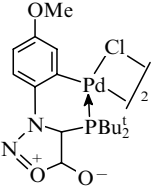
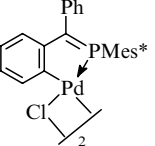
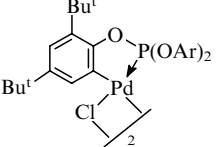
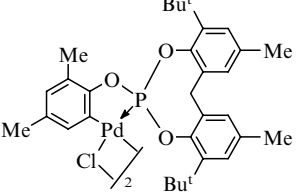
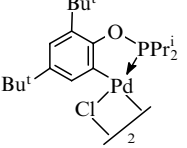
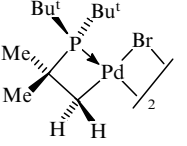
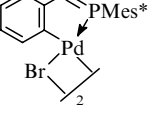
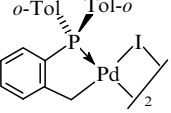
| Structure                                                                                                                                          | Number of the compound | C-Donor                       | P-Donor                        | $\frac{l(\text{Pd}-\text{X})}{\text{\AA}}$ |                 | $\Delta l / \text{\AA}$ | Code <sup>a</sup> | Ref. |
|----------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|-------------------------------|--------------------------------|--------------------------------------------|-----------------|-------------------------|-------------------|------|
|                                                                                                                                                    |                        |                               |                                | <i>trans</i> -P                            | <i>trans</i> -C |                         |                   |      |
| <b>X = Cl</b>                                                                                                                                      |                        |                               |                                |                                            |                 |                         |                   |      |
|                                                                   | 18                     | thienyl                       | PPh <sub>2</sub>               | 2.425                                      | 2.418           | −0.007                  | QANLAS            | 173  |
|                                                                   | 19                     | Ar                            | PBu <sub>2</sub> <sup>1</sup>  | 2.436<br>2.425                             | 2.442<br>2.435  | 0.006<br>0.010          | NAJXEB            | 174  |
| <br>(Mes* = 2,4,6-Bu <sub>3</sub> C <sub>6</sub> H <sub>2</sub> ) | 20                     | C <sub>6</sub> H <sub>4</sub> | C = PMes*                      | 2.389                                      | 2.438           | 0.049                   | TUHBON            | 86   |
| <br>(Ar = 2,4-Bu <sub>2</sub> C <sub>6</sub> H <sub>3</sub> )    | 11a                    | Ar                            | OP(OAr) <sub>2</sub>           | 2.407                                      | 2.418           | 0.011                   | GEGRAL            | 175  |
|                                                                 | 6                      | Ar                            | OP(OAr) <sub>2</sub>           | 2.390<br>2.399                             | 2.408<br>2.413  | 0.018<br>0.015          | OJUBOK            | 69   |
|                                                                 | 21                     | Ar                            | OPPr <sub>2</sub> <sup>i</sup> | 2.4313                                     | 2.433           | 0.002                   | OMAWEE            | 17   |
| <b>X = Br</b>                                                                                                                                      |                        |                               |                                |                                            |                 |                         |                   |      |
|                                                                 | 30                     | CH <sub>2</sub>               | PBu <sub>2</sub> <sup>1</sup>  | 2.550                                      | 2.592           | 0.042                   | FORXIT            | 176  |
|                                                                 | 22                     | Ar                            | C = PMes*                      | 2.508                                      | 2.560           | 0.052                   | REMQAB            | 177  |
| <b>X = I</b>                                                                                                                                       |                        |                               |                                |                                            |                 |                         |                   |      |
|                                                                 | 40                     | ArCH <sub>2</sub>             | P(o-Tol) <sub>2</sub>          | 2.665                                      | 2.723           | 0.058                   | CODJAG            | 84   |

Table 1 (continued).

| Structure                                                         | Number of the compound | C-Donor           | P-Donor                                   | $\frac{l(\text{Pd}-\text{X})}{\text{\AA}}$ |                 | $\Delta l/\text{\AA}$ | Code <sup>a</sup> | Ref. |
|-------------------------------------------------------------------|------------------------|-------------------|-------------------------------------------|--------------------------------------------|-----------------|-----------------------|-------------------|------|
|                                                                   |                        |                   |                                           | <i>trans</i> -P                            | <i>trans</i> -C |                       |                   |      |
| X = OCOR                                                          |                        |                   |                                           |                                            |                 |                       |                   |      |
|                                                                   | 4a                     | ArCH <sub>2</sub> | P( <i>o</i> -Tol) <sub>2</sub>            | 2.111                                      | 2.147           | 0.036                 | ZEPHOR            | 1, 2 |
|                                                                   |                        |                   |                                           | 2.127                                      | 2.134           | 0.007                 |                   |      |
|                                                                   |                        |                   |                                           | 2.118                                      | 2.149           | 0.031                 |                   |      |
|                                                                   |                        |                   |                                           | 2.111                                      | 2.156           | 0.045                 |                   |      |
|                                                                   | 7d                     | ArCH <sub>2</sub> | P <i>Bu</i> <sup>t</sup> ( <i>o</i> -Tol) | 2.120                                      | 2.136           | 0.016                 | ABTPBP            | 178  |
|                                                                   |                        |                   |                                           | 2.124                                      | 2.209           | 0.085                 |                   |      |
|                                                                   |                        |                   |                                           | 2.119                                      | 2.155           | 0.037                 |                   |      |
|                                                                   | 12b                    | Ar                | OPPh <sub>2</sub>                         | 2.141                                      | 2.149           | 0.008                 | OJOLAA            | 115  |
|                                                                   |                        |                   |                                           | 2.145                                      | 2.151           | 0.006                 |                   |      |
|                                                                   |                        |                   |                                           | 2.143                                      | 2.150           | 0.007                 |                   |      |
| (TFA is trifluoroacetate)                                         |                        |                   |                                           |                                            |                 |                       |                   |      |
| X = S                                                             |                        |                   |                                           |                                            |                 |                       |                   |      |
|                                                                   | 11e                    | Ar                | OP(OAr) <sub>2</sub>                      | 2.3739                                     | 2.3719          | 0.002                 | OJUBIE            | 69   |
| (Ar = 2,4- <i>Bu</i> <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ) |                        |                   |                                           |                                            |                 |                       |                   |      |
| X = P                                                             |                        |                   |                                           |                                            |                 |                       |                   |      |
|                                                                   | 23a                    | ArCH <sub>2</sub> | C(sp <sup>2</sup> )PHMes                  | 2.381                                      | 2.415           | 0.034                 | —                 | 179  |
| X = Cl                                                            |                        |                   |                                           |                                            |                 |                       |                   |      |
|                                                                   | 15a                    | BzCH              | C(sp <sup>3</sup> )PPh <sub>2</sub>       | 2.390                                      | 2.340           | −0.050                | —                 | 137  |
|                                                                   | 24                     | C=C(Ar)           | C(sp <sup>3</sup> )PPh <sub>2</sub>       | 2.378                                      | 2.394           | 0.016                 | WOKYIE            | 180  |
|                                                                   |                        |                   |                                           | 2.384                                      | 2.367           | −0.017                |                   |      |
| X = C                                                             |                        |                   |                                           |                                            |                 |                       |                   |      |
|                                                                   | 16c                    | BzCH              | C(sp <sup>3</sup> )PPh <sub>2</sub>       | 2.103                                      | 2.087           | −0.016                | VETNUD            | 138  |

<sup>a</sup> Code in the Cambridge Structural Database.

between them ( $\Delta l$ ), which characterises the difference between the STEs of these atoms.

In order to compare the regiochemistry of coordination of additional ligands to palladacycles containing P- and N-hetero-donor atoms, the corresponding parameters for CN-systems are given in Table 2 (taking the five-membered CN-palladacycles containing amine, imine or heterocyclic nitrogen atom as examples).

The  $\Delta l$  parameters given in Tables 1 and 2 indicate that PC- and CN-palladacycles are essentially different. In the case of CN-dimers with various C- and N-donors (see Table 2), the  $\Delta l_{av}$  parameters averaged for each group vary in the ranges of 0.115–0.180 and 0.094–0.103 Å for  $\mu$ -halide and  $\mu$ -carboxylate dimers, respectively, thus demonstrating a substantial difference between the STE values of C- and N-donor atoms of the palladacycle. These values imply a high degree of selectivity in the

**Table 2.** *trans*-Effect of N- and C-donor atoms in five-membered CN-palladacycles (on the basis of structural parameters of dimeric CPCs).

| No. | Structure elements <sup>a</sup> |         | R <sup>1</sup> | $l(\text{Pd}-\text{X}) / \text{\AA}$ |                 | $\Delta l / \text{\AA}$ | Ref. |
|-----|---------------------------------|---------|----------------|--------------------------------------|-----------------|-------------------------|------|
|     | C-Donor                         | N-Donor |                | <i>trans</i> -C                      | <i>trans</i> -N |                         |      |

|                |                                                                     |                   |                 |              |              |              |     |
|----------------|---------------------------------------------------------------------|-------------------|-----------------|--------------|--------------|--------------|-----|
| <b>X = Cl</b>  |                                                                     |                   |                 |              |              |              |     |
| 1              | {( $\eta^5$ -Cp)Fe( $\eta^5$ -C <sub>5</sub> H <sub>2</sub> Me-3)}C | NMe <sub>2</sub>  | H               | 2.489        | 2.320        | 0.169        | 181 |
|                |                                                                     |                   |                 | 2.484        | 2.318        | 0.166        |     |
| 2              | {3-R <sub>3</sub> SiC <sub>6</sub> H <sub>3</sub> }C                | NMe <sub>2</sub>  | H               | 2.4732       | 2.3105       | 0.163        | 182 |
|                |                                                                     |                   |                 | 2.4747       | 2.3154       | 0.159        |     |
| 3              | {3-MeOC <sub>6</sub> H <sub>3</sub> }C                              | NMe <sub>2</sub>  | H               | 2.472        | 2.341        | 0.131        | 183 |
| 4              | {4-MeOC <sub>6</sub> H <sub>3</sub> }C                              | NMe <sub>2</sub>  | H               | 2.489        | 2.334        | 0.155        | 183 |
| 5              | {5-MeOC <sub>6</sub> H <sub>3</sub> }C                              | NMe <sub>2</sub>  | H               | 2.466        | 2.338        | 0.128        | 183 |
|                |                                                                     |                   |                 | 2.477        | 2.338        | 0.139        |     |
| 6              | {C <sub>6</sub> H <sub>4</sub> }C                                   | NMe <sub>2</sub>  | Bu <sup>t</sup> | 2.466        | 2.341        | 0.125        | 184 |
|                |                                                                     |                   |                 | 2.473        | 2.330        | 0.143        |     |
| 7              | {2-C <sub>10</sub> H <sub>6</sub> }C                                | NMe <sub>2</sub>  | Me              | 2.474        | 2.336        | 0.138        | 185 |
|                |                                                                     |                   |                 | 2.465        | 2.338        | 0.149        |     |
|                |                                                                     |                   |                 | 2.487        | 2.336        | 0.129        |     |
|                |                                                                     |                   |                 | 2.474        | 2.334        | 0.140        |     |
| 8              | {1-C <sub>10</sub> H <sub>6</sub> }C <sup>b</sup>                   | NMe <sub>2</sub>  | Me              | 2.458        | 2.352        | 0.106        | 87  |
| 9              | {1-C <sub>10</sub> H <sub>6</sub> }C <sup>c</sup>                   | NMe <sub>2</sub>  | Me              | 2.475        | 2.336        | 0.139        | 87  |
| 10             | {( $\eta^5$ -Cp)Fe( $\eta^5$ -C <sub>5</sub> H <sub>3</sub> )}C     | NMe <sub>2</sub>  | Me              | 2.477        | 2.325        | 0.152        | 186 |
| 11             | {C <sub>6</sub> H <sub>4</sub> }C                                   | NHPr <sup>i</sup> | Me              | 2.493        | 2.331        | 0.162        | 187 |
|                |                                                                     |                   |                 | 2.464        | 2.347        | 0.117        |     |
|                |                                                                     | Average:          |                 | <b>2.475</b> | <b>2.333</b> | <b>0.142</b> |     |
| <b>X = Br</b>  |                                                                     |                   |                 |              |              |              |     |
| 12             | {C <sub>6</sub> H <sub>4</sub> }C                                   | NMe <sub>2</sub>  | Me              | 2.584        | 2.465        | 0.119        | 185 |
|                |                                                                     |                   |                 | 2.596        | 2.458        | 0.138        |     |
| 13             | {2-C <sub>10</sub> H <sub>6</sub> }C                                | NMe <sub>2</sub>  | Me              | 2.590        | 2.450        | 0.140        | 185 |
|                |                                                                     |                   |                 | 2.599        | 2.450        | 0.149        |     |
| 14             | {C <sub>6</sub> H <sub>4</sub> }C                                   | NHBn              | H               | 2.580        | 2.430        | 0.150        | 188 |
|                |                                                                     |                   |                 | 2.585        | 2.436        | 0.149        |     |
| 15             | {C <sub>6</sub> H <sub>4</sub> }C                                   | NH <sub>2</sub>   | Me              | 2.447        | 2.332        | 0.115        | 189 |
|                |                                                                     |                   |                 | 2.478        | 2.333        | 0.145        |     |
|                |                                                                     | Average:          |                 | <b>2.557</b> | <b>2.419</b> | <b>0.138</b> |     |
| <b>X = I</b>   |                                                                     |                   |                 |              |              |              |     |
| 16             | {C <sub>6</sub> H <sub>4</sub> }C                                   | NMe <sub>2</sub>  | Me              | 2.740        | 2.596        | 0.144        | 185 |
|                |                                                                     |                   |                 | 2.745        | 2.596        | 0.149        |     |
| <b>X = OAc</b> |                                                                     |                   |                 |              |              |              |     |
| 17             | {C <sub>6</sub> H <sub>4</sub> }C                                   | NBn <sub>2</sub>  | H               | 2.142        | 2.047        | 0.105        | 190 |
|                |                                                                     |                   |                 | 2.127        | 2.048        | 0.114        |     |
| 18             | {C <sub>6</sub> H <sub>4</sub> }C <sup>d</sup>                      | NMe <sub>2</sub>  | H               | 2.174        | 2.072        | 0.102        | 27  |
|                |                                                                     |                   |                 | 2.163        | 2.064        | 0.099        |     |
| 19             | {C <sub>6</sub> H <sub>4</sub> }C                                   | NMe <sub>2</sub>  | COOMe           | 2.150        | 2.053        | 0.097        | 191 |
|                |                                                                     |                   |                 | 2.146        | 2.052        | 0.094        |     |
|                |                                                                     | Average:          |                 | <b>2.150</b> | <b>2.056</b> | <b>0.094</b> |     |

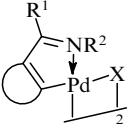
  
  

|               |                                     |                  |    |              |              |              |     |
|---------------|-------------------------------------|------------------|----|--------------|--------------|--------------|-----|
| <b>X = Cl</b> |                                     |                  |    |              |              |              |     |
| 20            | {CH <sub>2</sub> CH <sub>2</sub> }C | NMe <sub>2</sub> | H  | 2.524        | 2.337        | 0.187        | 192 |
| 21            | {CMe <sub>2</sub> CH(CHO)}C         | NMe <sub>2</sub> | Me | 2.476        | 2.334        | 0.142        | 193 |
|               |                                     | Average:         |    | <b>2.500</b> | <b>2.335</b> | <b>0.165</b> |     |

Table 2 (continued).

| No. | Structure elements <sup>a</sup> |         | R <sup>1</sup> | /(Pd–X) / Å     |                 | $\Delta l$ / Å | Ref. |
|-----|---------------------------------|---------|----------------|-----------------|-----------------|----------------|------|
|     | C-Donor                         | N-Donor |                | <i>trans</i> -C | <i>trans</i> -N |                |      |

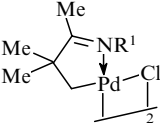
  



|                |                                                                           |                                                     |    |              |              |              |     |
|----------------|---------------------------------------------------------------------------|-----------------------------------------------------|----|--------------|--------------|--------------|-----|
| <b>X = Cl</b>  |                                                                           |                                                     |    |              |              |              |     |
| 22             | {C <sub>6</sub> H <sub>4</sub> }C                                         | NBn                                                 | Bz | 2.457        | 2.317        | 0.140        | 194 |
| 23             | {C <sub>6</sub> H <sub>4</sub> }C                                         | NC <sub>6</sub> H <sub>3</sub> Me <sub>2</sub> -2,6 | H  | 2.467        | 2.339        | 0.128        | 195 |
|                |                                                                           |                                                     |    | 2.452        | 2.331        | 0.121        |     |
| 24             | {(η <sup>5</sup> -Cp)Fe(η <sup>5</sup> -C <sub>5</sub> H <sub>3</sub> )}C | NTol- <i>p</i>                                      | Me | 2.469        | 2.331        | 0.138        | 196 |
|                |                                                                           |                                                     |    | 2.490        | 2.321        | 0.169        |     |
| 25             | {3-MeOC <sub>6</sub> H <sub>3</sub> }C                                    | NCH <sub>2</sub> pin <sup>c</sup>                   | H  | 2.462        | 2.340        | 0.122        | 197 |
|                |                                                                           |                                                     |    | 2.495        | 2.346        | 0.149        |     |
|                |                                                                           | Average:                                            |    | <b>2.469</b> | <b>2.330</b> | <b>0.139</b> |     |
| <b>X = Br</b>  |                                                                           |                                                     |    |              |              |              |     |
| 26             | {3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>2</sub> }C                  | NCy                                                 | H  | 2.565        | 2.439        | 0.126        | 198 |
| 27             | {5-MeC <sub>6</sub> H <sub>3</sub> }C                                     | NCy                                                 | H  | 2.598        | 2.447        | 0.151        | 199 |
|                |                                                                           |                                                     |    | 2.579        | 2.449        | 0.130        |     |
| 28             | {5-MeOC <sub>6</sub> H <sub>3</sub> }C                                    | NCH <sub>2</sub> pin                                | H  | 2.602        | 2.457        | 0.145        | 197 |
|                |                                                                           |                                                     |    | 2.564        | 2.454        | 0.110        |     |
| 29             | {(η <sup>5</sup> -Cp)Fe(η <sup>5</sup> -C <sub>5</sub> H <sub>3</sub> )}C | Nmmp <sup>f</sup>                                   | Me | 2.582        | 2.465        | 0.117        | 196 |
|                |                                                                           |                                                     |    | 2.601        | 2.437        | 0.164        |     |
|                |                                                                           | Average:                                            |    | <b>2.582</b> | <b>2.448</b> | <b>0.134</b> |     |
| <b>X = OAc</b> |                                                                           |                                                     |    |              |              |              |     |
| 30             | {C <sub>6</sub> H <sub>4</sub> }C                                         | NAn <sup>g</sup>                                    | Bz | 2.141        | 2.054        | 0.087        | 200 |
|                |                                                                           |                                                     |    | 2.119        | 2.030        | 0.089        |     |
| 31             | {C <sub>6</sub> H <sub>4</sub> }C                                         | NC <sub>6</sub> H <sub>4</sub> Cl- <i>p</i>         | Bz | 2.123        | 2.034        | 0.096        | 201 |
| 32             | {4-MeOC <sub>6</sub> H <sub>3</sub> }C                                    | NTol- <i>p</i>                                      | H  | 2.139        | 2.026        | 0.113        | 202 |
| 33             | {C <sub>6</sub> H <sub>4</sub> }C                                         | NCy                                                 | Ph | 2.166        | 2.041        | 0.125        | 203 |
| 34             | {3-MeOC <sub>6</sub> H <sub>3</sub> }C                                    | NCy                                                 | H  | 2.137        | 2.048        | 0.089        | 204 |
| 35             | {4-OCHC <sub>6</sub> H <sub>3</sub> }C                                    | NCy                                                 | H  | 2.146        | 2.041        | 0.105        | 205 |
|                |                                                                           |                                                     |    | 2.175        | 2.061        | 0.114        |     |
|                |                                                                           |                                                     |    | 2.168        | 2.034        | 0.134        |     |
|                |                                                                           |                                                     |    | 2.174        | 2.051        | 0.123        |     |
| 36             | {(η <sup>5</sup> -Cp)Fe(η <sup>5</sup> -C <sub>5</sub> H <sub>3</sub> )}C | NMes                                                | H  | 2.153        | 2.042        | 0.111        | 206 |
|                |                                                                           |                                                     |    | 2.092        | 2.027        | 0.065        |     |
| 37             | {(η <sup>5</sup> -Cp)Fe(η <sup>5</sup> -C <sub>5</sub> H <sub>3</sub> )}C | NCH <sub>2</sub> CO <sub>2</sub> Et                 | H  | 2.137        | 2.036        | 0.101        | 207 |
|                |                                                                           |                                                     |    | 2.135        | 2.041        | 0.094        |     |
|                |                                                                           | Average:                                            |    | <b>2.143</b> | <b>2.040</b> | <b>0.103</b> |     |

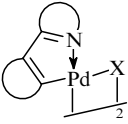
  



|    |                                      |          |       |              |              |              |     |
|----|--------------------------------------|----------|-------|--------------|--------------|--------------|-----|
| 38 | {CMe <sub>2</sub> CH <sub>2</sub> }C | N{NPhMe} | NPhMe | 2.490        | 2.334        | 0.156        | 208 |
| 39 | {CMe <sub>2</sub> CH <sub>2</sub> }C | N{OH}    | OH    | 2.546        | 2.341        | 0.205        | 209 |
|    |                                      | Average: |       | <b>2.518</b> | <b>2.338</b> | <b>0.180</b> |     |



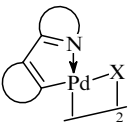
  

|               |                                   |                                       |  |              |              |              |     |
|---------------|-----------------------------------|---------------------------------------|--|--------------|--------------|--------------|-----|
| <b>X = Cl</b> |                                   |                                       |  |              |              |              |     |
| 40            | {C <sub>6</sub> H <sub>4</sub> }C | N{4-Bu <sup>t</sup> -ox} <sup>h</sup> |  | 2.455        | 2.323        | 0.132        | 210 |
|               |                                   |                                       |  | 2.470        | 2.320        | 0.150        |     |
| 41            | {C <sub>6</sub> H <sub>4</sub> }C | N{4-Ph-ox}                            |  | 2.434        | 2.329        | 0.105        | 211 |
|               |                                   |                                       |  | 2.472        | 2.323        | 0.143        |     |
|               |                                   |                                       |  | 2.433        | 2.312        | 0.160        |     |
|               |                                   |                                       |  | 2.466        | 2.341        | 0.092        |     |
| 42            | {C <sub>6</sub> H <sub>4</sub> }C | N{Py}                                 |  | 2.426        | 2.361        | 0.065        | 212 |
|               |                                   |                                       |  | 2.434        | 2.366        | 0.068        |     |
|               |                                   | Average:                              |  | <b>2.449</b> | <b>2.334</b> | <b>0.115</b> |     |

Table 2 (continued).

| No. | Structure elements <sup>a</sup> |         | R <sup>1</sup> | l(Pd–X) / Å |         | $\Delta l$ / Å | Ref. |
|-----|---------------------------------|---------|----------------|-------------|---------|----------------|------|
|     | C-Donor                         | N-Donor |                | trans-C     | trans-N |                |      |



**X = I**

|    |                                                                                                            |                                |  |              |              |              |     |
|----|------------------------------------------------------------------------------------------------------------|--------------------------------|--|--------------|--------------|--------------|-----|
| 43 | {(η <sup>5</sup> -Cp)Fe(η <sup>5</sup> -C <sub>5</sub> H <sub>2</sub> SiMe <sub>3</sub> -3)}C <sup>i</sup> | N{4-(MeOCEt <sub>2</sub> )-ox} |  | 2.738        | 2.587        | 0.151        | 213 |
| 44 | {(η <sup>5</sup> -Cp)Fe(η <sup>5</sup> -C <sub>5</sub> H <sub>2</sub> SiMe <sub>3</sub> -3)}C <sup>j</sup> | N{4-Bu <sup>t</sup> -ox}       |  | 2.736        | 2.587        | 0.149        | 213 |
|    |                                                                                                            | Average:                       |  | <b>2.739</b> | <b>2.590</b> | <b>0.149</b> |     |

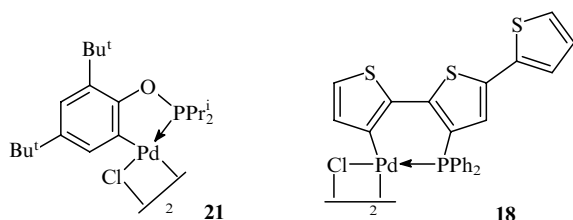
  

**X = OAc**

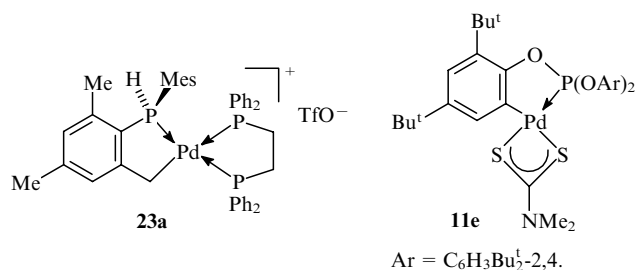
|    |                                                     |                            |  |              |              |              |     |
|----|-----------------------------------------------------|----------------------------|--|--------------|--------------|--------------|-----|
| 45 | {C <sub>6</sub> H <sub>4</sub> }C                   | N{4,4-Me <sub>2</sub> -ox} |  | 2.125        | 2.049        | 0.076        | 214 |
|    |                                                     |                            |  | 2.129        | 2.058        | 0.071        |     |
| 46 | {C <sub>6</sub> H <sub>4</sub> }C                   | N{4-Pr <sup>i</sup> -ox}   |  | 2.124        | 2.061        | 0.063        | 215 |
|    |                                                     |                            |  | 2.112        | 2.041        | 0.071        |     |
|    |                                                     |                            |  | 2.114        | 2.024        | 0.090        |     |
|    |                                                     |                            |  | 2.127        | 2.023        | 0.104        |     |
|    |                                                     |                            |  | 2.109        | 2.047        | 0.062        |     |
|    |                                                     |                            |  | 2.181        | 2.019        | 0.162        |     |
|    |                                                     |                            |  | 2.111        | 2.044        | 0.067        |     |
|    |                                                     |                            |  | 2.147        | 2.031        | 0.116        |     |
| 47 | {4-NO <sub>2</sub> C <sub>6</sub> H <sub>3</sub> }C | N{Py}                      |  | 2.14         | 2.03         | 0.11         | 216 |
| 48 | {C <sub>6</sub> H <sub>4</sub> }C                   | N{im}                      |  | 2.151        | 2.036        | 0.115        | 217 |
|    |                                                     | Average:                   |  | <b>2.133</b> | <b>2.038</b> | <b>0.095</b> |     |

<sup>a</sup> The ligand fragment to which this donor atom belongs is given in braces. <sup>b</sup> *R,R*-*cis*-Isomer. <sup>c</sup> *R,S*-*trans*-Isomer. <sup>d</sup> The parameters for the μ-fluoroacetate dimer are given. <sup>e</sup> Here and below pin is pinan-3-yl. <sup>f</sup> mmp is 2-(methoxymethyl)pyrrolidine. <sup>g</sup> An is anisyl. <sup>h</sup> Here and below, ox is oxazoline. <sup>i</sup> *R<sub>C</sub>,S<sub>Pl</sub>*-Diastereomer. <sup>j</sup> *S<sub>C</sub>,R<sub>Pl</sub>*-Diastereomer.

coordination of additional ligands to CN-palladacycles and account for the almost complete regioselectivity of these processes. Conversely, in the structures of dimeric CPC of the PC-type (see Table 1), the difference between the lengths of the two Pd–X bonds (X = Hal, RCOO) largely disappears: here the  $\Delta l_{av}$  values vary in the ranges of 0.010–0.058 and 0.007–0.037 Å for μ-halide and μ-carboxylate dimers, respectively. Moreover, for some complexes, the parameter  $\Delta l$  decreases to negligibly low values (0.002 Å for dimer **21**<sup>17</sup>) or even changes the sign (–0.007 Å for dimer **18**<sup>173</sup>).



More evidence supporting the similarity of STE values of C- and P-donor atoms of phosphapalladacycles comes from the structural parameters of mononuclear derivatives of PC-palladacycles with symmetric ligands. In the cationic adduct **23a**<sup>179</sup> with the diphosphine ligand dppe, the lengths of two Pd–P bonds



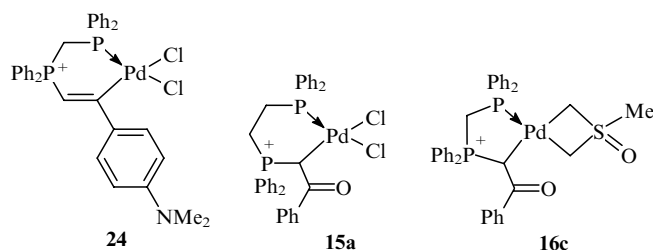
located in the *trans*-positions relative to the phosphapalladacycle C- and P-donor atoms differ only slightly ( $\Delta l$  = 0.034 Å), and in the dithiocarbamate derivative **11e**,<sup>69</sup> the difference between the lengths of two Pd–S bonds does not exceed the experimental error ( $\Delta l$  = 0.002 Å).

Analysis of these parameters entails quite a reasonable conclusion: the difference between the STEs of C- and P-donor atoms of phosphapalladacycles is too low to induce a satisfactory regioselectivity of their coordination to additional ligands. In most cases, one should expect a mixture of geometric isomers; the selective formation of one of these can rather be considered as an exception to the general rule.

Comparative analysis of the dependence of the Pd–Hal bond length located in the *trans*-position relative to the PC-palladacycle carbon atom on the hybridisation of the C-donor atom leads to the conclusion that the *trans*-effect of the aliphatic carbon atom is higher than that for the aromatic atom. For example, in the structures of μ-chloride dimers of the PC type (see Table 1), the Pd–Cl bond lengths on the C(sp<sup>2</sup>)–Pd–Cl and C(sp<sup>3</sup>)–Pd–Cl diagonals vary in non-overlapping ranges 2.408–2.446 and 2.455–2.487 Å, respectively (the averaged  $l_{av}$  values are 2.429 and 2.472 Å, respectively, over 14 and 6 palladacycles). This trend is also retained in the structures of μ-bromide PC-dimers, although the available information is limited to only two structures. The Pd–Br bond lengths on the C(sp<sup>2</sup>)–Pd–Br and C(sp<sup>3</sup>)–Pd–Br diagonals in complexes **22**<sup>177</sup> and **30**<sup>176</sup> are equal to 2.560 and 2.592 Å, respectively.

As was to be expected, the P-ylide carbon atom has the minimum STE. Indeed, in complexes **24**<sup>180</sup> and **15a**,<sup>137</sup> belonging to the common structural type [Pd(η<sup>2</sup>-L)Cl<sub>2</sub>], the Pd–Cl bonds located in the *trans*-position to the ylide carbon atom are 2.394 and 2.340 Å long, respectively, *i.e.*, they are substantially shorter than the average Pd–Cl bond lengths for the C(sp<sup>2</sup>)–Pd–Cl and C(sp<sup>3</sup>)–Pd–Cl diagonals in the classical μ-chloride PC-dimers (2.429 and 2.472 Å, respectively) and are below the lower limits of

the ranges for these values (2.408–2.446 and 2.455–2.487 Å, respectively, see Table 1).



This result appears quite a natural consequence of the substantial delocalisation of the carbanion charge over both the phosphonium fragment and the electron-withdrawing substituents. Therefore, STE values of the C- and P-donor atoms in P-ylide complexes become comparable: the  $\Delta I$  value for two Pd–Cl bonds on the C–Pd–Cl and P–Pd–Cl diagonals is only 0.016 Å in complex **24** and becomes negative ( $\Delta I = -0.050$  Å) in complex **15a**. The last-mentioned value shows that the STE of the P-donor substantially exceeds that for a  $\sigma$ -bonded carbon. This trend is retained for the bis(ylide) compound **16c**,<sup>138</sup> for which the parameter  $\Delta I(\text{Pd} - \text{C}) = -0.016$  Å attests to a greater *trans*-effect of the PPh<sub>2</sub> group compared to the P-ylide carbon.

Thus, using X-ray diffraction data, the C-donor phosphapalladacycles can be arranged in the following series in terms of increasing structural *trans*-effect: C(P-ylides)  $\ll$  C(sp<sup>2</sup>)<sup>–</sup> < C(sp<sup>3</sup>)<sup>–</sup>.

Unfortunately, the P-donor groups of various types cannot be classified legitimately in terms of their *trans*-effect relying on the Pd–X bond lengths available from X-ray diffraction data for dimeric complexes, due to both the scarcity of these data and too slight variations of this parameter (0.1–0.2 Å, see Table 1). As a preliminary estimate, one can consider the sequence of increasing STE for P-donors, which was derived from the averaged lengths of the Pd–Cl bond located in the *trans*-position to the P-donor atom of the phosphapalladacycle in  $\mu$ -chloride dimers:

|                                       |       |                      |                   |                    |                    |
|---------------------------------------|-------|----------------------|-------------------|--------------------|--------------------|
| P-donor                               | C=P   | OP(OAr) <sub>2</sub> | CPAr <sub>2</sub> | CPAlk <sub>2</sub> | OPAlk <sub>2</sub> |
| $I(\text{Pd} - \text{Cl})/\text{\AA}$ | 2.389 | 2.399                | 2.413             | 2.424              | 2.431              |

A greater *trans*-effect of the phosphinite phosphorus atom in OPR<sub>2</sub> compared to the phosphine atom is indicated by the decrease in the Pd–O bond length in  $\mu$ -acetate dimers (see Table 1)

|                                      |                   |                   |
|--------------------------------------|-------------------|-------------------|
| P-donor                              | CPAr <sub>2</sub> | OPAr <sub>2</sub> |
| $I(\text{Pd} - \text{O})/\text{\AA}$ | 2.117             | 2.143             |

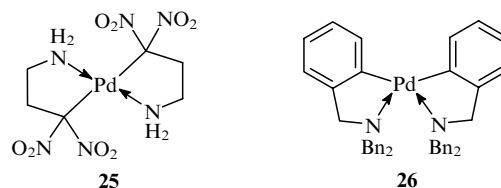
Nevertheless, the need to elucidate more correctly the dependence of the STE of P-donors on both their chemical nature and the steric features of their environment is obvious. This requires detailed analysis of X-ray diffraction data for a broader range of phosphapalladacycle derivatives. At the current stage of research, it can only be stated that in most classical PC-palladacycles, the carbanionic centre exhibits a greater *trans*-effect, than the P-donor centre, no matter what is the carbon hybridisation (sp<sup>2</sup> or sp<sup>3</sup>). However, in some classical PC-structures and in cyclopalladated derivatives of phosphino-P-ylides, the STE values of C- and P-donor atoms of a phosphapalladacycle are comparable, which implies a low regioselectivity of their reactions with auxiliary ligands.

#### d. Manifestation of the transphobia in phosphapalladacycles

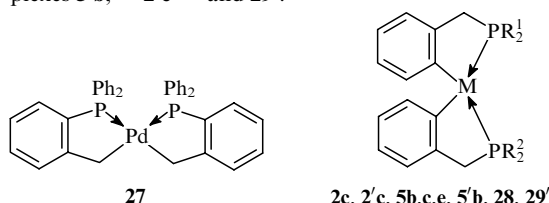
Analysis of the available data on the geometric configurations of various derivatives of PC-palladacycles largely confirms the above conclusions and demonstrates an essential difference between the PC- and CN-palladacycles.

**spiro-Complexes.** In conformity with much more pronounced *trans*-effect of the carbanionic C-donor centres compared to hard N-donor centres, the vast majority of palladium<sup>218–221</sup> and

platinum<sup>221–227</sup> bis(chelate) *spiro*-complexes with CN-type metallacycles exist as the *cis*(C,C)-configuration. Exceptions to this rule are scarce. The *trans*(C,C)-geometry of these complexes becomes possible only due to a sharp decrease in the difference between the STEs of the C- and N-donor atoms of the palladacycle. As an example, one can consider complex **25**,<sup>228</sup> in which the *trans*-effect of the carbanionic centre is sharply reduced due to the presence of two electron-withdrawing nitro groups, whereas the STE of the primary amino group is essentially higher than that of tertiary amino groups in analogous compounds (for example, in complex **26**<sup>221</sup>). As a consequence, the former complex exists as the *trans*(C,C)-isomer and the latter one has the standard *cis*(C,C)-geometry (the structures and configurations of both complexes were confirmed by X-ray diffraction).



At first glance, an increase in the transphobia in the order C/P < C/C<sup>111</sup> would be sufficient for predicting the regiochemistry of formation of bis(chelate) *spiro*-complexes involving phosphapalladacycles. Indeed, two standard PC-palladacycles are usually combined into the *spiro*-structure in the *cis*(C,C)-configuration. This geometry exists both with the sp<sup>3</sup>-hybridised carbanionic centre (for example, in complex **27**<sup>229, 230</sup>) and with the sp<sup>2</sup>-hybridised carbanionic centre [for example, in complexes **2c**<sup>†</sup> (see Ref. 71), **5b**,<sup>71</sup> **5e**,<sup>71, 231–233</sup> **5c**,<sup>71, 233</sup> **28**,<sup>71</sup>]. The regiochemistry also does not depend on the nature of the substituent at the phosphorus atom, which may be either aromatic or aliphatic. Note that the *cis*(C,C)-configuration has been confirmed unambiguously by X-ray diffraction analysis, for platinum *spiro*-complexes **5b**,<sup>234</sup> **2c**<sup>235</sup> and **29**.<sup>222</sup>

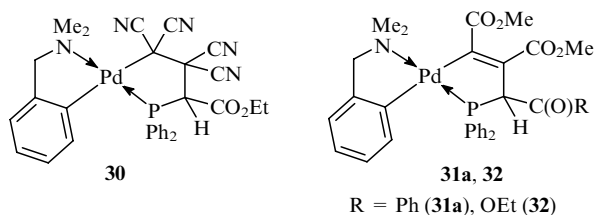


M = Pd: R<sup>1</sup> = R<sup>2</sup> = Ph (**2c**), Bu<sup>t</sup> (**5b**), Me (**28**);

R<sup>1</sup> = Bu<sup>t</sup>; R<sup>2</sup> = Ph (**5e**), Me (**5c**);

M = Pt: R<sup>1</sup> = R<sup>2</sup> = Ph (**2'c**), Bu<sup>t</sup> (**5'b**), Bn (**29'**).

However, analysis of the geometry of modified phosphapalladacyclic *spiro*-structures and conditions for their synthesis demonstrate that prohibition of the *trans*(C,C)-configuration is not very strict. For example, it does not apply to mixed-ligand *spiro*-complexes containing PC- and CN-palladacycles. Complex **30** with an alkyl<sup>236</sup> and complexes **31a**<sup>237</sup> and **32**<sup>236</sup> with an alkenyl C-donor in the phosphapalladacycle exist in solutions as *trans*(C,C)-isomers (the configuration of the former complex was determined by X-ray diffraction<sup>236</sup>).

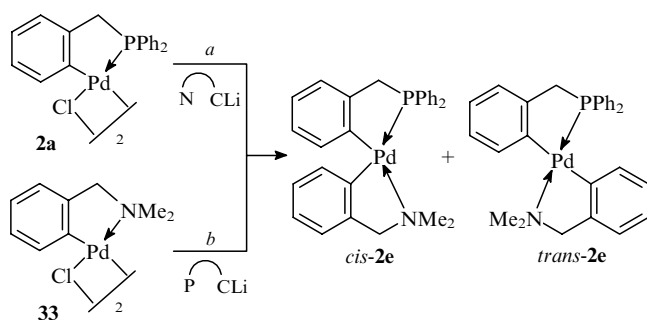


R = Ph (**31a**), OEt (**32**)

<sup>†</sup> Early studies<sup>232</sup> assumed the formation of a mixture of *cis*- and *trans*-isomers of this complex.

The *trans*-configuration appears abnormal only from the standpoint of the classical view of the maximum STE for any carbanionic centre. However, the *trans*-effects of C(sp<sup>3</sup>) in complex **30** and C(sp<sup>2</sup>) in compounds **31a** and **32** are substantially reduced due to the presence of strong electron-acceptor nitrile or methoxycarbonyl groups. Under these conditions, the *trans*-effect of the phosphine PPh<sub>2</sub> fragment becomes more significant; as a result, the *cis*-localisation of this fragment relative to the phenyl carbon atom of the benzylamine CN-palladacycle becomes quite justified from the standpoint of the transphobia concept.

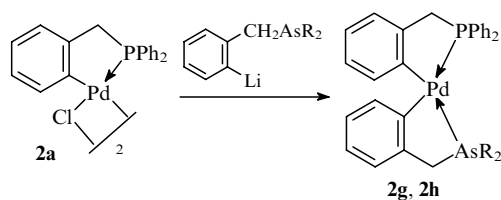
Yet another example of violation of classical rules is demonstrated by mixed-ligand complex **2e**, which is formed as a mixture of *cis*(C,C)- and *trans*(C,C)-isomers.<sup>72,73</sup> The structure of the predominant *cis*(C,C)-isomer has been confirmed by X-ray diffraction.<sup>238</sup> Probably, the dependence of the ratio of geometric isomers on the order in which the two palladacycles are closed is the most intriguing feature of this complex. Thus the formation of the CN-palladacycle on the PC-template (path *a*) results almost exclusively in the *cis*(C,C)-isomer, whereas the closure of the PC-palladacycle on the CN-template (path *b*) yields a mixture of *cis*(C,C)- and *trans*(C,C)-isomers, the former being the predominant product (~70%).<sup>72,73</sup>



*cis* : *trans* = 100 : 0 (*a*), 70 : 30 (*b*).

The formation of *trans*(C,C)-**2e** under conditions *b* was attributed to the possibility of system stabilisation due to a decrease in the electron density of the N-ligand (possessing strong  $\sigma$ -donor properties) by the *trans*-arranged P-donor atom. This explanation can hardly be accepted, because it implies the thermodynamic control of the process. Meanwhile, the differences between the two paths leading to the same complex are, most likely, due to changes in the reaction kinetics.

The dependence of the regiochemistry of the formation of *spiro*-complexes on the nature of the substituents in the hetero-donor fragments has not been actually studied. One can only mention the results obtained in the synthesis of two mixed-ligand complexes containing simultaneously phospho- and arsenapalladacycles.<sup>72</sup> Closure of an AsC-palladacycle on a PC-template affords only the *cis*(C,C)-isomer if R = Ar (compound **2g**) or a mixture of *cis*- and *trans*-isomers (*spiro*-complex **2h**) if R = Alk (the isomer ratio has not been reported).

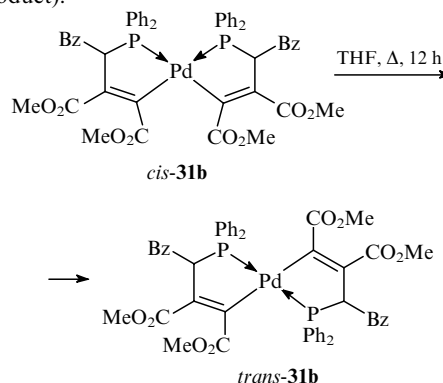


R = Ph (*cis*-**2g**), Me (*cis*/*trans*-**2h**).

The reasons for the difference between the regiochemistry of these two reactions have not been discussed in the study cited.<sup>72</sup> Since one can hardly expect a sharp increase in the STE upon the replacement of the AsPh<sub>2</sub> group by the more electron-enriched AsMe<sub>2</sub> fragment, it can only be assumed that either the geometry

of the complexes is subject to the kinetic control or these systems do not obey the transphobia principle.

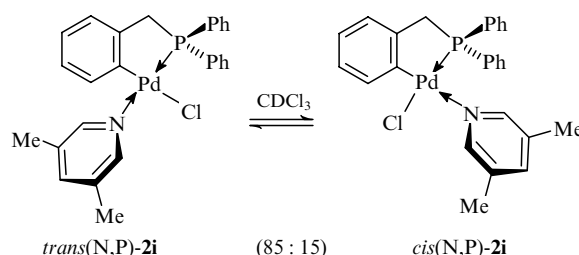
The behaviour of the alkenyl *spiro*-PC-complex **31b** should also be considered abnormal (from the standpoint of the transphobia concept).<sup>237,239</sup> This complex was obtained as the *cis*(C,C)-isomer (kinetically controlled product) under mild temperature conditions. However, the subsequent thermolysis of one diastereomer, *cis*(*R,S*)-**31b**, resulted in its quantitative conversion into the *trans*(C,C)-form (thermodynamically controlled product).



The structure and the configuration of both isomers, *cis*(*R,S*)-**31b**<sup>239</sup> and *trans*(C,C)-**31b**,<sup>237</sup> were confirmed by X-ray diffraction. These results provide a rare opportunity for estimating the relative STE of the P- and C-donor atoms in identical palladacycles. Similar Pd–P and Pd–C bond lengths in the two isomers prompted the conclusion<sup>237</sup> that the STEs of the phosphine and alkenyl groups are comparable. However, analysis of the variation dynamics of the bond lengths on passing from the P–Pd–C diagonal in the *cis*-isomer to the P–Pd–P and C–Pd–C diagonals in the *trans*-isomer shows that upon replacement of the *trans*-arranged vinylic carbon by a P-donor, the Pd–P bonds are elongated [ $\Delta l = 0.009(2)$  Å], whereas the reverse replacement resulted in shorter Pd–C bonds [ $\Delta l = -0.014(9)$  and  $-0.036(9)$  Å], the  $\Delta l$  values exceeding the experimental errors. These effects can be attributed to the greater STE of P-donor groups compared to the STE of the alkenyl carbon. However, the thermodynamic preference for the *trans*(C,C)-isomer cannot be explained in terms of the transphobia concept. Probably, in this case, steric effects make a significant contribution to the relative stability of the isomers.

Thus, even in the *spiro*-PC-complexes with two carbanionic C-donors (formally, possessing the highest *trans*-effect), the transphobia is not absolute, due to the insignificant difference between the STEs of the palladacycle C- and P-donor atoms.

**Adducts with N-donors.** In the coordination of the phosphine PC-palladacycles with N-donor ligands, the degree of transphobia should be nearly the same for any geometry of the complex (C/Hal ~ C/N<sup>153</sup>); therefore, in this case, an isomer mixture is expected to form. The reaction of benzylphosphine dimer **2a** with 3,5-lutidine affords a 85 : 15 mixture of *trans*(N,P)- and *cis*(N,P)-isomers of adduct **2i**, which undergo fast (on the NMR time scale) interconversion in solutions at room temperature.<sup>54</sup>

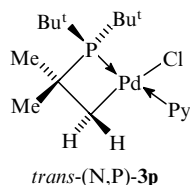


Assuming that the STE of four ligands in complex **2i** varies in a sequence similar to that for platinum compounds



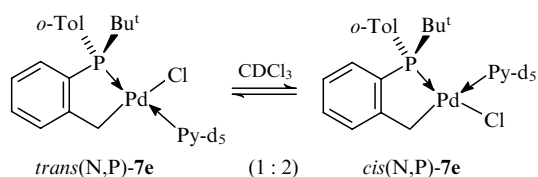
[Ph<sup>−</sup> > PPh<sub>3</sub> > Py > Cl<sup>−</sup>; NMR data ( $J_{\text{Pt-P}}$  158–160)], it is possible to explain the predominance of the *trans*(N,P)-isomer of adduct **2i** in which the softest (Ph<sup>−</sup>) and the hardest (Cl<sup>−</sup>) ligands are arranged on one diagonal.

It has been assumed<sup>88, 103</sup> that the pyridine adduct **3p** with a four-membered PC-palladacycle exists only in the *trans*(N,P)-geometry.<sup>88, 103</sup> This assumption was based on the low frequency  $\nu_{\text{Pd-Cl}} \approx 280 \text{ cm}^{-1}$  in the IR spectra and on the presence of only one signal in the <sup>31</sup>P spectrum and one set of signals in the <sup>1</sup>H NMR spectrum.



At a qualitative level, this is consistent with the STE scale. However, taking into account the change in the hybridisation of the carbon atom ( $\text{sp}^2 \rightarrow \text{sp}^3$ ) and the increase in the basicity of the P atom, one could expect that the STE values for C- and P-donors would approach each other. Indeed, according to NMR data for platinum compounds ( $J_{\text{Pt-P}}$ ), the following STE sequence was elucidated: Ph<sup>−</sup> > Me<sup>−</sup> ≥ PBu<sub>3</sub> > PPh<sub>3</sub> > Py > Cl.<sup>158–160</sup> Therefore, in this case, the existence of two geometric isomers should rather be expected in solutions. The deviation of the experimental data from those predicted in terms of the transphobia principle may be due to a fast equilibrium between the isomers, because the Pd ← N bond in both isomers should be substantially weakened due to the σ-bonded carbon atom or the PAlk<sub>2</sub> group arranged on the same diagonal. The dynamic behaviour of the N-donor ligands is typical of PC-complexes. Their dissociation can be partly suppressed by introducing an excess of the incoming ligand.<sup>60, 90</sup> The spectra of these systems are more informative when recorded at low temperatures.<sup>54</sup>

The regiochemistry predicted in terms of the STE is supported by the spectroscopic detection of comparable amounts of *trans*(N,P)- and *cis*(N,P)-isomers (in 1 : 2 ratio) of the d<sub>5</sub>-pyridine adduct **7e**, which belongs to the structural type characterised by the maximum STE for σ-C(sp<sup>3</sup>)- and PAlk<sub>2</sub>-donors.<sup>90</sup>



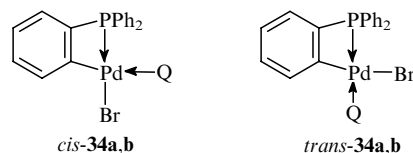
A reliable criterion for determining the geometry of these mononuclear adducts is provided by the opposite directions of shift of <sup>1</sup>H NMR signals for protons located most closely to the metallation site and belonging to P-substituents, caused by their moving towards the pyridine ring (shielding) or towards the halide ligand (deshielding). For example, in the spectrum of the *trans*-(N,P)-isomer of complex **7e**, the signal for the PdCH<sub>2</sub> methylene protons is shifted upfield ( $\Delta\delta = -0.42 \text{ ppm}$ ) with respect to its position in the spectrum of the *cis*(N,P)-isomer, whereas the signal for the PBu<sup>t</sup>-group protons moves downfield ( $\Delta\delta = +0.324 \text{ ppm}$ ).<sup>90</sup> Under the optimal conditions, the difference between the chemical shifts of the same proton in the spectra of the two geometric isomers may reach 2 ppm.<sup>145</sup>

**Adducts with P-donors.** According to the transphobia concept,<sup>152</sup> monodentate phosphines should be more prone to *trans*-coordination relative to the P-donor atom of the phosphine PC-palladacycle (see Supplement 1) than N-donor ligands due to the pronounced destabilisation of the *trans*(P,C)-geometry. Indeed, the coordination of the sterically overcrowded phosphines, phosphites and phospholes to palladacycle **1c** based on trimesitylphosphine yields only *trans*(P,P)-isomers.<sup>94</sup> This is the only form for

the triphenylphosphine adducts of cyclopalladated α-ferrocenyl-alkylphosphines **9b** and **10b**.<sup>78, 79</sup>

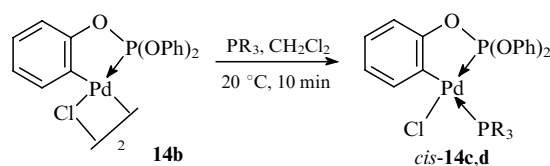
However, as opposed to CN-systems, the coordination of phosphines to phosphapalladacycles is not absolutely *trans*(P,P)-selective. The phosphine adducts formed by sterically non-hindered palladacycles are often formed as mixtures of *cis*- and *trans*-isomers with pronounced predominance of the latter. The recent repeated investigation of cyclopalladated di(*o*-tolyl)-*tert*-butylphosphine (HL<sup>7</sup>) has shown that its triphenylphosphine adduct exists as a mixture of *trans*- and *cis*-isomers (12 : 1).<sup>117</sup> The fact that only the *trans*-isomer was previously identified for this complex by spectroscopy<sup>60</sup> suggests that other non-selective systems of this type may also exist.

The essential deviations of the configuration of complexes from those predicted on the basis of the transphobia concept arise upon modification of the nature of the C- or P-donor centres of the palladacycle or its size. For example, the phosphine adducts of the *ortho*-palladated triphenylphosphine with a strained four-membered palladacycle are formed as mixtures of geometric isomers whose ratio varies over a broad range depending on the structure of the phosphine used.<sup>240, 241</sup>



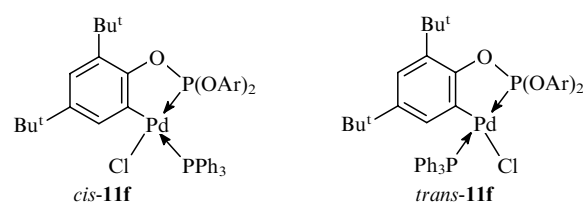
Q = PPh<sub>2</sub>(C<sub>6</sub>H<sub>4</sub>Cl-*o*) (**34a**), P(Tol-*p*)<sub>3</sub> (**34b**);  
*cis* : *trans* = 93 : 7 (**a**), 20 : 80 (**b**).

The regiochemistry of coordination of P-donor ligands to cyclopalladated derivatives of substrates having enhanced π-acidity depends on the electronic characteristics of the ligands and on the steric situation in the coordination sphere. Most triaryl phosphite-<sup>58, 69, 74, 242</sup> and arylphosphinite-based<sup>115</sup> CPCs bind monodentate phosphines and phosphites, preferably in the *cis*(P,P)-geometry (for example, complexes **14c,d**, see Supplement 1). This unusual fact may be explained by the clearly pronounced π-acceptor nature of the phosphorus atom in the phosphite palladacycle,<sup>101</sup> which accounts for system destabilisation upon *trans*-coordination of monodentate π-acceptor phosphites or phosphines.



R = Ph (**14c**, 96%), MeO (**14d**, 89%).

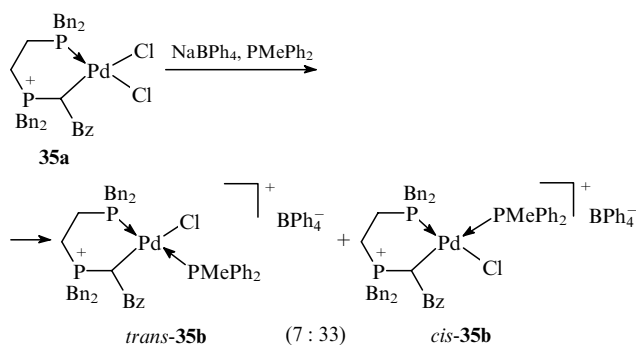
However, in the case of sterically crowded dimer **11a**, the *cis*(P,P)-regiospecificity is retained only in reactions with monodentate phosphites P(OR)<sub>3</sub> (R = Me, Et, Ph),<sup>69</sup> while on passing to phosphine auxiliary ligands, the formation of the *trans*(P,P)-isomer also becomes possible. For example dimer **11a** reacts with PPh<sub>3</sub> to give a mixture of *cis*(P,P)- and *trans*(P,P)-isomers **11f**, the latter being the major product (ratio 1 : 2.4).<sup>69</sup>



Ar = C<sub>6</sub>H<sub>3</sub>Bu<sub>2</sub>-2,4.

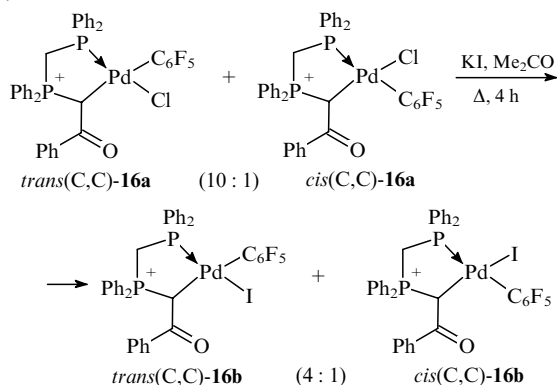
The formation of an isomer mixture has also been detected in reactions of dimer **11a** with  $\text{PCy}_3$  (under certain conditions).<sup>69</sup> In this case, the tendency for the formation of *trans*(P,P)-isomers of the phosphine (but not phosphite) adducts may be due to steric effects. Indeed, phosphines  $\text{PR}_3$  have a greater bulk than phosphites  $\text{P(OR)}_3$  with the same groups. For example, the Tolman cone angles  $\theta$  for the phosphines  $\text{PPh}_3$  and  $\text{PCy}_3$  are 145 and 179°, while for the similar phosphites  $\text{P(OPh)}_3$  and  $\text{P(OPr}^i)_3$ , these angles amount to 121 and 114°, respectively.<sup>95,243</sup> Therefore, the coordination of phosphines in the *cis*-position relative to the bulky  $\text{P(OAr)}_2$  fragment of dimer **11a** should be sterically hampered.

One more example of abnormal regioselectivity is the formation of phosphine derivatives of phosphino-P-ylide palladacycles. The replacement of the carbanion C-centre in cyclopalladated phosphines by an ylide centre (*i.e.*, bearing only a partial negative charge) results in a decrease in its *trans*-effect compared to the STE of the P-donor atom (see Section II.2.c). Under these conditions, one should expect an inverted regiochemistry of the coordination of auxiliary ligands. Indeed, the reaction of dichloride **35a** with phosphine  $\text{PMePh}_2$  yields a mixture of *trans*(P,P)- and *cis*(P,P)-isomers of cationic complex **35b**, the latter being the predominant product.<sup>136</sup>



The preference of the *trans*-coordination of phosphine  $\text{PMePh}_2$  relative to the ylide carbon atom is even more pronounced in its reaction with similar dichloride **15a**; in this case, the *trans*(P,P)- and *cis*(P,P)-isomer ratio for the cationic complex  $[\text{Pd}(\eta^2\text{-L}^{15})\text{Cl}(\text{PMePh}_2)]\text{BPh}_4$  (**15i**) increases to 1:7.<sup>132</sup>

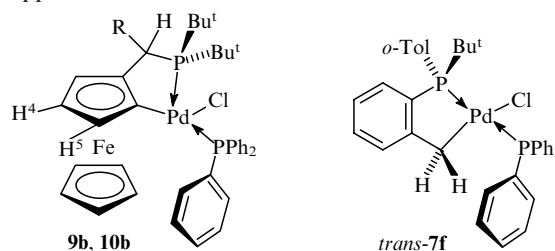
The reduced STE of the ylide carbon can also be illustrated by the preferred formation of the *trans*-(C,C)-isomers of monoarylated derivatives of phosphino-P-ylide palladacycles (this contradicts the formal prediction based on the transphobia concept<sup>111,113,152</sup>). In structures of this type (for example, in complex **16a**), the *trans*-(C,C)- to *cis*-(C,C)-isomer ratio varies over a rather broad range. In chloride complexes, it varies from 3:1 to 10:1. The content of the *cis*-(C,C)-isomer increases when the chloride in complex **16a** is replaced by softer iodide (complex **16b**).<sup>133</sup>



The magnitudes of the spin–spin coupling of two phosphorus nuclei may serve as a reliable criterion for estimating the geometric configuration of the adducts of various PC-palladacycles with P-donor ligands.<sup>244</sup> In the adducts of phosphine- and phosphinite-

based PC-palladacycles with phosphines having the *trans*(P,P)-configuration, the  $^2J_{\text{PP}}$  values vary in the range of 360–441 Hz. The  $^2J_{\text{PP}}$  values increase to 604–607 Hz when a phosphite phosphorus atom appears in either the palladacycle<sup>69</sup> or the auxiliary ligand<sup>94</sup> (see Supplement 1). In complexes having the *cis*(P,P)-geometry, this parameter decreases by more than an order of magnitude ( $^2J_{\text{PP}} = 19\text{--}56$  Hz). The legitimacy of this criterion is confirmed by the fact that in the mononuclear derivatives of PC-palladacycles with diphosphines, the coupling constants between the  $^{31}\text{P}$  nucleus of the metallacycle and diphosphine phosphorus nuclei located in the *trans* and *cis* positions vary approximately in the same ranges ( $^2J_{\text{PP}} = 333\text{--}540$  and  $30\text{--}52$  Hz, respectively).<sup>30,58,69,115</sup>

The  $^1\text{H}$  NMR spectra provide less unambiguous information on the geometric configuration of the coordination sphere of the PC-palladacycle adducts with P-donor ligands. The *trans*(P,P)-geometry of the phosphine adducts of the classical PC-palladacycles (with the phosphine donor atom) can be confirmed by shielding of the PC-palladacycle proton located most closely to the metallation site by the P-aryl groups of the auxiliary ligand.<sup>78,79,90</sup> For example, the  $^1\text{H}$  NMR spectra of the  $\text{PPh}_3$ -adducts **9b**<sup>79</sup> and **10b**<sup>78</sup> show the signal for the  $\text{H}^5$  proton of the palladated cyclopentadienyl fragment shifted upfield by  $\Delta\delta = 1.18$  and 0.92 ppm, respectively, with respect to its position in the spectra of the (*S*)-proline derivatives of the same palladacycles.<sup>90</sup> This effect is less pronounced in compounds with the  $\text{C(sp}^3\text{)}\text{--Pd}$  bond. For example, in the spectrum of adduct **7f**, the  $\Delta\delta$  value for the  $\text{PdCH}_2$ -protons in the *trans*(P,P)-isomer is only 0.33 ppm.<sup>117</sup>

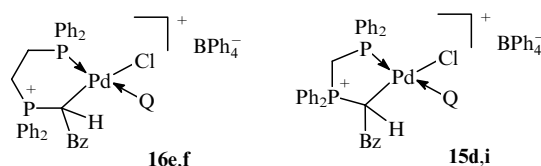


R = H (**9b**), Me (**10b**)

The idea of using, for diagnostic purposes, the direct through-space coupling of the proton nearest to the metallation site with the phosphorus nucleus seems attractive at first glance. However, this criterion should be used with caution. In the case of PC-palladacycle derivatives, the situation is complicated by the presence of two  $^{31}\text{P}$  nuclei, whose effects are to be differentiated. For example, in the  $^1\text{H}$  NMR spectrum of the *trans*(P,P)-isomer of complex **7f**, the diastereotopic protons of the  $\text{Pd--CH}_2$  fragment are coupled with both the  $\text{PPh}_3$  ligand ( $^3J_{\text{HP}} = 11.0$  and 5.7 Hz) and the  $^{31}\text{P}$  nucleus of the phosphapalladacycle ( $^3J_{\text{HP}} = 3.7$  and 2.8 Hz).<sup>117</sup> Since both phosphorus atoms are separated from the  $\text{PdCH}_2$ -protons by three bonds, it seemed justified to assign the much greater spin–spin coupling constants of these protons with the phosphine  $\text{PPh}_3$  to an additional contribution of the through-space coupling of these nuclei. However, the use of this criterion is complicated, first, by the dependence of the coupling constant on the geometry and the nature of bonds separating the nuclei and, second, by the possibility of spin–spin coupling through rather long bond sequences. For example, the spectrum of the complex **9b** mentioned above was found to exhibit quite a detectable constant  $^5J_{\text{HP}} = 0.5$  Hz (through five bonds!) for the remote  $\text{H}^4$  proton of the palladated cyclopentadienyl fragment.<sup>79</sup>

The  $^1\text{H}$  NMR-based criteria proved inapplicable to phosphino-P-ylide analogues. Indeed, a comparison of the chemical shifts of the ylide CH proton in the spectra of the starting dichlorides **15a**, **16d** ( $\delta = 6.05\text{--}6.01$  ppm)<sup>129,134</sup> and their adducts with the phosphines  $\text{PCy}_3$  and  $\text{PPh}_3$ <sup>131,132</sup> shows that the upfield shift of this signal is more pronounced for complexes

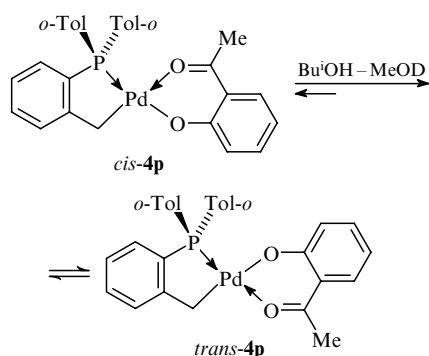
with the aliphatic phosphine ( $\delta = 4.02\text{--}4.47$  ppm for **15i**, **16f**) than with the aromatic one ( $\delta = 4.54\text{--}4.90$  ppm for **15d**, **16e**).



Q = PPh<sub>3</sub> (**15d**, **16e**), PCy<sub>3</sub> (**15i**, **16f**).

The researchers cited assume that this shift is due to either shielding of the ylide proton by the phosphorus nucleus<sup>131</sup> or by the increase in the electron density on the metallic centre upon the introduction of phosphine ligands.<sup>132</sup> The latter version seems more likely in view of the much higher basicity of the aliphatic phosphine compared to the aromatic phosphine (for PCy<sub>3</sub> and PPh<sub>3</sub>,  $pK_a = 9.70$  and  $2.73$ , respectively<sup>101</sup>).

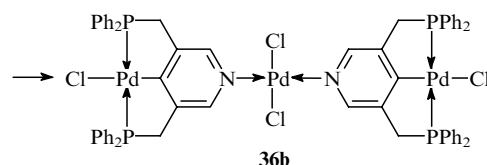
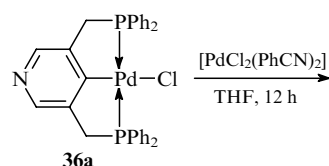
An example of low regioselectivity of coordination of non-symmetric bidentate ligands is provided by 2-acylphenolate derivatives of dimer **4a**, which are formed as mixtures of *cis*- and *trans*-isomers.<sup>118</sup> The researchers were able to increase the regioselectivity by varying the solvent. For example, complex **4p** exists as only the *trans*-isomer in a Bu<sup>t</sup>OH–MeOD mixture, whereas in CCl<sub>4</sub>, d<sub>8</sub>-toluene, C<sub>6</sub>D<sub>6</sub>, d<sub>6</sub>-DMSO and CDCl<sub>3</sub>, the *cis* : *trans* ratio varies from 1 : 2 to 1 : 9.<sup>118</sup>



In conclusion, we would like to note that the transphobia concept,<sup>111, 113, 152</sup> which describes rather adequately the behaviour of CN-palladacycles with respect to Lewis bases, is far from being always applicable to their PC-analogues as the reaction regiochemistry is strongly dependent on the electronic and steric factors. The predictive potential of this concept would be essentially increased by elucidation of detailed and correct *trans*-effect sequences for cyclopalladated compounds differentiated according to the types of P- and C-donors.

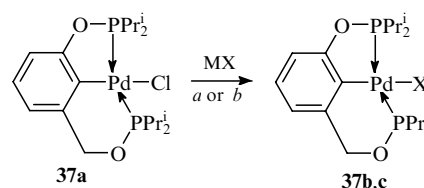
### 3. Bicyclic PCP-complexes

The derivatives of bicyclic PCP-systems are less diverse, because the possibility of their modification is usually restricted to one coordination site. Probably, the 'pincer' compound **36a** with the pyridine core, which can function as a metalloligand due to the pyridine nitrogen atom, is the only exception to this rule. For example, the reaction of this compound with palladium(II) benzonitrile complex affords trinuclear compound **36b** with two PCP fragments at the periphery.<sup>245</sup>



This method for aggregation of cyclometallated complexes may be useful for the design of multicentre polynuclear catalysts.

The standard initial form of PCP-complexes is a monomer with anionic ligand (Hal<sup>−</sup> or RCOO<sup>−</sup>). The exchange of these anions opens up the way to other derivatives. For example, chloride complex **37a**, prepared recently by direct cyclopalladation of non-symmetrical bis(phosphinite) HL<sup>37</sup> by [PdCl<sub>2</sub>(cod)] (cod is cyclo-octa-1,5-diene), was converted into iodide (**37b**) and acetate (**37c**) analogues.<sup>246</sup>

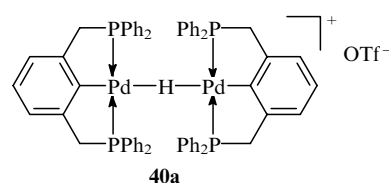
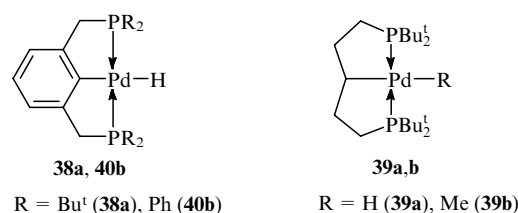


M = Na, Ag; X = I (**37b**), AcO (**37c**);

(a) NaI, Me<sub>2</sub>CO; (b) AgOAc, Et<sub>2</sub>O, ultrasound.

To replace chloride by the softer iodide, complex **37a** should be merely treated with NaI, whereas the replacement of the chloride by harder acetate requires dehalogenation of the initial chloride complex on treatment with AgOAc with ultrasonic activation.

The reactivity of PCP-complexes differs somewhat from that of their monocyclic PC-analogues. The formation of stable hydride derivatives (which are unknown for PC-structures) is the most interesting feature. The mononuclear hydrides, for example, **38a**<sup>247</sup> and **39a**,<sup>248</sup> are prepared by treating the chloride precursors with hydride reagents (NaBH<sub>4</sub> or LiAlH<sub>4</sub>), while the quantitative formation of binuclear hydride **40a** is attained by elimination of the chloride by the action of AgOTf followed by introduction of sodium formate.<sup>249, 250</sup>



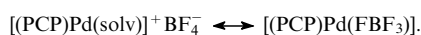
Presumably,<sup>250</sup> the stability of the PCP-complexes with the Pd–H bond unusual for hydrides is determined by efficient shielding of this bond by bulky PBu<sub>2</sub><sup>t</sup> groups. This is consistent with both the higher stability of binuclear hydrides (in which the Pd–H–Pd fragment is not destroyed even under the action of CO or alkenes<sup>249</sup>) compared to the mononuclear ones and the lower stability of mononuclear CPC hydride derivatives based on sterically non-hindered diphosphines. For example, the formation of hydride **40b** from the PCP-complex with PPh<sub>2</sub> groups (through β-H elimination from the amide derivative) has been detected only by spectroscopy, whereas on attempted isolation, it was converted

into more stable binuclear complex **40a** with the bridging hydride ligand.<sup>251</sup> Conversely, mononuclear hydride **39a** with bulky Bu<sup>t</sup> substituents at the phosphorus atoms does not decompose even on heating above 100 °C.<sup>248</sup>

Probably, it is due to the low steric protection of the Pd–H bond in binuclear hydride **40a** that this hydride is easily converted into the chloride [Pd(η<sup>3</sup>-L<sup>40</sup>)Cl] (**40c**). This was the case, for example, on attempted crystallisation of complex **40a** as the BPh<sub>4</sub> salt from a solvent mixture including dichloromethane.<sup>252</sup>

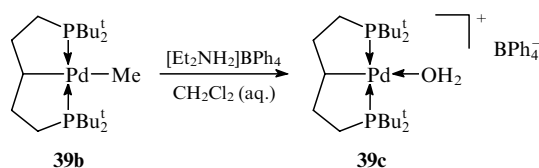
Derivatives of PCP-complexes with molecular hydrogen like [(η<sup>3</sup>-L)Pd(η<sup>2</sup>-H<sub>2</sub>)]<sup>+</sup> might be of interest for the use in catalytic hydrogenation. However, attempts to generate such species by protonation of hydride **38a** with acids such as TfOH, HBF<sub>4</sub>·OEt<sub>2</sub> or [H(OEt)<sub>2</sub>]BAR<sub>4</sub> have not met with success.<sup>253</sup> Note for comparison that platinum analogues have been detected by spectroscopy at low temperatures.<sup>254</sup>

The replacement of the chloride in PCP-complexes by a methyl group on treatment with MeLi is a route to convenient catalyst precursors. Protolysis of these methyl derivatives<sup>255</sup> (for example, on treatment of complex **39b** with the salt [Me<sub>3</sub>NH]BF<sub>4</sub><sup>248</sup>) yields active coordinatively unsaturated species capable of functioning in a catalytic cycle by binding either the substrate or the reagent. These species can also be generated by dehalogenation of appropriate chloride PCP-complexes with AgBF<sub>4</sub> or TlPF<sub>6</sub>.<sup>256</sup> The coordination vacancy is usually occupied by a solvent molecule (THF, dioxane, acetone, CH<sub>2</sub>Cl<sub>2</sub>, CDCl<sub>3</sub>);<sup>256</sup> weak binding of the anion is also possible:<sup>248</sup>



When solvated, PCP-complexes are most convenient for the preparation or generation *in situ* of the adducts with weakly coordinated neutral monodentate ligands. The stability of these cationic adducts depends to a large extent on electronic and steric characteristics of both the PCP-template and the ligand entering the metal coordination sphere.

For example, the solvated derivative of PCP-template **39** with bulky PBu<sub>2</sub><sup>t</sup> groups generated *in situ* by the protolysis of Me-substituted complex **39b** proved incapable of forming adducts with secondary and tertiary amines (Et<sub>2</sub>NH, Me<sub>3</sub>N).<sup>248</sup> In particular, the reaction of compound **39b** with the ammonium salt [Et<sub>2</sub>NH<sub>2</sub>]BPh<sub>4</sub> (this reagent performed a dual function, being a protonating agent and a potential source of the amine ligand) in moist dichloromethane gave aqua complex **39c**, whose structure was confirmed by X-ray diffraction, instead of the expected adduct with the amine.<sup>248</sup>

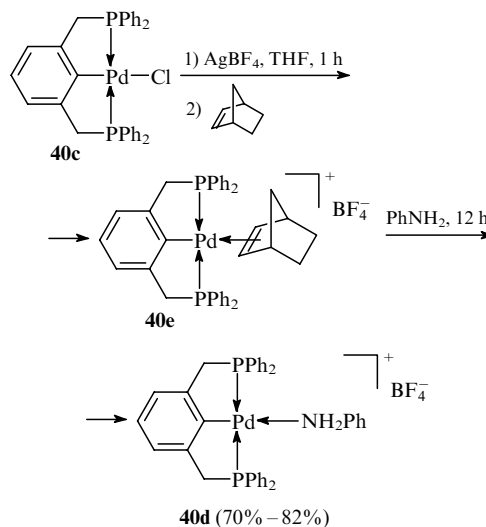


The researchers attributed this outcome to blocking of the newly formed coordination vacancy by bulky PBu<sub>2</sub><sup>t</sup> donor groups of the PCP-template<sup>248</sup> (apparently, some contribution is made by relatively high steric requirements of the amines Et<sub>2</sub>NH and Me<sub>3</sub>N, for which θ = 125 and 132°, respectively<sup>257</sup>).

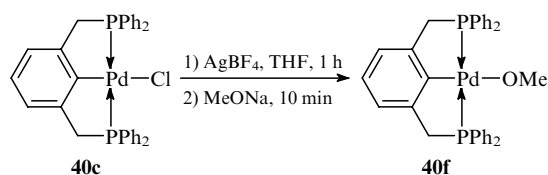
Conversely, complex **40c** with less bulky Ph<sub>2</sub>P donor groups forms an adduct with Me<sub>2</sub>NH,<sup>251, 258</sup> apparently, owing to the less pronounced steric restrictions from both the PCP-core and the amine. After deprotonation of the secondary amine incorporated in [Pd(η<sup>3</sup>-L<sup>40</sup>)(NHMe<sub>2</sub>)]OTf, the amide derivative [Pd(η<sup>3</sup>-L<sup>40</sup>)(NMe<sub>2</sub>)]<sup>+</sup>,<sup>251</sup> an analogue of an intermediate involved in palladium-catalysed amination, has been detected by spectroscopy.<sup>13</sup>

The coordination of the PCP template **40** with aniline is also facilitated by both factors: the lower steric requirements of the PCP-fragment and the relatively small size of the amine (aniline) (θ = 111°).<sup>257</sup> Complex **40d** was prepared in a high yield upon the substitution of aniline for norbornene (nb) in the intermediate

adduct [Pd(η<sup>3</sup>-L<sup>40</sup>)(η<sup>2</sup>-nb)]BF<sub>4</sub> (**40e**) generated *in situ* from chloride **40c**. The structure of complex **40d** was confirmed by X-ray diffraction.<sup>256</sup>

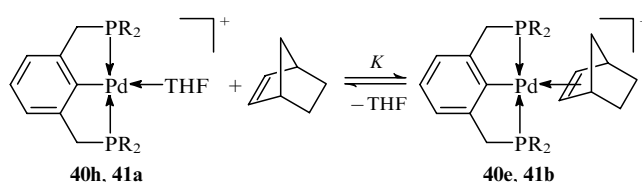


Within the framework of the same study devoted to the simulation of transformations like the Wacker process, hydroxy and some alkoxy derivatives of complex **40c** were synthesised and characterised by spectroscopy.<sup>256</sup> Thus dehalogenation of chloride **40c** with the subsequent introduction of sodium methoxide gave methoxide **40f**.<sup>256</sup>



Undoubtedly, a substantial contribution to weakening of the palladium bond with the incoming monodentate ligand is made by the strong *trans*-effect of the carbanionic centre of the PCP-template located opposite to this ligand. As an illustration, one can consider the protolytic displacement of the relatively small aliphatic phosphine PEt<sub>3</sub> (θ = 132°) from the complex [Pd(η<sup>3</sup>-L<sup>40</sup>)(PEt<sub>3</sub>)]BF<sub>4</sub> (**40g**) with the sterically non-hindered template. The structure of adduct **40g** was confirmed by X-ray diffraction.<sup>259</sup> The displacement of the phosphine from the coordination sphere is attained by mere treatment of complex **40g** with a 0.1 M solution of HBF<sub>4</sub> in MeCN. The initial CPC can be regenerated as the acetonitrile solvate. It is significant that the attempts to displace PEt<sub>3</sub> from its adducts with PNP-, PSP- and POP-templates containing the central heterodonor atom failed.

The possibility of the electronic control of the complexation of PCP-templates with additional ligands is illustrated by the results of a study dealing with norbornene binding to two complexes differing by the P-substituents. Adducts **40e** and **41b** have not been isolated due to the substantial weakening of alkene coordination, caused by the pronounced *trans*-effect of the carbanion centre of the PCP-template, but they have been identified by spectroscopy. Determination of the equilibrium constants between the starting solvates **40h**, **41a** and their norbornene adducts **40e**, **41b** showed

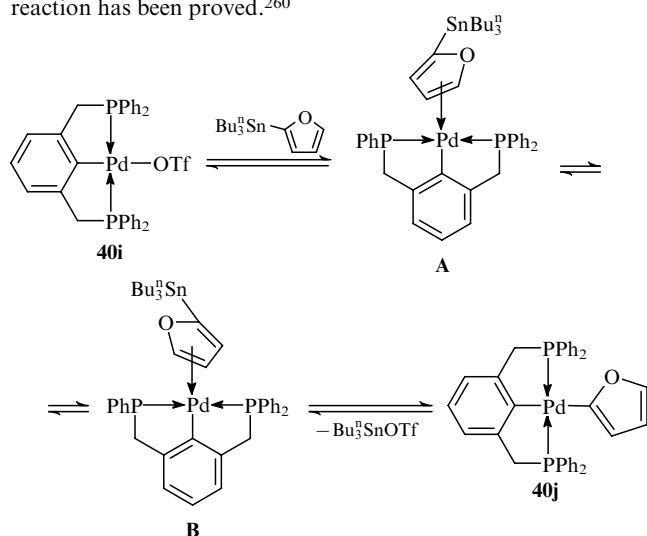


R = Ph (**40h,e**; K = 0.17), 4-Me<sub>2</sub>NC<sub>6</sub>H<sub>4</sub> (**41a,b**; K = 0.41).

that binding of the bicyclic alkene becomes stronger upon the introduction of the electron-donor  $\text{Me}_2\text{N}$  substituents into the benzene rings of the template  $\text{PPh}_2$  groups.<sup>256</sup>

The high stability of the alkene adduct **41b** is attributed to the increase in the electron density on the metal (the effect is transmitted from the heterodonor  $\text{PAr}_2$  groups), resulting in a greater contribution of the back  $d\text{-}\pi$ -backbonding of the metal to the alkene.<sup>256</sup>

The above examples clearly demonstrate the good prospects for the use of PCP-structures for stoichiometric simulation of the intermediates in the catalytic processes. This becomes possible due to the exceptionally high stability of this type of CPC, caused by the efficient steric shielding of the reaction centre. Using PCP-complex **40i** as the catalyst, the intermediates in the Stille coupling have been identified and the  $\text{Pd}^{\text{II}}/\text{Pd}^{\text{IV}}$  route of this catalytic reaction has been proved.<sup>260</sup>



The hetarylation product of catalyst **40i** with  $\alpha$ -stannylfuran, complex **40j**, has been not only isolated but also studied by X-ray diffraction. The intermediate with a  $\eta^2$ -coordinated organotin reagent existing as two isomers **A** and **B**, which directly precedes complex **40j** in the catalytic cycle, has been identified by low-temperature spectroscopy. The structure and stereochemistry of complexes **A** and **B** in solutions were convincingly proved by the whole set of advanced spectral methods ( $^1\text{H}$ ,  $^{31}\text{P}$ ,  $^{119}\text{Sn}$  NMR) including the NOE technique (Nuclear Overhauser Effect).

As a result, the sequence of reversible stages of this process was established and the thermodynamic parameters for substrate  $\eta^2$ -coordination and transmetalation were determined.<sup>260</sup>

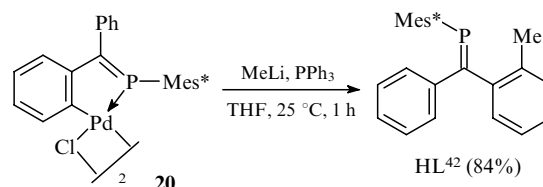
### III. Transformations of phosphapalladacycles

We have discussed so far the reactions that involved the metallic centre but left the phosphapalladacycles intact, only the metal coordination environment being varied due to the introduction of auxiliary ligands. This Section deals with processes affecting the metal-containing rings. These can be divided into three types: (1) reactions at the  $\text{Pd}-\text{C}$  bond of the palladacycle, which allow regioselective introduction of substituents into the initial P-containing ligand (Section III.1); (2) structural modification of the phosphapalladacycle not affecting the  $\text{Pd}-\text{C}$  and  $\text{Pd}-\text{P}$  bonds (Section III.2); (3) dechelation and destruction of PC-palladacycles (Section III.3).

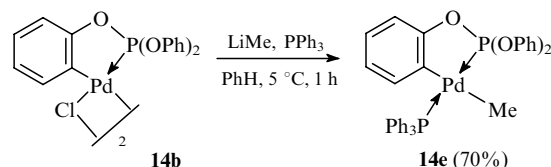
#### 1. Reactions of phosphapalladacycles involving the $\text{Pd}-\text{C}$ bond

The reactions of phosphapalladacycles involving the  $\text{Pd}-\text{C}$  bond are of considerable interest as a method for regioselective modification of the P-donor ligands. Unlike CN-palladacycles for which these reactions have been extensively studied within the framework of development of the routes of regioselective organic

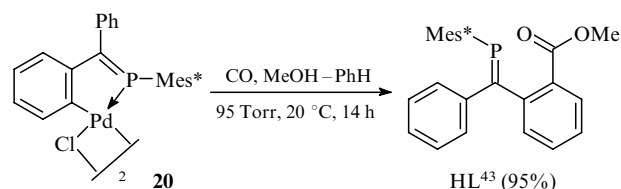
synthesis,<sup>261–265</sup> studies of the transformations of PC-palladacycles are limited to a few examples. Of the few known publications, a brief communication dealing with the reactions of cyclopalladated phosphalkenes with some nucleophiles deserves attention.<sup>86</sup> Thus by treating the dimeric complex **20** with an organolithium reagent in the presence of triphenylphosphine, the *ortho*-methylated analogue of the initial ligand HL<sup>20</sup>, phosphalkene HL<sup>42</sup>, has been obtained.



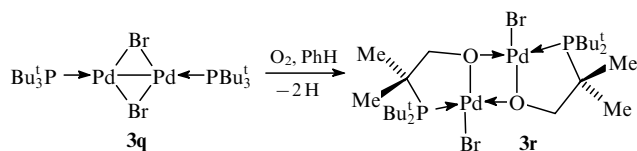
When MeLi was replaced by  $\text{Bu}^n\text{Li}$  or PhLi, the product yield markedly decreased and alkylation with more bulky  $\text{Bu}^n\text{Li}$  proved impossible at all (apparently, due to steric restrictions). It should be noted that an attempt to obtain *ortho*-substituted phosphites failed: in this case, the reaction stopped after replacement of the chloride in the intermediate phosphine adduct  $[\text{Pd}(\eta^2\text{-L})(\text{PPh}_3)\text{Cl}]$  by the organic ligand R. For example, dimer **14b** is converted into mononuclear complex **14e** under these conditions.<sup>74</sup>



The carbonylation of the phosphalkene complex **20** at room temperature but at high CO pressure gave new ligand HL<sup>43</sup>, containing a methoxycarbonyl group in the *ortho*-position of one benzene ring, in an almost quantitative yield.<sup>86</sup>



Two other examples of reactions involving the  $\text{Pd}-\text{C}$  bond refer to transformations of strained four-membered PC-palladacycles. The oxidation of dimeric  $\text{Pd}(\text{I})$  complex **3q** with atmospheric oxygen affords binuclear  $\text{Pd}(\text{II})$  complex **3r** with a new phosphino-alcoholate ligand.<sup>176</sup>

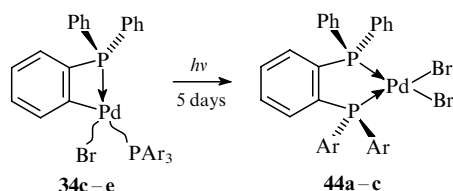


In view of the ease of cyclopalladation of tris(*tert*-butyl)phosphine,<sup>12</sup> participation of a cyclopalladated intermediate in the oxidation of complex **3q** seems quite practicable, the more so, because a small amount of the dimeric CPC  $[(\eta^2\text{-L}^3)\text{Pd}(\mu\text{-Br})_2]$  (**3o**) has been isolated from the reaction mixture. Presumably, this process includes coordination of the oxygen molecule, cleavage of the metal-activated  $\text{O}=\text{O}$  bond, cyclopalladation of the phosphines and the subsequent formal insertion of oxygen into the resulting  $\text{Pd}-\text{C}$  bond. The structures of both the final product **3r** and intermediate dimer **3o** were proved by X-ray diffraction analysis.<sup>176</sup>

It is noteworthy that the  $\mu$ -iodide analogue of complex **3q** was absolutely inert with respect to atmospheric oxygen. The depend-

ence of the ability of compounds of this class to undergo oxidative addition on the nature of the halide ( $\text{Br} \gg \text{I}$ ) has also been noted for their reactions with other small molecules ( $\text{CO}$ ,  $\text{H}_2$ ,  $\text{RCN}$ ).<sup>176</sup>

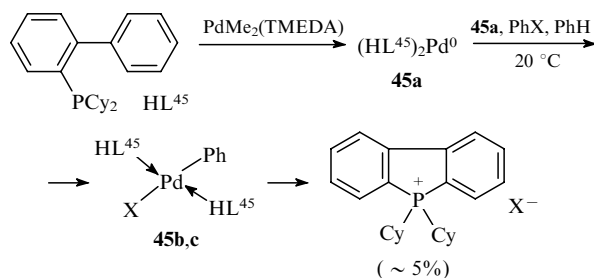
A more practically interesting process has been discovered in a study of the behaviour of phosphine adduct **34c**, containing sterically strained four-membered PC-palladacycle, under photochemical activation.<sup>266</sup> A mixture of *cis*- and *trans*-isomers of this complex in the solid state is converted in the light at room temperature into coordination compound **44a** with *o*-phenylenediphosphine, formed upon the formal insertion of the  $\text{PPh}_2$  group into the  $\text{Pd}-\text{C}$  bond. The fact that the second phosphine fragment  $\text{PPh}_2$  is formed from the phosphine  $\text{PPh}_3$ , bound in the monodentate mode in the initial complex **34c**, was confirmed by experiments with deuterated ( $\text{Ar} = \text{C}_6\text{D}_5$ , complex **34d**) and structurally modified ( $\text{Ar} = \text{Tol-}p$ , complex **34e**) analogues of adduct **34c**. The structure of one product of this unusual reaction, complex **44a**, was proved by X-ray diffraction.



$\text{Ar} = \text{Ph}$  (**34c**, **44a**),  $\text{C}_6\text{D}_5$  (**34d**, **44b**),  $\text{Tol-}p$  (**34e**, **44c**).

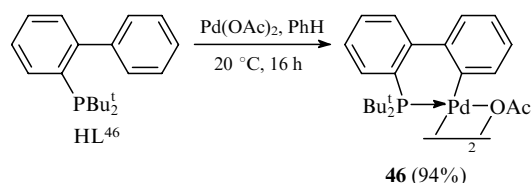
Apparently, the formation of the  $\text{P}-\text{C}$  bond may be either an inter- or an intramolecular process. A study of the reactions of aryl halides with  $\text{Pd}(0)$  complex **45a** containing bulky phosphine ligands  $\text{HL}^{45}$  has shown the formation (in addition to the standard oxidative addition products **45b,c**) of a small amount ( $\sim 5\%$ ) of cyclic phosphonium salts.<sup>267</sup>

The structures of complex **45a** and two phosphonium salts with  $\text{X}^- = \text{Br}^-$  and  $\text{I}^-$  were confirmed by X-ray diffraction. When discussing the origin of these salts, the authors reasonably suggest that they result from metallation of the *ortho*-carbon atom in the remote benzene ring of the biphenylphosphine  $\text{HL}^{45}$  followed by reductive elimination of the  $\text{P}-\text{C}$  bond in the intermediate phosphapalladacycle.



$\text{X} = \text{Br}$  (**45b**),  $\text{I}$  (**45c**); TMEDA —  $\text{Me}_2\text{N}(\text{CH}_2)_2\text{NMe}_2$ .

This reaction route is supported by a number of considerations. First, a similar six-membered phosphapalladacycle **46** has been obtained recently in an almost quantitative yield under mild conditions.<sup>18</sup>

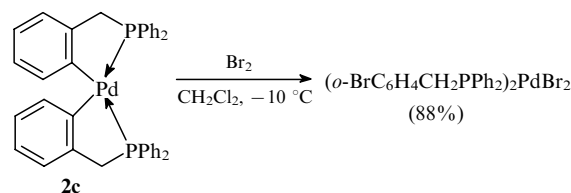


Second, X-ray diffraction and spectroscopic studies of the  $\text{Pd}(0)$ -containing starting complex **45a** has revealed  $\pi$ -coordination of the metal to the remote benzene ring of biphenylphosphine, which is usually considered as an initial step of cyclometallation.<sup>12</sup> Presumably, interactions of this type are also possible in com-

plexes **45b,c**, containing  $\text{Pd}(\text{II})$ . Finally, the presence of the  $\text{Ph}-\text{Pd}$  fragment in intermediate complexes **45b,c** should largely facilitate the cyclometallation.<sup>12</sup>

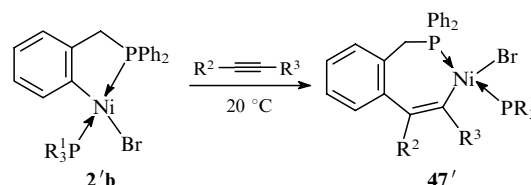
Note for comparison that the intermolecular formal insertion of the  $\text{PR}^1\text{R}^2$  fragments into the  $\text{Pd}-\text{C}$  bond of more stable five-membered  $\text{CN}$ -palladacycles has been carried out only using lithium phosphides  $\text{LiPR}^1\text{R}^2$  (Refs 268–270) or  $\text{PhPCl}_2$ .<sup>271</sup>

Studies of the reactivity of bis(chelate) *spiro*-PC-complexes of benzylphosphines have shown that their reactions with bromine result in the destruction of the phosphapalladacycle through the formal insertion of bromine into the  $\text{Pd}-\text{C}$  bond. This gave coordination complexes of palladium bromide with *ortho*-brominated phosphines in high yields.<sup>67</sup>



A practical significance of this process is problematic, because *o*-bromobenzylphosphines formed serve as the starting substrates for the synthesis of *ortho*-lithiated ligands (in particular,  $\text{LiL}^2$ ), necessary for the preparation of *spiro*-complexes. Note for comparison that analogous platinum(II) compounds undergo oxidative addition under these conditions with retention of the phosphametallacycle in the intermediate platinum(IV) complexes of the type  $[(\text{P}^{\text{C}})_2\text{PtBr}_2]$ .<sup>67, 71</sup>

Strange as it seems, reactions of phosphapalladacycles with alkynes have not yet been studied, although this line of research is being developed most extensively in the chemistry of  $\text{CN}$ -analogues.<sup>263, 264</sup> The possibility of these reactions for PC-complexes is supported by their implementation for nickel analogues like **2'b** under exceptionally mild conditions.<sup>272, 273</sup>



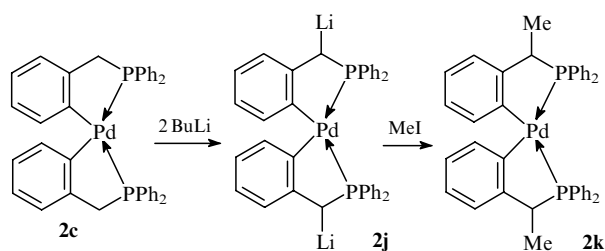
The structure of the products of formal insertion of alkyne into the  $\text{M}-\text{C}$  bond (complexes **47'**) was proved by various methods including X-ray diffraction analysis.<sup>272, 273</sup> Theoretical studies of insertion were carried out.<sup>274</sup>

If one takes into account the fact that the initial phosphanickelacycles are obtained by oxidative addition of *ortho*-bromosubstituted benzylphosphines to  $[\text{Ni}(\text{cod})_2]$ , while their palladium analogues are prepared by direct intramolecular activation of the  $\text{C}-\text{H}$  bond in unsubstituted phosphine,<sup>12, 54</sup> development of similar processes for phosphapalladacycles seems quite a promising path in the regioselective organic synthesis.

## 2. Modification of phosphapalladacycles with retention of the $\text{Pd}-\text{C}$ bond

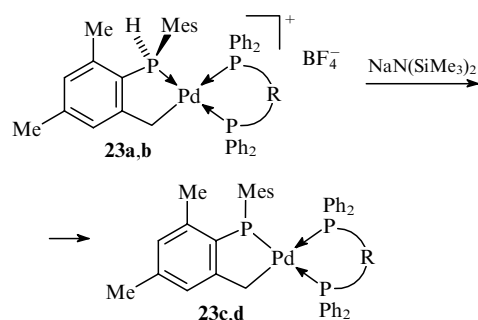
The functionalisation of  $\text{P}$ -donor ligands activated by cyclometallation not involving the  $\text{Pd}-\text{C}$  bond is even less studied. Of certain practical value is the electronic and steric modification of the benzylphosphine ligands incorporated in bis(chelate) cyclopalladated complexes by lithiation<sup>†</sup> into the  $\alpha$ -position followed by 'quenching' of the carbanion formed with an appropriate electrophile.<sup>71, 275</sup>

<sup>†</sup> Note for comparison that reactions of  $\text{CN}$ -palladacycles with organolithium reagents involve the  $\text{Pd}-\text{C}$  bond.<sup>264</sup>



Using platinum analogues, it has been shown that this procedure ensures the introduction of not only alkyl groups but also silyl or phosphine groups ( $\text{Me}_3\text{Si}$ ,  $\text{Ph}_2\text{P}$ ) into the  $\alpha$ -position of the benzyl fragment.<sup>71, 275</sup> The reactions of cyclopalladated benzylphosphine ligands with salts of other metals, for example, with  $[\text{AuCl}(\text{PPh}_3)]$ , give heterobimetallic compounds with two different  $\text{M}-\text{C}$  bonds.<sup>275</sup> An advantage of this method for modification of benzylphosphines is the regioselectivity of metallation, which involves only the  $\alpha$ -benzyl position, whereas in the case of lithiation of free ligands, several routes are possible.<sup>12</sup>

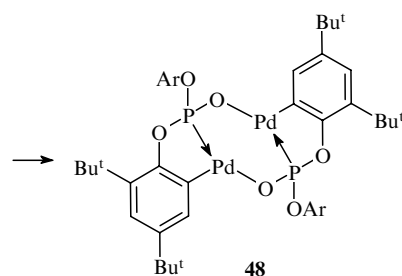
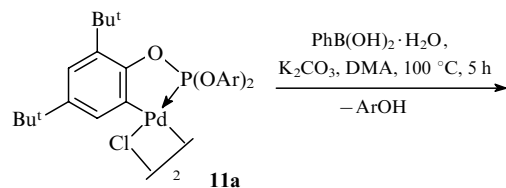
One more example of modification of a phosphapalladacycle not affecting the  $\text{Pd}-\text{C}$  and  $\text{Pd}-\text{P}$  bonds is the deprotonation of the cationic derivatives of the cyclopalladated secondary phosphine  $\text{HPMe}_2$  (**23a** and **23b**) by treatment with the silylamides  $\text{M}'\text{N}(\text{SiMe}_3)_2$  ( $\text{M}' = \text{Li}$  or  $\text{Na}$ ) as bases.<sup>276</sup>



$\text{R} = \text{CH}_2\text{CH}_2$  (**23a,c**, 55%), *cis*- $\text{CH}=\text{CH}$  (**23b,d**, 82%).

The resulting neutral complexes **23c,d**, containing an unusual non-charged phosphapalladacycle with a covalent  $\text{Pd}-\text{P}$  bond (rather than the coordination  $\text{Pd} \leftarrow \text{P}$  bond, as all of the structures considered previously), are distinguished by high stability and do not tend to decompose through the reductive elimination of the  $\text{P}-\text{C}$  bond. In the case of analogues of complexes **23c,d** with a monodentate phosphite (for example,  $[(\text{dppe})\text{MePd}-\text{P}(\text{H}).\text{Mes}^*)]$ ), this process takes place even below room temperature. It is typical of organometallic complexes with a terminal phosphide ligand.<sup>276</sup>

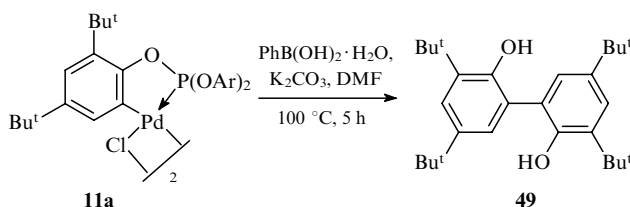
In order to evaluate the activation routes of phosphite- and phosphinite-based cyclopalladated catalysts, the behaviour of triarylphosphite derivative **11a** has been studied under the conditions used normally to prepare biaryls by the Suzuki reaction.<sup>277</sup> Heating of dimer **11a** with phenylboronic acid hydrate in dimethylacetamide (DMA) in the presence of a base furnished unusual CPC dimer **48**, containing the central six-membered  $\{\text{Pd}_2\text{P}_2\text{O}_2\}$  ring (the structure of dimer **48** was established by X-ray diffraction).



$\text{Ar} = 2,4\text{-Bu}_2\text{C}_6\text{H}_3$ .

Dimer **48** is a cyclopalladated derivative of diarylphosphite  $(\text{ArO})_2\text{P}(\text{OH})$  ( $\text{H}_2\text{L}^{48}$ ), formed upon the hydrolytic elimination of an aryl group from the initial triarylphosphite  $\text{HL}^{11}$ . The bridging function in dimer **48** is performed by the oxygen atoms of the deprotonated hydroxy group of the diarylphosphite ligand. The hydrated reagent  $\text{PhB}(\text{OH})_2 \cdot \text{H}_2\text{O}$  is assumed to serve as the source of water needed for hydrolysis.

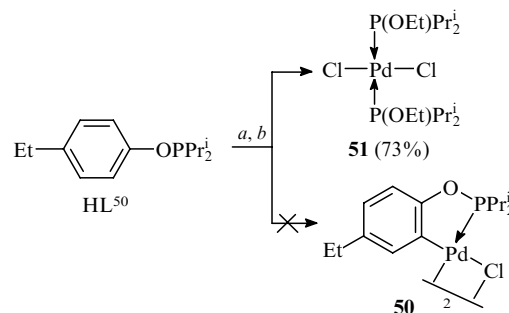
In the same reaction carried out in DMF, biphenol **49** was formed upon the oxidative coupling of two aryloxy fragments; its structure was confirmed by X-ray diffraction.<sup>277</sup>



$\text{Ar} = 2,4\text{-Bu}_2\text{C}_6\text{H}_3$ .

The true mechanism of this transformation is unknown. The researchers consider two possible routes: (1) coupling involving free phenol molecules, liberated upon hydrolysis of CPC **11a** (see above), assisted by the metal centre; (2) coupling between two aryloxy fragments incorporated into phosphite ligands (this route includes intramolecular reorganisation and reductive elimination).

It is reasonable to suggest that the ligands in cyclopalladated phosphites and phosphinites can undergo not only hydrolysis but also solvolysis under appropriate conditions. Unfortunately, no reliable information on this subject is available; it is only known<sup>277</sup> that an attempted *ortho*-palladation of aryldialkylphosphinite  $\text{HL}^{50}$  with  $\text{PdCl}_2$  on refluxing in 2-methoxyethanol (MET) (a) followed by recrystallisation from a  $\text{EtOH}-\text{CH}_2\text{Cl}_2$  mixture (b) gave, instead of the expected CPC **50**, coordination complex **51**, whose structure was proved by X-ray diffraction.



In the researchers' opinion, the new phosphinite  $\text{P}(\text{OEt})\text{Pr}_2^i$  ( $\text{HL}^{51}$ ) is the product of transesterification of the initial ligand  $\text{HL}^{50}$  with the solvent. However, the instant the solvolysis takes place remains unknown; this may occur either within the coordination intermediate  $[\text{Pd}(\text{HL}^{50})_2\text{Cl}_2]$  or in the intermediate CPC **50**, because no attempts to carry out solvolysis of dimer **50** have been

made. It is only known<sup>277</sup> that palladium complexes with less electron-enriched aryl diarylphosphinites  $\text{P}(\text{OAr})\text{Ar}_2$  and triaryl phosphites  $\text{P}(\text{OAr})_3$  are not susceptible to transesterification.

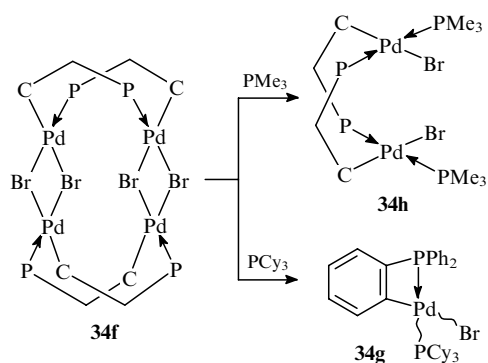
### 3. Dechelation and destruction of phosphapalladacycles

Three variants of cleavage of palladacycles without modification of the ligand structure are, in principle, possible: (1) transition to a monodentate coordination due to cleavage of the  $\text{Pd} \leftarrow \text{E}$  bond ( $\text{E}$  is the heteroatom); (2) the same due to cleavage of the  $\text{Pd} - \text{C}$  bond; (3) transformation of a chelating ligand into a bridging one. The first route is typical of  $\text{CN}^-$ ,<sup>111, 198, 278–280</sup> and  $\text{CO}$ -palladacycles<sup>281</sup> with hard heterodonor nitrogen and oxygen atoms, which are readily displaced from the metal coordination sphere by excess auxiliary ligand with a softer donor atom (most often, phosphine). This gives mononuclear complexes *trans*- $[(\eta^1\text{-E}^-\text{C})\text{PdX}(\text{PR}_3)_2]$  ( $\text{E} = \text{N}, \text{O}$ ) with the monodentate  $\eta^1\text{-C}$ -bonded ligand (the heterodonor  $\text{E}$  atom remains in the non-coordinated state). The other two variants are unlikely for systems with hard heterodonor atoms, as they are weakly coordinated to soft palladium. To our knowledge, only one structure with a bridging  $\text{CN}$ -ligand has been reported.<sup>282</sup>

#### a. Dechelation of phosphapalladacycles

In the case of phosphapalladacycles, decoordination of the heterodonor atom appears problematic due to the strong binding of the soft phosphorus atom to the soft palladium centre. We have not found any examples of dechelation of  $\text{PC}$ -structures according to this pattern. The cleavage of  $\text{PC}$ -palladacycles is accompanied most often by transition of the ligand from the  $\eta^2$ -binding to bridging position.

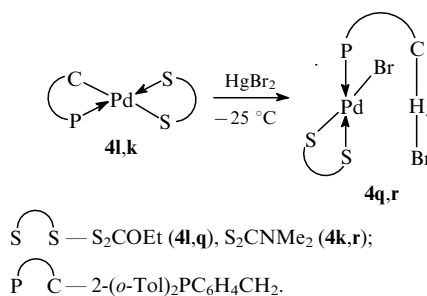
As an illustration, one can consider the dechelation of cyclopalladated triphenylphosphine.<sup>241</sup> The steric strain of the four-membered phosphapalladacycle with the  $\text{Pd}-\text{C}(\text{sp}^2)$  bond accounts for its easy opening to give the tetramer  $[\{\text{Pd}(\mu\text{-L}^{34})(\mu\text{-X})\}_4]$  (**34f**) with bridging  $\text{P}, \text{C}$ -bound ligands  $(\text{L}^{34})^-$ , which combine four metallic centres to form a macrocycle. The mononuclear species with this  $\text{PC}$ -palladacycle really exist in solutions only in the presence of excess auxiliary phosphine ligand, the equilibrium between complexes with ligands of two types —  $\mu\text{-L}^{34}$  and  $\eta^2\text{-L}^{34}$  — being displaced towards the cyclopalladated structure (for example, **34g**) with an increase in the steric requirements of the auxiliary ligand (when  $\theta > 150^\circ$ ).<sup>241</sup>



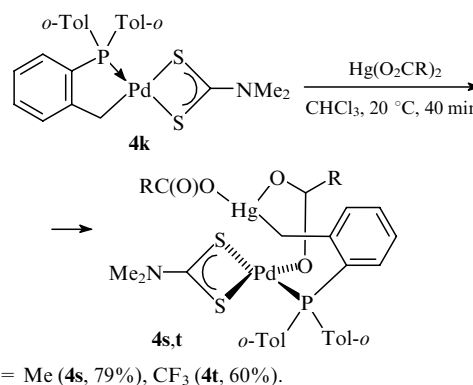
It is noteworthy that structures with the bridging  $\text{PC}$ -ligands like  $(\text{R}_2\text{PC}_6\text{H}_4)^-$  are frequently encountered in dirhodium complexes,<sup>283–288</sup> in which they form the five-membered rings  $\{\text{RhPCCRh}\}$  involving the  $\text{Rh}_2$  fragment.

At first glance, this type of dechelation with transition from  $\eta^2$ - to  $\mu$ -binding of the  $\text{PC}$ -ligand may seem impracticable for non-strained and rather stable five-membered phosphapalladacycles. Nevertheless, transformations of this type are still possible under certain conditions. For example, the reaction of xanthate (**4l**) and dithiocarbamate (**4k**) derivatives of cyclopalladated tris(*o*-tolyl)-phosphine with mercury bromide gave binuclear heterobimetallic

compounds **4q,r** with the bridging anionic ligand  $(\mu\text{-L}^4)^-$  (see Ref. 53).



The dechelation giving analogous binuclear compounds **4s,t** has also been observed in the reaction of complex **4k** with mercury dicarboxylates.<sup>122</sup>



$\text{R} = \text{Me}$  (**4s**, 79%),  $\text{CF}_3$  (**4t**, 60%).

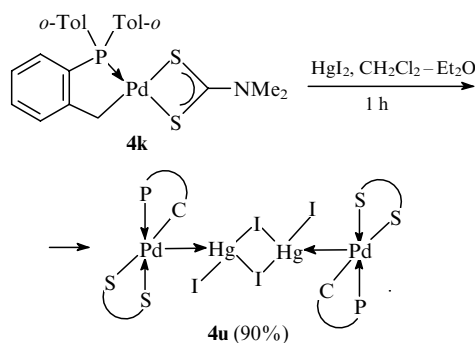
The structures of complexes **4q**<sup>53</sup> and **4s**<sup>122</sup> were proved by X-ray diffraction. In both cases, the bridging ligand  $(\text{L}^4)^-$  remains  $\text{P}$ -coordinated to palladium, the carbanionic centre being lent to mercury. As was to be expected, compounds of this type are relatively unstable. For example, halide complexes **4q,r** dissociate in solutions at room temperature with recovery of the starting  $\text{CPCs}$  **4l,k**; this process can be 'frozen' by lowering the temperature to  $-55^\circ\text{C}$  only in the case of dithiocarbamate derivative **4k**.<sup>53</sup>

A number of unusual features of these processes deserve attention. First, fairly unexpected is the cleavage of the  $\text{Pd}-\text{C}$  covalent bond rather than the  $\text{Pd} \leftarrow \text{P}$  coordination bond. In principle, this result can be attributed to stronger binding of palladium(II) to phosphorus than to the carbanionic fragment of the  $\text{PC}$  ligand (see Section II.2.c). However, the reason may also be in the reaction mechanism. The transmetalation is assumed<sup>122</sup> to occur *via* an electrophilic attack by the mercury salt on the  $\text{Pd}-\text{C}(\text{sp}^3)$  bond rather than on the  $\text{Pd}(\text{II})$  centre or, the more so, the phosphorus atom.

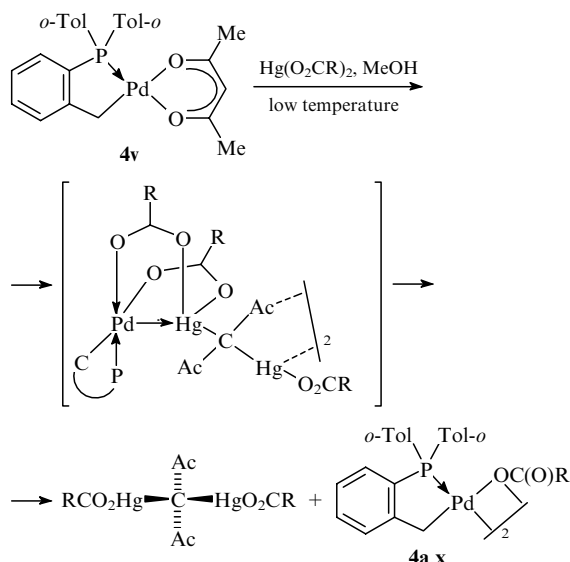
The second unusual fact is that mercury(II), having high affinity to  $\text{S}$ -donor atoms, remains indifferent towards the dithiocarboxylate ligands. Note for comparison that an X-ray diffraction study of the structure of the binuclear compound  $[\text{Pt}(\eta^2\text{-L}^4)(\kappa^2\text{-}\mu\text{-S}_2\text{CNMe}_2)\{\text{Ag}(\text{PPh}_3)\}]$ , isolated upon the reaction of the platinum analogue of complex **4k** with  $[\text{Ag}(\text{OCIO}_3)(\text{PPh}_3)]$ , revealed the interaction of the silver ion with one sulfur atom of the dithiocarbamate ligand.<sup>123</sup>

The third unusual fact is the strong influence of not only the nature of the metal incorporated into the  $\text{PC}$ -metallacycle but also the auxiliary ligand and the anion in the mercury salt on the reaction pathway. For example, in the reaction of dithiocarbamate **4k** with  $\text{HgI}_2$  carried out under mild conditions, the  $\text{PC}$ -palladacycle is retained, the reaction yielding the tetranuclear complex with a dative  $\text{Pd} \rightarrow \text{Hg}$  bond.<sup>53</sup>





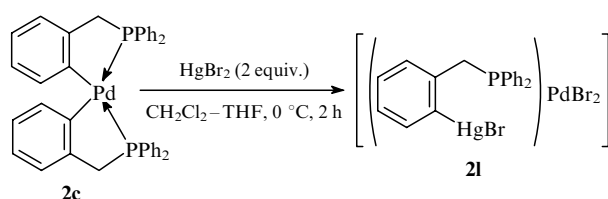
However, a close analogue of this complex — xanthate derivative **4l** of the same palladacycle — does not react with mercury iodide even on refluxing.<sup>53</sup> The reactions of the acetylacetonate derivative **4v** with mercury bromide and carboxylate were found to result in the recovery of the starting  $\mu$ -bromide (**4w**) or  $\mu$ -carboxylate dimeric CPCs (**4a** or **4x**). In the latter case, the  $\beta$ -diketonate ligand is displaced from the palladium(II) coordination sphere by mercury in the  $\gamma$ -C-bound state, as the compound  $[\text{Ac}_2\text{C}(\text{HgO}_2\text{CR})_2]$  ( $\text{R} = \text{Me}, \text{CF}_3$ ).<sup>121</sup>



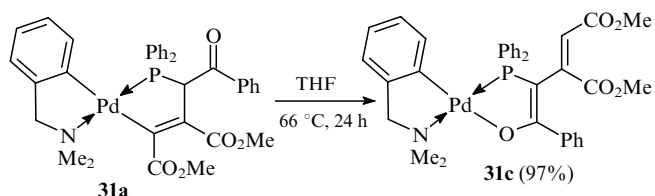
$\text{R} = \text{Me}$  (**4a**),  $\text{CF}_3$  (**4x**).

The behaviour of the platinum analogues in the reactions with mercury salts differs appreciably from the behaviour of PC-palladacycles such as **4**. For platinum systems, the formation of donor–acceptor  $\text{Pt} \rightarrow \text{Hg}$  bonds is most typical;<sup>53, 121, 289</sup> the oxidative addition of  $\text{HgX}_2$  to give  $\text{Pt}(\text{IV})$  compounds is also possible.<sup>122</sup> However, no examples of dechelation of PC-platinacycles have been found so far.

Note that dechelation induced by mercuriation has also been observed for a five-membered PC-palladacycle with a  $\text{C}(\text{sp}^2) - \text{Pd}$  bond incorporated in *spiro*-complex **2c** when it has been made to react with mercury bromide.<sup>71</sup> In this case, mercury also attacks the carbon end of the palladacycle to give coordination complex **2l** with the monodentate P-coordinated *ortho*-mercurated phosphine.



An absolutely different principle underlies the cleavage of the phosphapalladacycle in *spiro*-complex **31a**. The thermolysis of this complex is accompanied by almost quantitative isomerisation of the PC-palladacycle into PO-chelating phosphinoenolate to give complex **31c**. This process also involves rupture of the  $\text{Pd} - \text{C}$  bond (but not the  $\text{Pd} \leftarrow \text{P}$  bond) followed by 1,3-migration of hydrogen from the carbon atom adjacent to phosphorus to the metallated alkenyl carbon atom.<sup>237, 239</sup>

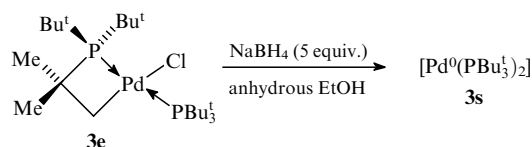


The structure of complex **31c** and the retention of the *E*-configuration of the exocyclic alkene fragment were confirmed by X-ray diffraction.<sup>239</sup> The researchers assume the tendency for the formation of a system of conjugated double bonds in the new  $\beta$ -phosphinoenolate ligand to be the driving force of the process.<sup>237</sup> However, if one estimates the relative stability of complexes **31a** and **31c** from the standpoint of the transphobia concept, the higher stability of the latter may be due to the replacement of the unfavourable *trans*-arrangement of two carbanionic centres ( $\text{C} - \text{Pd} - \text{C}$ ) with the highest *trans*-effect in one axis by a more favourable combination of the softest and the hardest donor atoms on one diagonal ( $\text{C} - \text{Pd} - \text{O}$ ). This also accounts for more preferred binding, unexpected at first glance, of the soft palladium to the hard enolate oxygen atom rather than to the soft carbanionic atom.

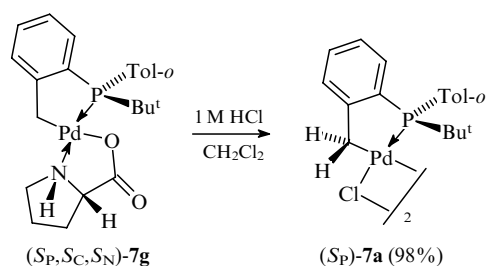
## b. Destruction of phosphapalladacycles

A fundamentally different pattern of cleavage of phosphapalladacycles is induced by treatment with reducing agents or acids. In this case, the reaction involves the  $\text{Pd} - \text{C}$  bond and results in the recovery of the ligand HL. However, unlike these processes for CN-systems, in this case, the liberated ligand remains bound to palladium through the heteroatom to form a coordination compound. These reactions carried out with deuterated reagents ( $\text{DCl}$  or  $\text{LiAlD}_4$ ) can be used, in principle, for regioselective introduction of an isotope label into the ligand molecule or to confirm cyclometallation and establish its path (for example, using mass spectrometry<sup>290</sup>).

The reduction of PC complexes can be used to prepare phosphine compounds of zerovalent palladium. For instance, treatment of dimer **3b** or its mononuclear adduct **3e** with the same phosphine HL<sup>3</sup> with sodium tetrahydroborate in ethanol results in the synthesis of the bis(phosphine) complex  $[\text{Pd}^0(\text{PBu}_3)_2]$  (**3s**).<sup>88, 102</sup>

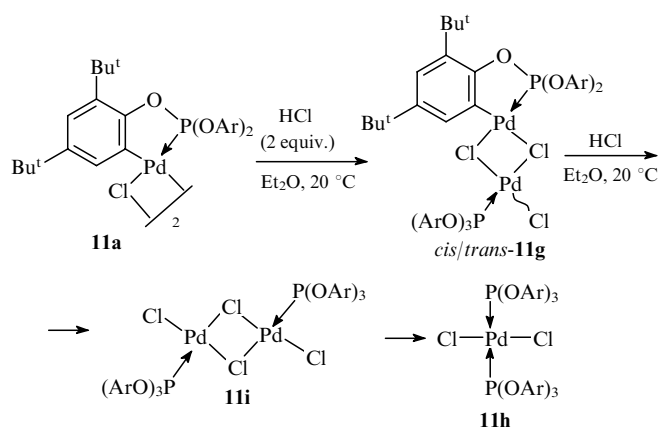


The classical PC-type complexes are not highly prone to protolysis. Treatment of mononuclear PC-palladacycles with a dilute aqueous solution of hydrochloric acid in a biphasic system with an organic solvent is often used to remove the auxiliary ligand (amine or amino acid) from these complexes (for example, in the optical resolution of the PC-palladacycles<sup>79, 117, 125</sup>). This procedure virtually does not affect the starting palladacycle, which can be recovered as the  $\mu$ -chloride dimer (for example, **7a**<sup>117</sup>) in an almost quantitative yield.



It is reasonable to suggest that the protolytic destruction of the PC-palladacycles can take place under more drastic conditions, for example, upon an increase in the strength and concentration of the acid and the reaction temperature and time and also on passing to homogeneous media. More evidence is provided by the fact that scalemic CN-palladacycle with the Pd–C\* bond is fully racemised on long-term storage of its (*S*)-leucinate derivative in a solution of HCl in aqueous methanol.<sup>291</sup> When a weaker acid is used (AcOH in methanol), the enantiomeric composition changes insignificantly.<sup>292</sup>

Useful information on the course of acidolysis was gained from a spectroscopic (<sup>31</sup>P NMR) study of the reactions of cyclopalladated phosphite **11a** with a stoichiometric amount of anhydrous hydrogen chloride in the organic medium.<sup>69</sup>



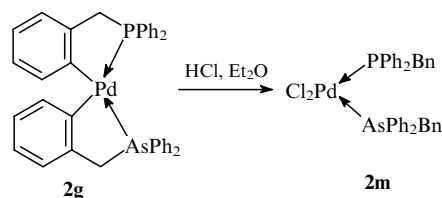
Ar = 2,4-Bu<sub>2</sub>C<sub>6</sub>H<sub>3</sub>.

The order in which the signals corresponding to the species shown in the scheme appear in the spectrum implies the initial destruction of only one of the two PC-palladacycles to give binuclear complex **11g** (as a ~4.8:1 mixture of *cis*- and *trans*-isomers). The subsequent cleavage of the second palladacycle yields binuclear coordination complex **11i** with monodentate ligands HL<sup>11</sup>, which is partially converted into mononuclear analogue **11h**. Three hours later, the ratio of the initial complex to the complexes formed upon protolysis, **11a**:**11g**:**11i**:**11h**, was 8.5:37.5:52:2, indicating rather high stability of the PC-palladacycles of this type against protolysis: almost a half of the phosphite ligand retains the cyclopalladated structure.

The susceptibility of phosphapalladacycles to protolysis markedly increases when they are incorporated into *spiro*-structures. The reactions of these complexes with hydrogen chloride are exothermal; they are carried out at reduced temperatures.<sup>71</sup> The reactions give mono- or binuclear coordination compounds of palladium(II) with *ortho*-unsubstituted benzylphosphines.<sup>71–73</sup> The geometry of the mononuclear products like [Pd(HL)<sub>2</sub>Cl<sub>2</sub>] depends on the steric situation at the P-donor atom: the coordination compounds of sterically less hindered phosphines PhCH<sub>2</sub>PR<sub>2</sub> (R = Me, Ph) are formed as mixtures of *cis*- and *trans*-isomers, whereas for more bulky di(*tert*-butyl)benzylphosphine, this process is selective and gives only the *cis*-isomer.<sup>71</sup>

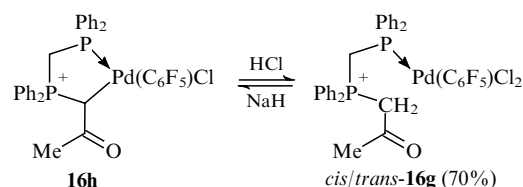
The practical use of these transformations appears problematic in view of the multistage character of the synthesis of *spiro*-PC-complexes *via* *ortho*-bromo-substituted benzylphosphines.<sup>12</sup>

These reactions may be of some practical value as applied to heteroligand *spiro*-structures, which are converted upon protolysis into mixed-ligand coordination compounds. For example, the reaction of complex **2g** with a stoichiometric amount of hydrogen chloride gave arsino-phosphine coordination complex **2m** in a high yield.<sup>72, 73</sup>



It should be noted that the protolytic stability of phosphapalladacycles in *spiro*-structures is higher than the stability of their N- and As-analogues. Spectroscopic studies of the behaviour of mixed-ligand *spiro*-complexes **2g** and *cis*-[(η<sup>2</sup>-L<sup>2</sup>)Pd(η<sup>2</sup>-C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>NMe<sub>2</sub>)] (**2e**) in relatively weak acetic acid have shown that in both cases, protolysis takes place for the less stable AsC- or CN-metallacycle, whereas the PC-palladacycle is retained as dimeric CPC **2b** with acetate bridges.<sup>293</sup> Note that in a stronger acid (HCl), both palladacycles of complex **2g** are destroyed, benzylamine is removed as the ammonium salt, while benzylphosphine HL<sup>2</sup> remains in the metal coordination sphere in the resulting binuclear complex [(Pd(κ<sup>1</sup>-HL<sup>2</sup>)Cl(μ-Cl))<sub>2</sub>].<sup>72</sup>

The phosphino-P-ylide palladacycles are also destroyed under the action of acids to give coordination complexes with the monodentate P-bonded cationic phosphonio-phosphine.<sup>133</sup> However, unlike the reactions of *spiro*-complexes considered above, the protonation of phosphino-P-ylide CPC is reversible, and the phosphapalladacycle can be regenerated by deprotonation of phosphonium ligands in coordination species. Thus complex **16g**, formed upon the protolysis of complex **16h**, can be recovered in the initial state on treatment with sodium hydride in THF.<sup>133</sup>



The information presented in this Section demonstrates that the data on the reactivity of phosphapalladacycles are scarce, which calls for further systematic research along this line.

## IV. Conclusion

The future development of the chemistry of phosphapalladacycles is of interest not only from the fundamental standpoint; its topicality is determined first of all by the demands of homogeneous catalysis, which has entered a new phase after PC- and PCP-complexes have been included in the range of available (pre)catalysts. Several promising lines of research can be distinguished.

First, one should expect the solution of the mechanistic problem related to the true role of phosphapalladacycles in the catalysis: whether they function as such in the catalytic cycle or serve only as convenient sources of zerovalent palladium? This point is still debated. With rare exceptions,<sup>294</sup> the possibility of the Pd<sup>II</sup>/Pd<sup>IV</sup> interconversion in a catalytic cycle<sup>2, 3, 6, 295</sup> is considered together with classical Pd<sup>II</sup>/Pd<sup>0</sup> schemes;<sup>2, 5, 294</sup> it has also been suggested that a PC-palladacycle can be retained as an anionic Pd<sup>0</sup>-containing intermediate.<sup>296</sup> Elucidation of the behaviour of phosphapalladacycles in catalytic processes requires conducting the reactions under stoichiometric conditions with isolation or spectroscopic identification of possible intermediates. Therefore, knowledge of the reactivity of phosphapalladacycles becomes especially important.

Realisation of the fact that the efficiency of many classical catalytic systems containing palladium(0) and bulky monodentate phosphines may be determined by the *in situ* generation of PC-species can also stimulate further, more extensive development of the chemistry of phosphapalladacycles. Indeed, the unique efficiency of these catalytic systems in the cross-coupling and the formation of carbon–heteroatom bonds is known. It is also evident that under conditions standard for the reactions of this type (80–160 °C, the presence of a base), the formation of PC-palladacycles with ligands such as  $\text{P}(\text{Bu}^t)_3$ ,<sup>297–299</sup>  $\text{P}(\text{Tol-}o)_3$ ,<sup>297, 300, 301</sup>  $\text{P}(\text{OAr})_3$ <sup>302</sup> and 2-phosphinobiaryls<sup>303, 304</sup> is inevitable.

Even if the role of PC- or PCP-complexes in some reactions would be restricted only to the supply of palladium(0) into the catalytic cycle, the unique thermal and hydrolytic stability of these compounds makes them fairly promising as (pre)catalysts. Many phosphapalladacycles withstand long-term heating (up to 300 h, 140–320 °C) without any signs of decomposition,<sup>295, 305–307</sup> which allows one to avoid the precipitation of palladium black during the process.<sup>302</sup> Therefore, more extensive involvement of not only standard (usually dimeric) PC-palladacycles but also their various derivatives into catalytic processes should be expected. The results obtained to date<sup>14–19, 22</sup> demonstrate that modification of the environment of the metallic centre in these complexes can serve as a potent method for increasing their catalytic activity.

## V. Supplements

### Supplement 1. Derivatives of classical phosphapalladacycles of the PC type.

| Complex                                                          | Number of the compound <sup>a</sup> | Q or E/E'                                             | X                     | <sup>2</sup> J <sub>PP</sub> /Hz           | Starting complexes, reagents and reaction conditions <sup>b</sup>                                                                                                    | Yield (%) <sup>c</sup> | Ref.   |
|------------------------------------------------------------------|-------------------------------------|-------------------------------------------------------|-----------------------|--------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|--------|
| Five-membered palladacycles with the C(sp <sup>3</sup> )–Pd bond |                                     |                                                       |                       |                                            |                                                                                                                                                                      |                        |        |
|                                                                  | <b>4b</b>                           |                                                       | pz <sup>−</sup>       |                                            | <b>4a</b> , pzH, NEt <sub>3</sub> , MeOH, Δ, 1 h                                                                                                                     | 91                     | 64     |
|                                                                  | <b>4c</b>                           |                                                       | 4-mpz <sup>−</sup>    |                                            | <b>4a</b> , 4-mpzH, NEt <sub>3</sub> , MeOH, Δ, 1 h                                                                                                                  | 87                     | 64     |
|                                                                  | <b>4d</b>                           |                                                       | 3,5-dmpz <sup>−</sup> |                                            | <b>4a</b> , 3,5-dmpzH, NEt <sub>3</sub> , MeOH, Δ, 1 h                                                                                                               | 97                     | 63, 64 |
|                                                                  | <b>4g</b>                           |                                                       | Cl                    |                                            | 1) <b>4a</b> , LiCl, MeOH–CH <sub>2</sub> Cl <sub>2</sub> , 20 °C<br>2) <b>4a</b> , [Bu <sub>4</sub> N]Cl, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h              | 99.7                   | 53     |
|                                                                  | <b>4w</b>                           |                                                       | Br                    |                                            | <b>4a</b> , [Bu <sub>4</sub> N]Br, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h                                                                                      | 100                    | 51     |
|                                                                  | <b>4y*</b>                          |                                                       |                       |                                            | <b>4a</b> , HNEt <sub>2</sub> , C <sub>5</sub> H <sub>12</sub> , 70 °C, 30 min                                                                                       | 98                     | 51     |
|                                                                  | <b>4k</b>                           | Me <sub>2</sub> NC(S)S <sup>−</sup>                   |                       |                                            | a) <b>4g</b> , AgClO <sub>4</sub> , THF, 20 °C, 15 min;<br>b) NaS <sub>2</sub> CNMe <sub>2</sub> ·2 H <sub>2</sub> O, MeOH                                           | 94                     | 53     |
|                                                                  | <b>4l</b>                           | EtOC(S)S <sup>−</sup>                                 |                       |                                            | a) <b>4g</b> , AgClO <sub>4</sub> , THF, 20 °C;<br>b) KS <sub>2</sub> COEt, THF, 20 °C, 15 min                                                                       | 76                     | 53     |
|                                                                  | <b>4m</b>                           | pz <sub>2</sub> BH <sub>2</sub> <sup>−</sup>          |                       |                                            | <b>4w</b> , K[pz <sub>2</sub> BH <sub>2</sub> ], Me <sub>2</sub> CO, 20 °C, 24 h                                                                                     | 96                     | 116    |
|                                                                  | <b>4n*</b>                          | pz <sub>3</sub> BH <sup>−</sup>                       |                       |                                            | <b>4w</b> , K[pz <sub>3</sub> BH], Me <sub>2</sub> CO, 20 °C, 24 h                                                                                                   | 100                    | 116    |
|                                                                  | <b>4p*</b>                          | 2-AcC <sub>6</sub> H <sub>4</sub> O <sup>−</sup>      |                       |                                            | <b>4a</b> , 2-AcC <sub>6</sub> H <sub>4</sub> OH, PhMe, KOBu <sup>t</sup> , 20 °C, 12 h                                                                              | 86                     | 118    |
|                                                                  | <b>4v</b>                           | acac <sup>−</sup>                                     |                       |                                            | <b>4g</b> , Ti(acac) (2 equiv.), CHCl <sub>3</sub> , Δ                                                                                                               | —                      | 121    |
|                                                                  | <b>4z</b>                           | 2-Ac-4-FC <sub>6</sub> H <sub>3</sub> O <sup>−</sup>  |                       |                                            | <b>4a</b> , 2-Ac-4-FC <sub>6</sub> H <sub>3</sub> OH, PhMe, KOBu <sup>t</sup> , 20 °C, 12 h                                                                          | 92                     | 118    |
|                                                                  | <b>4aa*</b>                         | 2-BzC <sub>6</sub> H <sub>4</sub> O <sup>−</sup>      |                       |                                            | <b>4a</b> , 2-BzC <sub>6</sub> H <sub>4</sub> OH, PhMe, KOBu <sup>t</sup> , 20 °C, 12 h                                                                              | 77                     | 118    |
|                                                                  | <b>4bb*</b>                         | 2-AcC <sub>10</sub> H <sub>6</sub> O <sup>−</sup>     |                       |                                            | <b>4a</b> , 2-AcC <sub>10</sub> H <sub>6</sub> OH, PhMe, KOBu <sup>t</sup> , 20 °C, 12 h                                                                             | 79                     | 118    |
|                                                                  | <b>4cc</b>                          | 2-Bz-4-MeC <sub>6</sub> H <sub>3</sub> O <sup>−</sup> |                       |                                            | <b>4a</b> , 2-Bz-4-MeC <sub>6</sub> H <sub>3</sub> OH, PhMe, KOBu <sup>t</sup> , 20 °C, 12 h                                                                         | 76                     | 118    |
|                                                                  | <b>4i</b>                           |                                                       | Cl                    |                                            | <b>4g</b> , Ph <sub>2</sub> P(CH <sub>2</sub> ) <sub>3</sub> PPh <sub>2</sub> , MeOH, 20 °C, 3 h                                                                     | —                      | 30     |
|                                                                  | <b>4j</b>                           |                                                       | PF <sub>6</sub>       | 333 ( <i>trans</i> ),<br>36 ( <i>cis</i> ) | a) <b>4g</b> , Ph <sub>2</sub> P(CH <sub>2</sub> ) <sub>3</sub> PPh <sub>2</sub> , MeOH, 20 °C, 3 h;<br>b) [NH <sub>4</sub> ]PF <sub>6</sub> , MeOH–H <sub>2</sub> O | 85                     | 30     |

## Supplement 1 (continued).

| Complex                                                          | Number of the compound <sup>a</sup>                                | Q or E <sup>+</sup> E'                                                        | X                                | <sup>2</sup> J <sub>PP</sub> /Hz                  | Starting complexes, reagents and reaction conditions <sup>b</sup>                                                                                                                                                                                                                            | Yield (%) <sup>c</sup>                      | Ref.                        |
|------------------------------------------------------------------|--------------------------------------------------------------------|-------------------------------------------------------------------------------|----------------------------------|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|-----------------------------|
| Five-membered palladacycles with the C(sp <sup>3</sup> )–Pd bond |                                                                    |                                                                               |                                  |                                                   |                                                                                                                                                                                                                                                                                              |                                             |                             |
|                                                                  | 4f                                                                 | Ph <sub>3</sub> P=NCN                                                         |                                  |                                                   | a) 4g, AgClO <sub>4</sub> , MeCN, 20 °C;                                                                                                                                                                                                                                                     | 55                                          | 105                         |
|                                                                  | 4h                                                                 | MeCN                                                                          |                                  |                                                   | b) Ph <sub>3</sub> P=NCN, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 30 min<br>4g, AgClO <sub>4</sub> , MeCN, 20 °C <sup>d</sup>                                                                                                                                                               | —                                           | 105                         |
|                                                                  | 8c<br>8d                                                           |                                                                               | OAc<br>OBz                       |                                                   | 8a, AgOAc, Me <sub>2</sub> CO, 20 °C, 12 h<br>8a, AgOBz, Me <sub>2</sub> CO, 20 °C, 12 h                                                                                                                                                                                                     | 80<br>71                                    | 60<br>60                    |
|                                                                  | 8b                                                                 |                                                                               |                                  | 382                                               | 8a, PPh <sub>3</sub> (2.5 equiv.), CH <sub>2</sub> Cl <sub>2</sub>                                                                                                                                                                                                                           | 95                                          | 60                          |
|                                                                  | 8c                                                                 |                                                                               |                                  |                                                   | 8a, Tl(acac), PhH, 20 °C, 5 h                                                                                                                                                                                                                                                                | 63                                          | 60                          |
|                                                                  | 52                                                                 |                                                                               |                                  |                                                   | [{Pd(η <sup>2</sup> -L <sup>52</sup> )(μ-OAc)} <sub>2</sub> ], [Bu <sub>4</sub> N]Br, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h                                                                                                                                                           | 53                                          | 51                          |
|                                                                  | 7d<br>7h                                                           |                                                                               | OAc<br>OBz                       |                                                   | 7a, AgOAc, Me <sub>2</sub> CO, 20 °C, 12 h<br>7a, AgOBz, Me <sub>2</sub> CO, 20 °C, 12 h                                                                                                                                                                                                     | 77<br>65                                    | 60<br>60                    |
|                                                                  | 7b<br>7e <sup>c</sup><br>7f<br>7f' <sup>c</sup><br>7i <sup>c</sup> | (–)-α-MBA<br>d <sub>5</sub> -Py<br>PPh <sub>3</sub><br>PPh <sub>3</sub><br>Py |                                  | 401<br>399 ( <i>trans</i> ),<br>42 ( <i>cis</i> ) | 7a, (–)-α-MBA, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h<br>7a, d <sub>5</sub> -Py, CDCl <sub>3</sub> , 20 °C, 5 min<br>1) 7a, PPh <sub>3</sub> (2.1 equiv.), PhH, 50 °C, 1 min<br>2) 7a, PPh <sub>3</sub> , PhH, 50 °C, 10 min<br>7a, Py, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 5 min | 91<br>(~100) <sup>f</sup><br>84<br>84<br>79 | 60<br>90<br>60<br>117<br>60 |
|                                                                  | 7g <sup>g</sup><br>7g' <sup>g</sup><br>7j                          | (S)-Pro <sup>–</sup><br>(S)-Pro <sup>–</sup><br>acac <sup>–</sup>             |                                  |                                                   | 1) 7a, (S)-ProK, CH <sub>2</sub> Cl <sub>2</sub> –H <sub>2</sub> O, 20 °C, 1 h<br>2) 7a, (S)-ProK, MeOH, 20 °C, 1 h<br>7a, Tl(acac), CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 30 min                                                                                                         | 76<br>~100<br>70                            | 117<br>117<br>60            |
|                                                                  | 7c                                                                 |                                                                               |                                  |                                                   | 7a, (R,R)-stien, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h                                                                                                                                                                                                                                | 92                                          | 60                          |
|                                                                  | 53                                                                 |                                                                               |                                  |                                                   | [{Pd(η <sup>2</sup> -L <sup>53</sup> )(μ-OAc)} <sub>2</sub> ], [Bu <sub>4</sub> N]Br, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h                                                                                                                                                           | —                                           | 51                          |
|                                                                  | 1b<br>1c<br>1e<br>1f                                               |                                                                               | Br<br>Cl<br>I<br>pz <sup>–</sup> |                                                   | 1) 1a, [Bu <sub>4</sub> N]Br, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h<br>2) 1c, KBr, Me <sub>2</sub> CO, 20 °C<br>1a, [Bu <sub>4</sub> N]Cl, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h<br>1c, KI or NaI, Me <sub>2</sub> CO, 20 °C<br>1c, pzH, NaOH–MeOH, 20 °C, 20 h                | 86<br>44<br>—<br>83<br>80                   | 51<br>55<br>51<br>55<br>62  |

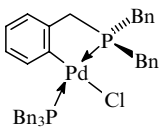
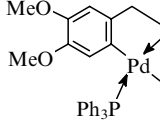
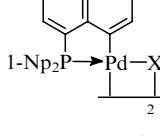
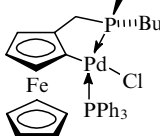
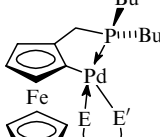
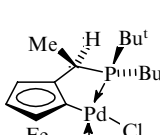
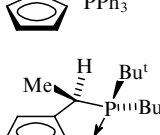
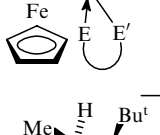
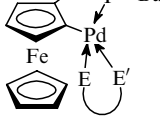
## Supplement 1 (continued).

| Complex                                                          | Number of the compound <sup>a</sup> | Q or E <sup>+</sup> E'                             | X               | <sup>2</sup> J <sub>PP</sub> /Hz | Starting complexes, reagents and reaction conditions <sup>b</sup>                                                                                                           | Yield (%) <sup>c</sup> | Ref. |
|------------------------------------------------------------------|-------------------------------------|----------------------------------------------------|-----------------|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------|
| Five-membered palladacycles with the C(sp <sup>3</sup> )–Pd bond |                                     |                                                    |                 |                                  |                                                                                                                                                                             |                        |      |
|                                                                  | <b>1d</b>                           | 4-Me <sub>2</sub> NC <sub>5</sub> H <sub>4</sub> N | Cl              |                                  | <b>1c</b> , 4-Me <sub>2</sub> NC <sub>5</sub> H <sub>4</sub> N (excess), CDCl <sub>3</sub> , 20 °C                                                                          | —                      | 92   |
|                                                                  | <b>1g</b>                           | PPh <sub>3</sub>                                   | Cl              | 419                              | <b>1c</b> , PPh <sub>3</sub> , PhH, Δ, 30 min, N <sub>2</sub>                                                                                                               | 97                     | 94   |
|                                                                  | <b>1h</b>                           | PPh <sub>3</sub>                                   | Br              | 416                              | see <sup>h</sup>                                                                                                                                                            | —                      | 94   |
|                                                                  | <b>1i</b>                           | PPh <sub>3</sub>                                   | I               | 414                              | see <sup>h</sup>                                                                                                                                                            | —                      | 94   |
|                                                                  | <b>1j</b>                           | PPh <sub>3</sub>                                   | pz <sup>−</sup> | 420                              | see <sup>h</sup>                                                                                                                                                            | —                      | 94   |
|                                                                  | <b>1k</b>                           | AsPh <sub>3</sub>                                  | Cl              |                                  | <b>1c</b> , AsPh <sub>3</sub> , PhH, Δ, 1.5 h, N <sub>2</sub>                                                                                                               | 85                     | 94   |
|                                                                  | <b>1l</b>                           | DBP                                                | Cl              | 421                              | <b>1c</b> , DBP, PhH, Δ, 30 min, N <sub>2</sub>                                                                                                                             | 85                     | 94   |
|                                                                  | <b>1m</b>                           | P(OPh) <sub>3</sub>                                | Cl              | 607                              | <b>1c</b> , P(OPh) <sub>3</sub> , PhH, Δ                                                                                                                                    | 94                     | 94   |
|                                                                  | <b>54a</b>                          | PPh <sub>3</sub>                                   |                 |                                  | [{Pd(η <sup>2</sup> -L <sup>54</sup> )(μ-OAc)} <sub>2</sub> ], PPh <sub>3</sub> (2.2 equiv.), PhH, Δ                                                                        | 82                     | 97   |
|                                                                  | <b>54b</b>                          | PMe <sub>2</sub> Ph                                |                 |                                  | [{Pd(η <sup>2</sup> -L <sup>54</sup> )(μ-OAc)} <sub>2</sub> ], PMe <sub>2</sub> Ph (2.2 equiv.), PhH, Δ                                                                     | 76                     | 97   |
|                                                                  | <b>54c</b>                          |                                                    |                 |                                  | [{Pd(η <sup>2</sup> -L <sup>54</sup> )(μ-OAc)} <sub>2</sub> ], Tl(acac), PhH, 20 °C, 22 h                                                                                   | 58                     | 97   |
|                                                                  | <b>55</b>                           |                                                    |                 | 371                              | [{Pd(η <sup>2</sup> -L <sup>55</sup> )(μ-Cl)} <sub>2</sub> ], PPh <sub>3</sub> , PhH, Δ, 5 min                                                                              | —                      | 99   |
| Four-membered palladacycles with the C(sp <sup>3</sup> )–Pd bond |                                     |                                                    |                 |                                  |                                                                                                                                                                             |                        |      |
|                                                                  | <b>3a</b>                           |                                                    | Cl, MeO         |                                  | <b>3b</b> , MeOH, NaOH, 40 °C, 2 h                                                                                                                                          | 70                     | 61   |
|                                                                  | <b>3c</b>                           | PPh <sub>3</sub>                                   |                 | 422                              | <b>3b</b> , PPh <sub>3</sub> , PhH, 20 °C, 12 h                                                                                                                             | —                      | 88   |
|                                                                  | <b>3d</b> <sup>i</sup>              | AsPh <sub>3</sub>                                  |                 |                                  | <b>3b</b> , AsPh <sub>3</sub> , PhH, 20 °C, 12 h                                                                                                                            | —                      | 88   |
|                                                                  | <b>3f</b>                           | diars                                              |                 |                                  | <b>3b</b> , diars, PhH, 20 °C, 12 h, N <sub>2</sub>                                                                                                                         | 68                     | 106  |
|                                                                  | <b>3g</b>                           | bipy                                               |                 |                                  | <b>3b</b> , bipy, PhH, 40 °C, 8 h                                                                                                                                           | 74                     | 106  |
|                                                                  | <b>3h</b>                           | ape                                                |                 | 420                              | <b>3b</b> , ape, PhH, 40 °C, 5 h                                                                                                                                            | 86                     | 106  |
|                                                                  | <b>3p</b>                           | Py                                                 |                 |                                  | <b>3b</b> , Py, PhH, 20 °C, 2 h                                                                                                                                             | —                      | 88   |
|                                                                  | <b>3t</b>                           | PCy <sub>3</sub>                                   |                 | 409                              | <b>3b</b> , PCy <sub>3</sub> , PhH, 20 °C, 12 h                                                                                                                             | —                      | 88   |
|                                                                  | <b>3u</b>                           | PEt <sub>3</sub>                                   |                 | 441                              | <b>3b</b> , PEt <sub>3</sub> , PhH, 20 °C, 12 h                                                                                                                             | —                      | 88   |
|                                                                  | <b>3v</b>                           | PPr <sub>3</sub>                                   |                 | 403                              | <b>3b</b> , PPr <sub>3</sub> , PhH, 20 °C, 12 h                                                                                                                             | —                      | 88   |
|                                                                  | <b>3w</b>                           | PPh <sub>2</sub> Me                                |                 | 440                              | <b>3b</b> , PPh <sub>2</sub> Me, PhH, 20 °C, 12 h                                                                                                                           | —                      | 88   |
|                                                                  | <b>3x</b>                           | PBu <sub>2</sub> <sup>i</sup> Me                   |                 | 413                              | <b>3b</b> , PBu <sub>2</sub> <sup>i</sup> Me, PhH, 20 °C, 12 h                                                                                                              | —                      | 88   |
|                                                                  | <b>3y</b>                           | P( <i>o</i> -Tol) <sub>3</sub>                     |                 | 413                              | <b>3b</b> , P( <i>o</i> -Tol) <sub>3</sub> , PhH, 20 °C, 12 h                                                                                                               | —                      | 88   |
|                                                                  | <b>3j</b>                           |                                                    |                 | 420                              | <b>3b</b> , dppm (2 equiv.), PhH, 20 °C, 6 h                                                                                                                                | 89                     | 106  |
|                                                                  | <b>3k</b>                           | ape                                                |                 | 360                              | <i>a</i> ) <b>3b</b> , AgPF <sub>6</sub> , CH <sub>2</sub> Cl <sub>2</sub> –Me <sub>2</sub> CO, 20 °C, 30 min; <i>b</i> ) ape, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 4 h | 78                     | 106  |
|                                                                  | <b>3l</b>                           | diars                                              |                 |                                  | <i>a</i> ) <b>3b</b> , AgPF <sub>6</sub> , CH <sub>2</sub> Cl <sub>2</sub> –Me <sub>2</sub> CO, 20 °C, 30 min; <i>b</i> ) diars, 20 °C, 5 h                                 | 74                     | 106  |
|                                                                  | <b>3m</b>                           | bipy                                               |                 |                                  | <i>a</i> ) <b>3b</b> , AgPF <sub>6</sub> , CH <sub>2</sub> Cl <sub>2</sub> –Me <sub>2</sub> CO, 20 °C, 30 min; <i>b</i> ) bipy, 20 °C, 5 h                                  | 69                     | 106  |
|                                                                  | <b>3n</b>                           | Cp                                                 |                 |                                  | <b>3b</b> , TiCp, PhH, 20 °C, 30 min                                                                                                                                        | 77                     | 124  |
|                                                                  | <b>3z</b>                           | Cp*                                                |                 |                                  | <b>3b</b> , LiCp*, PhH, 20 °C, 3 h                                                                                                                                          | 60                     | 124  |

## Supplement 1 (continued).

| Complex                                                           | Number of the compound <sup>a</sup> | Q or E <sup>+</sup> E'                                            | X   | <sup>2</sup> J <sub>PP</sub> /Hz | Starting complexes, reagents and reaction conditions <sup>b</sup>                                                                               | Yield (%) <sup>c</sup> | Ref.    |
|-------------------------------------------------------------------|-------------------------------------|-------------------------------------------------------------------|-----|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|---------|
| Four-membered palladacycles with the C(sp <sup>3</sup> )–Pd bond  |                                     |                                                                   |     |                                  |                                                                                                                                                 |                        |         |
|                                                                   | <b>13b</b>                          | Cp                                                                |     |                                  | <b>13a</b> , TlCp, PhH, 20 °C, 30 min                                                                                                           | 67                     | 124     |
|                                                                   | <b>13c</b>                          | Cp*                                                               |     |                                  | <b>13a</b> , LiCp*, PhH, 20 °C, 3 h                                                                                                             | 39                     | 124     |
| Three-membered palladacycles with the C(sp <sup>3</sup> )–Pd bond |                                     |                                                                   |     |                                  |                                                                                                                                                 |                        |         |
|                                                                   | <b>56</b>                           |                                                                   |     | 397                              | [{Pd(η <sup>2</sup> -L <sup>56</sup> )(μ-OAc)} <sub>2</sub> ], PPh <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 10 min               | 80                     | 96      |
|                                                                   | <b>57</b>                           |                                                                   |     | 393                              | [{Pd(η <sup>2</sup> -L <sup>57</sup> )(μ-OAc)} <sub>2</sub> ], PPh <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 10 min               | 67                     | 96      |
| Six-membered palladacycles with the C(sp <sup>2</sup> )–Pd bond   |                                     |                                                                   |     |                                  |                                                                                                                                                 |                        |         |
|                                                                   | <b>18</b>                           |                                                                   |     |                                  | [Pd(η <sup>2</sup> -L <sup>18</sup> )(μ-Cl) <sub>2</sub> ], Bu <sup>t</sup> NC, CH <sub>2</sub> Cl <sub>2</sub> , N <sub>2</sub> , 25 °C, 0.5 h | 78                     | 173     |
| Five-membered palladacycles with the C(sp <sup>2</sup> )–Pd bond  |                                     |                                                                   |     |                                  |                                                                                                                                                 |                        |         |
|                                                                   | <b>5a</b>                           |                                                                   | Cl  |                                  | [Pd(η <sup>2</sup> -L <sup>5</sup> ) <sub>2</sub> ], [PdCl <sub>2</sub> (SEt <sub>2</sub> ) <sub>2</sub> ], CHCl <sub>3</sub> , Δ, 1–2 h        | 100                    | 67      |
|                                                                   | <b>5f</b>                           |                                                                   | Br  |                                  | 1) [Pd(η <sup>2</sup> -L <sup>5</sup> ) <sub>2</sub> ], HgBr <sub>2</sub> , THF, 20 °C, 1 h; Δ, 5 h                                             | 92                     | 67      |
|                                                                   | <b>5g</b>                           |                                                                   | I   |                                  | 2) <b>5a</b> , LiBr, Me <sub>2</sub> CO, 20 °C, 20 h                                                                                            | 80                     | 57      |
|                                                                   | <b>5h</b>                           |                                                                   |     |                                  | <b>5a</b> , NaI, Me <sub>2</sub> CO, 20 °C, 20 h                                                                                                | 85                     | 57      |
|                                                                   | <b>5c</b>                           | 2-Me <sub>2</sub> PCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub>  |     | 22                               | <b>5a</b> , 2-Me <sub>2</sub> PCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Li, Et <sub>2</sub> O, –20 to 20 °C, 2 h                           | 61                     | 71      |
|                                                                   | <b>5e</b>                           | 2-Ph <sub>2</sub> PCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub>  |     | 19                               | <b>5a</b> , 2-Ph <sub>2</sub> PCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Li, PhH, 20 °C, ~2 h                                               | 87                     | 71, 232 |
|                                                                   | <b>5h</b>                           | acac                                                              |     |                                  | <b>5a</b> , Tl(acac), PhH, 20 °C, 2.5 h                                                                                                         | 94                     | 57      |
|                                                                   | <b>2a</b>                           |                                                                   | Cl  |                                  | 1) [Pd(η <sup>2</sup> -L <sup>2</sup> ) <sub>2</sub> ], PdCl <sub>2</sub> , Me <sub>2</sub> C <sub>6</sub> H <sub>4</sub> , Δ                   | —                      | 67      |
|                                                                   | <b>2b</b>                           |                                                                   | OAc |                                  | 2) [Pd(η <sup>2</sup> -L <sup>2</sup> ) <sub>2</sub> ], [PdCl <sub>2</sub> (SEt <sub>2</sub> ) <sub>2</sub> ], CHCl <sub>3</sub> , Δ, 1–2 h     | 92                     | 67      |
|                                                                   | <b>2d</b>                           |                                                                   | Br  |                                  | 3) <b>2b</b> , LiCl, Me <sub>2</sub> CO–H <sub>2</sub> O, 20 °C, 24 h                                                                           | 86                     | 54      |
|                                                                   | <b>2i</b>                           |                                                                   |     |                                  | <b>2a</b> , AgOAc, Me <sub>2</sub> CO, 20 °C, 24 h                                                                                              | 76                     | 54      |
|                                                                   | <b>2f</b>                           |                                                                   |     |                                  | 1) [Pd(η <sup>2</sup> -L <sup>2</sup> ) <sub>2</sub> ], Hg(OAc) <sub>2</sub> , THF, 20 °C, 1 h; Δ, 5 h                                          | 77                     | 67      |
|                                                                   | <b>2g</b>                           |                                                                   |     |                                  | 2) [Pd(η <sup>2</sup> -L <sup>2</sup> ) <sub>2</sub> ], HgBr <sub>2</sub> , THF, 20 °C, 1 h; Δ, 5 h                                             | 86                     | 67      |
|                                                                   | <b>2h</b>                           |                                                                   |     |                                  | <b>2b</b> , 3,5-dmpy, Me <sub>2</sub> CO, 20 °C, 20 h                                                                                           | 50                     | 54      |
|                                                                   | <b>2n</b>                           |                                                                   |     |                                  |                                                                                                                                                 |                        |         |
|                                                                   | <b>2f</b>                           | acac <sup>–</sup>                                                 |     |                                  | <b>2a</b> , Tl(acac), CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 20 h                                                                             | 41                     | 54      |
|                                                                   | <b>2g</b>                           | 2-Me <sub>2</sub> NCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub>  |     |                                  | <b>2a</b> , 2-Me <sub>2</sub> NCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Li, Et <sub>2</sub> O, –20 to 20 °C, 2–3 h                         | 89                     | 72, 73  |
|                                                                   | <b>2h</b>                           | 2-Me <sub>2</sub> AsCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> |     |                                  | <b>2a</b> , 2-Me <sub>2</sub> AsCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Li, Et <sub>2</sub> O, –20 to 20 °C, 2–3 h                        | 46                     | 72, 73  |
|                                                                   | <b>2n</b>                           | 2-Ph <sub>2</sub> AsCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> |     |                                  | <b>2a</b> , 2-Ph <sub>2</sub> AsCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Li, Et <sub>2</sub> O, –20 to 20 °C, 2–3 h                        | 82                     | 72, 73  |

## Supplement 1 (continued).

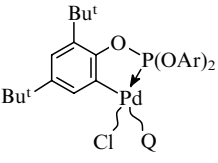
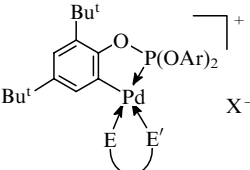
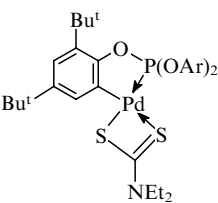
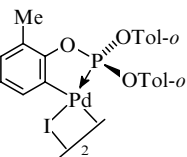
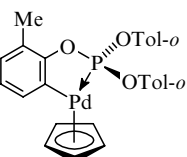
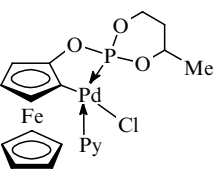
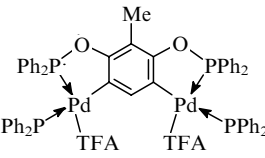
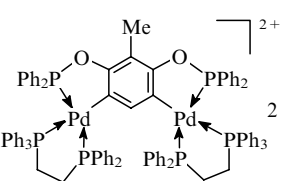
| Complex                                                                             | Number of the compound <sup>a</sup> | Q or E <sup>+</sup> E' | X               | <sup>2</sup> J <sub>PP</sub> /Hz | Starting complexes, reagents and reaction conditions <sup>b</sup>                                            | Yield (%) <sup>c</sup> | Ref. |
|-------------------------------------------------------------------------------------|-------------------------------------|------------------------|-----------------|----------------------------------|--------------------------------------------------------------------------------------------------------------|------------------------|------|
| Five-membered palladacycles with the C(sp <sup>2</sup> )–Pd bond                    |                                     |                        |                 |                                  |                                                                                                              |                        |      |
|    | 29                                  |                        |                 |                                  | [Pd(η <sup>2</sup> -L <sup>29</sup> )(μ-Cl)] <sub>2</sub> , PBn <sub>3</sub>                                 | —                      | 311  |
|    | 58                                  |                        |                 | 395                              | [[Pd(η <sup>2</sup> -L <sup>58</sup> )(μ-Cl)] <sub>2</sub> ], PPh <sub>3</sub> (2.2 equiv.), EtOH, Δ, 10 min | 67                     | 98   |
|    | 59a                                 |                        | I               | —                                | —                                                                                                            | —                      | 22   |
|                                                                                     | 59b                                 |                        | Br              | —                                | —                                                                                                            | —                      | 22   |
|   | 9b                                  |                        |                 | 398                              | 9a, PPh <sub>3</sub> (2.1 equiv.), PhH, 20 °C, 20 min                                                        | 91                     | 79   |
|  | 9c <sup>i</sup>                     | (S)-Pro <sup>−</sup>   |                 |                                  | 9a, (S)-ProK, MeOH, 20 °C, 3 h                                                                               | 96                     | 79   |
|  | 10b*                                |                        |                 | 399                              | 10a, PPh <sub>3</sub> (2.1 equiv.), PhH, 20 °C, 20 min                                                       | 79                     | 78   |
|  | 10c                                 | acac <sup>−</sup>      |                 |                                  | 10a, acacH, KOH, MeOH, 20 °C, 5.5 h                                                                          | 28                     | 90   |
|                                                                                     | 10d <sup>j</sup>                    | (S)-Pro <sup>−</sup>   |                 |                                  | 10a, (S)-ProK, MeOH, 20 °C, 2 h                                                                              | 94                     | 90   |
|  | 10e                                 | phen                   | PF <sub>6</sub> |                                  | a) 10a, phen, MeOH, 20 °C, 4 h;                                                                              | 70                     | 90   |
|                                                                                     | 10f <sup>i</sup>                    | (R,R)-stien            | Cl              |                                  | b) KPF <sub>6</sub> , H <sub>2</sub> O, 20 °C, 30 min                                                        | (~100)                 | 90   |
|                                                                                     |                                     |                        |                 |                                  | 10a, (R,R)-stien, MeOH, 20 °C, 1 h                                                                           |                        |      |
|  | 60a                                 |                        |                 |                                  | [[PdCl(η <sup>3</sup> -μ-L <sup>60</sup> )] <sub>2</sub> ], KBr, Me <sub>2</sub> CO                          | —                      | 56   |

## Supplement 1 (continued).

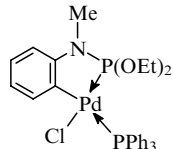
| Complex                                                          | Number of the compound <sup>a</sup> | Q or E <sup>+</sup> E' | X                                    | <sup>2</sup> J <sub>PP</sub> /Hz           | Starting complexes, reagents and reaction conditions <sup>b</sup>                                                | Yield (%) <sup>c</sup> | Ref.    |
|------------------------------------------------------------------|-------------------------------------|------------------------|--------------------------------------|--------------------------------------------|------------------------------------------------------------------------------------------------------------------|------------------------|---------|
| Five-membered palladacycles with the C(sp <sup>2</sup> )–Pd bond |                                     |                        |                                      |                                            |                                                                                                                  |                        |         |
|                                                                  | 60b                                 |                        |                                      |                                            | [{PdCl(η <sup>3</sup> :μ-L <sup>60</sup> )} <sub>2</sub> ], PPh <sub>3</sub> , Me <sub>2</sub> CO, 20 °C         | —                      | 56      |
|                                                                  | 60c                                 |                        |                                      |                                            | [{PdCl(η <sup>3</sup> :μ-L <sup>60</sup> )} <sub>2</sub> ], bipy, NaClO <sub>4</sub> , Me <sub>2</sub> CO, 20 °C | —                      | 56      |
|                                                                  | 14f                                 |                        |                                      |                                            | 14b, NaI, Me <sub>2</sub> CO, 20 °C                                                                              | 95                     | 58      |
|                                                                  | 14c                                 | PPh <sub>3</sub>       |                                      | 48                                         | 14b, PPh <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 10 min                                          | 96                     | 58      |
|                                                                  | 14d                                 | P(OMe) <sub>3</sub>    |                                      | 55                                         | 14b, P(OMe) <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 10 min                                       | 89                     | 58      |
|                                                                  | 14g                                 | P(OPh) <sub>3</sub>    |                                      | 56                                         | 14b, P(OPh) <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 10 min                                       | 99                     | 58, 242 |
|                                                                  | 14h                                 | AsPh <sub>3</sub>      |                                      |                                            | 14b, AsPh <sub>3</sub>                                                                                           | —                      | 58      |
|                                                                  | 14i                                 | Py                     |                                      |                                            | 14b, Py, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C                                                                 | 94                     | 58      |
|                                                                  | 14j                                 | Bu <sup>t</sup> NC     |                                      |                                            | 14b, Bu <sup>t</sup> NC (2 equiv.)                                                                               | 100                    | 58      |
|                                                                  | 14k                                 | CyNC                   |                                      |                                            | 14b, CyNC (2 equiv.)                                                                                             | 100                    | 58      |
|                                                                  | 14e                                 |                        | Me                                   | 32                                         | a) 14b, PPh <sub>3</sub> , MeLi, PhH, 5 °C, 1 h;<br>b) MeOH                                                      | 70                     | 74      |
|                                                                  | 14l                                 |                        | Ph                                   | 35                                         | a) 14b, PPh <sub>3</sub> , PhLi, PhH, 5 °C, 1 h;<br>b) H <sub>2</sub> O                                          | —                      | 74      |
|                                                                  | 14m                                 |                        | n-C <sub>5</sub> H <sub>11</sub> C≡C | 35                                         | a) 14b, PPh <sub>3</sub> , n-C <sub>5</sub> H <sub>11</sub> C≡CLi, PhH, 5 °C, 1 h; b) H <sub>2</sub> O           | —                      | 74      |
|                                                                  | 14a*                                |                        |                                      |                                            | 14b, TICp, THF, 20 °C, 16 h                                                                                      | 72                     | 58      |
|                                                                  | 14n                                 | dppe                   |                                      | 515 ( <i>trans</i> ),<br>30 ( <i>cis</i> ) | 14b, dppe, CDCl <sub>3</sub>                                                                                     | 100                    | 58      |
|                                                                  | 61a                                 |                        | MeO                                  | 45                                         | —                                                                                                                | 90                     | 58      |
|                                                                  | 61b                                 |                        | Me                                   | 47                                         | —                                                                                                                | 90                     | 58      |
|                                                                  | 61c                                 |                        | NO <sub>2</sub>                      | 42                                         | —                                                                                                                | 90                     | 58      |



## Supplement 1 (continued).

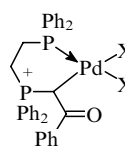
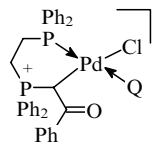
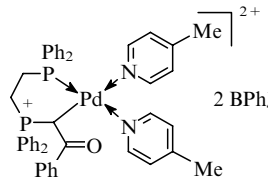
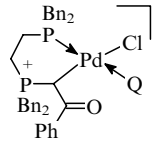
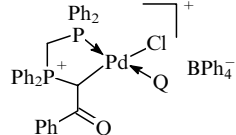
| Complex                                                                             | Number of the compound <sup>a</sup> | Q or E <sup>+</sup> E' | X   | <sup>2</sup> J <sub>PP</sub> /Hz           | Starting complexes, reagents and reaction conditions <sup>b</sup>                                                                                                 | Yield (%) <sup>c</sup> | Ref. |
|-------------------------------------------------------------------------------------|-------------------------------------|------------------------|-----|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------|
| Five-membered palladacycles with the C(sp <sup>2</sup> )–Pd bond                    |                                     |                        |     |                                            |                                                                                                                                                                   |                        |      |
|    | <b>11b</b>                          | P(OMe) <sub>3</sub>    |     | 53                                         | <b>11a</b> , P(OMe) <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 30 min                                                                                | 62                     | 69   |
|                                                                                     | <b>11f</b>                          | PPh <sub>3</sub>       |     | 604 ( <i>trans</i> ),<br>41 ( <i>cis</i> ) | <b>11a</b> , PPh <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 30 min                                                                                   | 92 <sup>f</sup>        | 69   |
|                                                                                     | <b>11j</b>                          | P(OEt) <sub>3</sub>    |     | 50                                         | <b>11a</b> , P(OEt) <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 30 min                                                                                | 41                     | 69   |
|                                                                                     | <b>11k</b>                          | P(OPh) <sub>3</sub>    |     | 52                                         | <b>11a</b> , P(OPh) <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 30 min                                                                                | 41                     | 69   |
|                                                                                     | <b>11l</b>                          | PCy <sub>3</sub>       |     | 41                                         | <b>11a</b> , Cy <sub>3</sub> P·CS <sub>2</sub> , PhMe, 110 °C, 2 h                                                                                                | 61                     | 69   |
| (Ar = 2,4-Bu <sub>2</sub> C <sub>6</sub> H <sub>3</sub> )                           |                                     |                        |     |                                            |                                                                                                                                                                   |                        |      |
|    | <b>11d</b>                          | dppf                   | OTf | 540 ( <i>trans</i> ),<br>52 ( <i>cis</i> ) | <i>a</i> <b>11a</b> , AgOTf, MeCN, 20 °C, 5 min;<br><i>b</i> dppf, 20 °C, 1 h                                                                                     | 65                     | 69   |
|                                                                                     | <b>11m</b>                          | dppe                   | Cl  | 502 ( <i>trans</i> ),<br>33 ( <i>cis</i> ) | <b>11a</b> , dppe, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 30 min                                                                                                | 96                     | 69   |
| (Ar = 2,4-Bu <sub>2</sub> C <sub>6</sub> H <sub>3</sub> )                           |                                     |                        |     |                                            |                                                                                                                                                                   |                        |      |
|   | <b>11e*</b>                         |                        |     |                                            | <b>11a</b> , [Et <sub>2</sub> NCS <sub>2</sub> ]Na·3 H <sub>2</sub> O,<br>CH <sub>2</sub> Cl <sub>2</sub> –EtOH–H <sub>2</sub> O (10:10:1),<br>20 °C, 5 min       | 63                     | 69   |
| (Ar = 2,4-Bu <sub>2</sub> C <sub>6</sub> H <sub>3</sub> )                           |                                     |                        |     |                                            |                                                                                                                                                                   |                        |      |
|  | <b>62a</b>                          |                        |     | see <sup>k</sup>                           | [{Pd(η <sup>2</sup> -L <sup>62</sup> )(μ-Cl)} <sub>2</sub> ], NaI,<br>Me <sub>2</sub> CO, 20 °C                                                                   | 95                     | 59   |
|  | <b>62b</b>                          |                        |     |                                            | [{Pd(η <sup>2</sup> -L <sup>62</sup> )(μ-Cl)} <sub>2</sub> ], TICp, THF,<br>20 °C, 15 h                                                                           | 70                     | 59   |
|  | <b>63*</b> (see <sup>l</sup> )      |                        |     |                                            | [{Pd(η <sup>2</sup> -L <sup>63</sup> )(μ-Cl)} <sub>2</sub> ], Py, CH <sub>2</sub> Cl <sub>2</sub>                                                                 | —                      | 89   |
|  | <b>12b</b>                          |                        |     | 28                                         | [{Pd <sub>2</sub> (η <sup>2</sup> :η <sup>2</sup> -L <sup>12</sup> )(μ-TFA)} <sub>2</sub> ]*, PPh <sub>3</sub> ,<br>CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 18 h | —                      | 115  |
|  | <b>12c<sup>m</sup></b>              |                        |     | 379 ( <i>trans</i> ),<br>24 ( <i>cis</i> ) | [{Pd <sub>2</sub> (η <sup>2</sup> :η <sup>2</sup> -L <sup>12</sup> )(μ-TFA) <sub>2</sub> ] <sub>2</sub> *, dppe,<br>CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 18 h | —                      | 115  |

## Supplement 1 (continued).

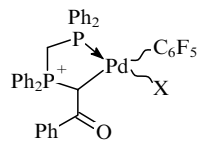
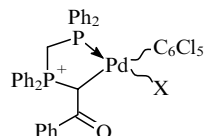
| Complex                                                                           | Number of the compound <sup>a</sup> | Q or E'E' | X | <sup>2</sup> J <sub>PP</sub> /Hz | Starting complexes, reagents and reaction conditions <sup>b</sup> | Yield (%) <sup>c</sup> | Ref. |
|-----------------------------------------------------------------------------------|-------------------------------------|-----------|---|----------------------------------|-------------------------------------------------------------------|------------------------|------|
| Five-membered palladacycles with the C(sp <sup>2</sup> )–Pd bond                  |                                     |           |   |                                  |                                                                   |                        |      |
|  | <b>64</b>                           |           |   | 46                               | —                                                                 | —                      | 58   |

<sup>a</sup> The complexes studied by X-ray diffraction are asterisked. <sup>b</sup> Here and below, the digits designate different methods for the preparation of a complex, while letters mark the preparation stages. <sup>c</sup> The isolated yield is given; the yield determined from spectroscopic data is indicated in parentheses. <sup>d</sup> The synthesis was carried out under conditions described <sup>310</sup> for the Pt-analogue. <sup>e</sup> The complex exists in solution as a mixture of *cis*- and *trans*-isomers. <sup>f</sup> The complex was generated *in situ* and identified by spectroscopy. <sup>g</sup> The complex represents a mixture of two diastereomers (1 : 1), each existing as geometric *cis*- and *trans*-isomers (<sup>31</sup>P NMR). <sup>h</sup> The complex was prepared similarly to the chloride analogue. <sup>i</sup> The adduct is unstable and dissociates in solutions. <sup>j</sup> The complex consists of two diastereomers. <sup>k</sup> For the adduct with P(Tol-*o*)<sub>3</sub>, the constant <sup>2</sup>J<sub>PP</sub> = 54 Hz is given.<sup>242</sup> <sup>l</sup> A mixture of two diastereomeric racemates. <sup>m</sup> Mixed with a small amount of tetranuclear species with a bridged phosphine.

## Supplement 2. Derivatives of phosphino-P-ylide PC-palladacycles.

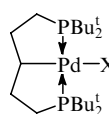
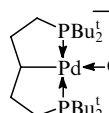
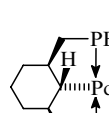
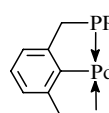
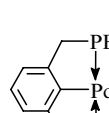
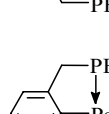
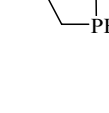
| Complex                                                                             | Number of the compound  | Q                                   | X   | Starting complexes, <sup>a</sup> reagents and reaction conditions                                                                                      | Yield (%) <sup>c</sup> | Ref.     |
|-------------------------------------------------------------------------------------|-------------------------|-------------------------------------|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|----------|
| Six-membered palladacycles                                                          |                         |                                     |     |                                                                                                                                                        |                        |          |
|  | <b>15b</b> <sup>b</sup> |                                     | NCS | <b>15a</b> , KSCN, MeOH–CH <sub>2</sub> Cl <sub>2</sub>                                                                                                | 26                     | 130, 131 |
|                                                                                     | <b>15k</b>              |                                     | Br  | <b>15a</b> , NaBr, MeOH–CH <sub>2</sub> Cl <sub>2</sub>                                                                                                | 59                     | 130, 131 |
|                                                                                     | <b>15l</b>              |                                     | I   | <b>15a</b> , NaI, MeOH–CH <sub>2</sub> Cl <sub>2</sub>                                                                                                 | 24                     | 130, 131 |
|  | <b>15d</b>              | PPh <sub>3</sub>                    |     | <b>15a</b> , PPh <sub>3</sub> , NaBPh <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 30 min                                                   | 39                     | 131, 132 |
|                                                                                     | <b>15e</b>              | AsPh <sub>3</sub>                   |     | <b>15a</b> , AsPh <sub>3</sub> , NaBPh <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 30 min                                                  | 41                     | 132      |
|                                                                                     | <b>15f</b>              | SbPh <sub>3</sub>                   |     | <b>15a</b> , SbPh <sub>3</sub> , NaBPh <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 30 min                                                  | 37                     | 132      |
|                                                                                     | <b>15h</b>              | 4-MeC <sub>5</sub> H <sub>4</sub> N |     | <b>15a</b> , 4-MeC <sub>5</sub> H <sub>4</sub> N (1.2 equiv.), NaBPh <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> –Me <sub>2</sub> CO, Δ, 5 h        | 34                     | 132      |
|                                                                                     | <b>15i</b> <sup>c</sup> | PPh <sub>2</sub> Me                 |     | <b>15a</b> , PPh <sub>2</sub> Me, NaBPh <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> –Me <sub>2</sub> O, 20 °C, 30 min                               | 54                     | 132      |
|                                                                                     | <b>15j</b>              | PCy <sub>3</sub>                    |     | <b>15a</b> , PCy <sub>3</sub> , NaBPh <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> –Me <sub>2</sub> O, 20 °C, 30 min                                 | 32                     | 131, 132 |
|                                                                                     | <b>15m</b>              | P(OMe) <sub>3</sub>                 |     | <b>15a</b> , P(OMe) <sub>3</sub> , NaBPh <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> –Me <sub>2</sub> O, 20 °C, 30 min                              | 23                     | 132      |
|                                                                                     | <b>15n</b>              | 3,5-dmpz                            |     | <b>15a</b> , 3,5-dmpz, NaBPh <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> –Me <sub>2</sub> O, 20 °C, 30 min                                          | 24                     | 132      |
|  | <b>15g</b>              |                                     |     | <b>15a</b> , 4-MeC <sub>5</sub> H <sub>4</sub> N (4.2 equiv.), NaBPh <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> –Me <sub>2</sub> CO, 20 °C, 30 min | 14                     | 132      |
|                                                                                     |                         |                                     |     |                                                                                                                                                        |                        |          |
|  | <b>35b</b> <sup>c</sup> | PPh <sub>3</sub>                    |     | <b>35a</b> , PPh <sub>3</sub> , NaBPh <sub>4</sub>                                                                                                     | —                      | 136      |
|                                                                                     | <b>35c</b>              | PPh <sub>2</sub> Me                 |     | <b>35a</b> , PPh <sub>2</sub> Me, NaBPh <sub>4</sub>                                                                                                   | —                      | 136      |
|                                                                                     | <b>35d</b>              | AsPh <sub>3</sub>                   |     | <b>35a</b> , AsPh <sub>3</sub> , NaBPh <sub>4</sub>                                                                                                    | —                      | 136      |
| Five-membered palladacycles                                                         |                         |                                     |     |                                                                                                                                                        |                        |          |
|  | <b>16e</b>              | PPh <sub>3</sub>                    |     | <b>16d</b> , PPh <sub>3</sub> , NaBPh <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 30 min                                                   | 33                     | 131, 132 |
|                                                                                     | <b>16f</b>              | PCy <sub>3</sub>                    |     | <b>16d</b> , PCy <sub>3</sub> , NaBPh <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 30 min                                                   | 20                     | 131, 132 |

## Supplement 2 (continued).

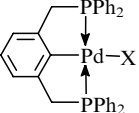
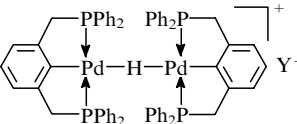
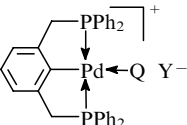
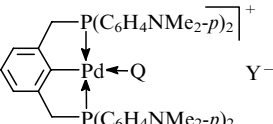
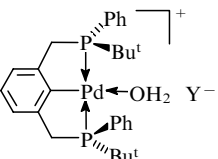
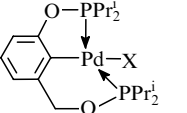
| Complex                                                                           | Number of the compound     | Q | X   | Starting complexes, <sup>a</sup> reagents and reaction conditions                                           | Yield (%) <sup>c</sup> | Ref. |
|-----------------------------------------------------------------------------------|----------------------------|---|-----|-------------------------------------------------------------------------------------------------------------|------------------------|------|
| Five-membered palladacycles                                                       |                            |   |     |                                                                                                             |                        |      |
|  | <b>16b</b> <sup>c, d</sup> |   | I   | <b>16a</b> , KI, Me <sub>2</sub> CO, Δ, 4 h                                                                 | 62                     | 133  |
|                                                                                   | <b>16i</b> <sup>c, d</sup> |   | SCN | <b>16a</b> , KSCN, Me <sub>2</sub> CO, Δ, 4 h                                                               | 73                     | 133  |
|  | <b>16j</b> <sup>c, e</sup> |   | SCN | [(C <sub>6</sub> Cl <sub>5</sub> )ClPd(η <sup>2</sup> -L <sup>16</sup> )], KSCN, Me <sub>2</sub> CO, Δ, 4 h | 71                     | 133  |
|                                                                                   | <b>16k</b> <sup>c, f</sup> |   | I   | [(C <sub>6</sub> Cl <sub>5</sub> )ClPd(η <sup>2</sup> -L <sup>16</sup> )], KI, Me <sub>2</sub> CO, Δ, 4 h   | 62                     | 133  |

<sup>a</sup> The complexes [Pd(η<sup>2</sup>-L)X<sub>2</sub>] or [ArPd(η<sup>2</sup>-L)X] were used as the starting compounds. <sup>b</sup> The complex exists in solutions as a 2 : 1 mixture of isomers with N- and S-bonded anions. <sup>c</sup> The complex exists in solutions as a mixture of *cis*- and *trans*-isomers. <sup>d</sup> The ratio *trans*(C,C) : *cis*(C,C) = 4 : 1. <sup>e</sup> The ratio *trans*(C,C) : *cis*(C,C) = 8 : 1. <sup>f</sup> Mixture *trans*(C,C) : *cis*(C,C) = 3 : 1.

## Supplement 3. Derivatives of pincer PCP complexes.

| Complex                                                                             | Number of the compound <sup>a</sup> | Q                   | X     | Y <sup>-</sup> | Starting complexes, <sup>b</sup> reagents and reaction conditions                                                                                                                                                  | Yield (%) <sup>c</sup> | Ref.     |
|-------------------------------------------------------------------------------------|-------------------------------------|---------------------|-------|----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|----------|
| Five-membered palladacycles annelated at the C(sp <sup>3</sup> )—Pd bond            |                                     |                     |       |                |                                                                                                                                                                                                                    |                        |          |
|  | <b>39a</b>                          |                     | H     |                | [(η <sup>3</sup> -L <sup>39</sup> )PdCl], LiAlH <sub>4</sub> , THF, 20 °C, 4 h                                                                                                                                     | 75                     | 248      |
|                                                                                     | <b>39b</b> <sup>*</sup>             |                     | Me    |                | [(η <sup>3</sup> -L <sup>39</sup> )PdCl], Et <sub>2</sub> O, MeLi, 20 °C, 1 h                                                                                                                                      | 84                     | 248, 255 |
|  | <b>39c</b> <sup>*</sup>             | H <sub>2</sub> O    |       |                | 1. a) [(η <sup>3</sup> -L <sup>39</sup> )PdCl], Et <sub>2</sub> O, MeLi, 20 °C, 1 h; b) [Et <sub>2</sub> NH <sub>2</sub> ]BPh <sub>4</sub> (1 equiv.), moist ethylene atmosphere, 3 min;                           | 53                     | 248      |
|                                                                                     | <b>39d</b>                          | CD <sub>3</sub> CN  |       |                | 2. a) [(η <sup>3</sup> -L <sup>39</sup> )PdCl], Et <sub>2</sub> O, MeLi, 20 °C, 1 h; b) [Et <sub>2</sub> NH <sub>2</sub> ]BPh <sub>4</sub> (1 equiv.), CD <sub>2</sub> Cl <sub>2</sub> —H <sub>2</sub> O (~ 1 : 1) | ~ 100                  | 248      |
|  |                                     |                     |       |                | a) [(η <sup>3</sup> -L <sup>39</sup> )PdCl], Et <sub>2</sub> O, MeLi, 20 °C, 1 h; b) [PhNH <sub>3</sub> ]BPh <sub>4</sub> (1 equiv.), CD <sub>3</sub> CN (excess)                                                  | see <sup>d</sup>       | 312      |
|                                                                                     | <b>65</b> <sup>c</sup>              |                     |       |                | [(η <sup>3</sup> -L <sup>65</sup> )PdCl], NaI, THF, 20 °C, 2 h                                                                                                                                                     | 93                     | 313      |
| Five-membered palladacycles annelated at the C(sp <sup>2</sup> )—Pd bond            |                                     |                     |       |                |                                                                                                                                                                                                                    |                        |          |
|  | <b>66b</b> <sup>*</sup>             |                     | Ph    |                | [(η <sup>3</sup> -L <sup>66</sup> )PdOC(O)CF <sub>3</sub> ], PhLi                                                                                                                                                  | 81                     | 305      |
|                                                                                     | <b>66c</b>                          |                     | I     |                | a) [(η <sup>3</sup> -L <sup>66</sup> )PdOC(O)CF <sub>3</sub> ], PhLi; b) PhI                                                                                                                                       | (~ 100) <sup>d</sup>   | 305      |
|  | <b>38a</b>                          |                     | H     |                | [(η <sup>3</sup> -L <sup>38</sup> )PdCl], EtOH, NaBH <sub>4</sub> , Δ, 1.5 h                                                                                                                                       | 96                     | 247      |
|                                                                                     | <b>38b</b>                          |                     | I     |                | 1. a) [(η <sup>3</sup> -L <sup>38</sup> )PdCl], NaBH <sub>4</sub> , EtOH, Δ, 1.5 h; b) <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> I                                                                                | (~ 100) <sup>d</sup>   | 305      |
|  | <b>38c</b>                          |                     | C≡CPh |                | 2. [(η <sup>3</sup> -L <sup>38</sup> )Pd(TFA)], LiI                                                                                                                                                                | —                      | 305      |
|                                                                                     |                                     |                     |       |                | [(η <sup>3</sup> -L <sup>38</sup> )PdCl], HC≡CPh, Bu <sup>n</sup> Li, PhH, Δ, 4 h                                                                                                                                  | 93                     | 247      |
|  | <b>38d</b>                          | d <sub>8</sub> -THF |       |                | [(η <sup>3</sup> -L <sup>38</sup> )PdCl], AgBF <sub>4</sub> , d <sub>8</sub> -THF                                                                                                                                  | (> 95)                 | 253      |
|                                                                                     | <b>38e</b> <sup>*</sup>             | H <sub>2</sub> O    |       |                | [(η <sup>3</sup> -L <sup>38</sup> )PdCl], AgBF <sub>4</sub> , d <sub>8</sub> -THF, traces H <sub>2</sub> O, 20 °C, 15 min                                                                                          | —                      | 253      |

## Supplement 3 (continued).

| Complex                                                                             | Number of the compound <sup>a</sup> | Q                               | X                                                   | Y <sup>−</sup>   | Starting complexes, <sup>b</sup> reagents and reaction conditions                                                                                                                                                                                                     | Yield (%) <sup>c</sup> | Ref. |
|-------------------------------------------------------------------------------------|-------------------------------------|---------------------------------|-----------------------------------------------------|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------|
| Five-membered palladacycles annelated at the C(sp <sup>2</sup> )–Pd bond            |                                     |                                 |                                                     |                  |                                                                                                                                                                                                                                                                       |                        |      |
|    | <b>40b</b>                          |                                 | H                                                   |                  | $[(\eta^3\text{-L}^{40})\text{Pd}(\text{HNMe}_2)]\text{OTf}$ , <sup>e</sup> LiNCy <sub>2</sub> (excess), d <sub>8</sub> -THF, −78 °C                                                                                                                                  | see <sup>d</sup>       | 251  |
|                                                                                     | <b>40n</b>                          |                                 | NMe <sub>2</sub>                                    |                  | $[(\eta^3\text{-L}^{40})\text{Pd}(\text{HNMe}_2)]\text{OTf}$ , <sup>e</sup> LiNCy <sub>2</sub> (1 equiv.), d <sub>8</sub> -THF, −78 °C, 2 h                                                                                                                           | see <sup>d</sup>       | 251  |
|                                                                                     | <b>40f</b>                          |                                 | OMe                                                 |                  | a) <b>40c</b> , AgBF <sub>4</sub> , THF, 20 °C;<br>b) NaOMe, THF, 10 min                                                                                                                                                                                              | —                      | 256  |
|                                                                                     | <b>40j*</b>                         |                                 | α-furyl<br>(α-C <sub>4</sub> H <sub>3</sub> O)      |                  | <b>40i</b> , η <sup>2</sup> -2-Bu <sub>3</sub> SnC <sub>4</sub> H <sub>3</sub> O (excess), Me <sub>2</sub> CO (anhydrous), cooling                                                                                                                                    | 100                    | 260  |
|                                                                                     | <b>40k</b>                          |                                 | OH                                                  |                  | a) <b>40c</b> , AgBF <sub>4</sub> , THF, 20 °C, 2 h;<br>b) NaOH, H <sub>2</sub> O, 20 °C, 12 h                                                                                                                                                                        | —                      | 256  |
|                                                                                     | <b>40l</b>                          |                                 | O(CH <sub>2</sub> ) <sub>4</sub> CH=CH <sub>2</sub> |                  | a) <b>40c</b> , AgBF <sub>4</sub> ,<br>b) LiO(CH <sub>2</sub> ) <sub>4</sub> CH=CH <sub>2</sub> , THF, 1 h                                                                                                                                                            | —                      | 256  |
|    | <b>40a</b>                          |                                 |                                                     | OTf              | 1. a) <b>40c</b> , AgCF <sub>3</sub> SO <sub>3</sub> , Me <sub>2</sub> CO, 30 min;<br>b) NaO <sub>2</sub> CH (excess) MeOH, 30 min<br>2. $[(\eta^3\text{-L}^{40})\text{Pd}(\text{HNMe}_2)]\text{OTf}$ , <sup>e</sup> LiNCy <sub>2</sub> (10 equiv.), THF, −78 °C, 2 h | ~100                   | 250  |
|                                                                                     | <b>40m<sup>f</sup></b>              |                                 |                                                     | BPh <sub>4</sub> | <b>40a</b> , Na[BPh <sub>4</sub> ], MeOH                                                                                                                                                                                                                              | —                      | 250  |
|   | <b>40d*</b>                         | PhNH <sub>2</sub>               |                                                     | BF <sub>4</sub>  | a) <b>40c</b> , AgBF <sub>4</sub> , THF, 1 h;<br>b) nb, <sup>g</sup> PhNH <sub>2</sub> , 12 h                                                                                                                                                                         | 70–82                  | 256  |
|                                                                                     | <b>40e</b>                          | nb <sup>g</sup>                 |                                                     | BF <sub>4</sub>  | a) <b>40c</b> , AgBF <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 20 min;<br>b) nb, <sup>g</sup> 10 min                                                                                                                                                    | —                      | 256  |
|                                                                                     | <b>40g</b>                          | PEt <sub>3</sub>                |                                                     | BF <sub>4</sub>  | a) $[(\eta^3\text{-L}^{40})\text{Pd}(\text{MeCN})]\text{BF}_4$ , $[\text{Pd}(\text{MeCN})_4](\text{BF}_4)_2$ , THF–MeCN, 20 °C, 12 h; b) PEt <sub>3</sub> , 20 °C, 2 h                                                                                                | 64                     | 259  |
|                                                                                     | <b>40h</b>                          | THF                             |                                                     | BF <sub>4</sub>  | <b>40c</b> , AgBF <sub>4</sub> , THF, 20 °C, 20 min                                                                                                                                                                                                                   | —                      | 256  |
|                                                                                     | <b>40o</b>                          | Me <sub>2</sub> CO              |                                                     | OTf              | <b>40c</b> , AgOTf, Me <sub>2</sub> CO, 30 min                                                                                                                                                                                                                        | —                      | 250  |
|                                                                                     | <b>40p</b>                          | CH <sub>2</sub> Cl <sub>2</sub> |                                                     | BF <sub>4</sub>  | <b>40c</b> , AgBF <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C                                                                                                                                                                                              | —                      | 256  |
|  | <b>41a</b>                          | THF                             |                                                     | PF <sub>6</sub>  | $[(\eta^3\text{-L}^{41})\text{PdCl}]\text{, TIPF}_6$ , THF, 20 °C, 20 min                                                                                                                                                                                             | see <sup>d</sup>       | 256  |
|                                                                                     | <b>41b</b>                          | nb <sup>g</sup>                 |                                                     | PF <sub>6</sub>  | a) $[(\eta^3\text{-L}^{41})\text{PdCl}]\text{, TIPF}_6$ , THF, 20 °C, 20 min;<br>b) nb, <sup>g</sup> THF                                                                                                                                                              | see <sup>d</sup>       | 256  |
|                                                                                     | <b>41c</b>                          | THF                             |                                                     | BF <sub>4</sub>  | $[(\eta^3\text{-L}^{41})\text{PdCl}]\text{, AgBF}_4$ , THF, 20 °C, 20 min                                                                                                                                                                                             | see <sup>d</sup>       | 256  |
|                                                                                     | <b>41d</b>                          | H <sub>2</sub> Cl <sub>2</sub>  |                                                     | BF <sub>4</sub>  | $[(\eta^3\text{-L}^{41})\text{PdCl}]\text{, AgBF}_4$ , CH <sub>2</sub> Cl <sub>2</sub>                                                                                                                                                                                | see <sup>d</sup>       | 256  |
|  | <b>67a</b>                          |                                 |                                                     | OTf              | $[(\eta^3\text{-L}^{66})\text{PdBr}]\text{, AgOTf}$ , Me <sub>2</sub> CO–H <sub>2</sub> O, 20 °C, 1 h                                                                                                                                                                 | 95                     | 314  |
|                                                                                     | <b>67b</b>                          |                                 |                                                     | BF <sub>4</sub>  | $[(\eta^3\text{-L}^{66})\text{PdBr}]\text{, AgBF}_4$ , Me <sub>2</sub> CO–H <sub>2</sub> O, 20 °C, 1 h                                                                                                                                                                | —                      | 314  |
|  | <b>37b</b>                          |                                 | I                                                   |                  | <b>37a</b> , NaI, Me <sub>2</sub> CO                                                                                                                                                                                                                                  | —                      | 246  |
|                                                                                     | <b>37c</b>                          |                                 | OAc                                                 |                  | <b>37a</b> , AgOAc, Et <sub>2</sub> O, ultrasound                                                                                                                                                                                                                     | —                      | 246  |

<sup>a</sup> The complexes studied by X-ray diffraction are asterisked. <sup>b</sup> The formula or the number of the starting complex is given. <sup>c</sup> The yield based on spectroscopic data is given in parentheses. <sup>d</sup> The complex was identified on the basis of spectroscopic data. <sup>e</sup> The synthesis of  $[(\eta^3\text{-L}^{40})\text{Pd}(\text{HNMe}_2)]\text{OTf}$  has been reported.<sup>258</sup> <sup>f</sup> The complex is unstable and decomposes in solutions to give Pd(0). <sup>g</sup> nb is norbornene.

\* \* \*

During the preparation of this manuscript for publication (2004–2005), a number of new studies dealing with this subject have appeared. A series of reviews on the chemistry of palladacycles<sup>315</sup> and their use in catalysis<sup>316–320</sup> published during this period demonstrates the persistent interest in this field of knowledge. Studies on the activation of C–H bonds,<sup>321</sup> estimation of the phosphine basicity<sup>322</sup> and coordination properties<sup>323</sup> have con-

tinued; new data on the STE of coordination<sup>324</sup> and organometallic<sup>325</sup> palladium compounds have appeared.

As regards the design of new phosphapalladacyclic structures, attention has been focused on pincer PCP-complexes. Methods for the synthesis of new CPCs of this type have been developed;<sup>326–332</sup> in particular, the first complexes with the ferrocenyl core<sup>330,331</sup> and non-symmetric PCP'-structures with two different palladacycles were obtained.<sup>332</sup> The linear and branched bi- and trinuclear compounds with two or three PCP fragments<sup>333</sup> have been synthesised (for platinum, a tetra-PCP complex with the

porphyrin core has been prepared<sup>334</sup>). The unsuccessful attempt at cyclopalladation of diphosphine with the *m*-terphenyl core<sup>335</sup> emphasises once again the lack of stability for systems with two annelated seven-membered palladacycles.

The range of monocyclic PC-structures has been barely extended.<sup>336,337</sup> The development of a new method for the synthesis of mixed-ligand *spiro*-complexes<sup>338</sup> and the study of the rotation isomerism of PC-palladacycles<sup>339</sup> deserve attention.

The works dealing with reactions of phosphapalladacycles remain scarce. Of obvious interest are the results obtained in a study of the transformations of PCP-complexes under the action of reducing agents.<sup>340</sup> Further development of the chemistry of CPCs would be facilitated by the use of mass spectrometry. The potential of this method has recently been demonstrated in relation to the reactions of PCP-complexes with compounds of other metals (Pt, Au, Hg).<sup>326</sup> New derivatives of both known and new CPCs of the PC<sup>336,341</sup> and PCP types<sup>326,331,342,343</sup> have been synthesised, in particular, unusual dimers with a bridging anion (Cl<sup>−</sup>, CN<sup>−</sup>, COO<sup>2−</sup>) or a diphosphine linking two PCP-fragments.<sup>326,331,342,343</sup> A derivative of the ferrocenyl PCP-complex with a monodentate borohydride ligand has been isolated and studied by X-ray diffraction. This compound is unusual not only for a CPC but also for the coordination chemistry of palladium as a whole.<sup>331,342</sup> Study of the electrochemical behaviour of ferrocenyl PCP-complexes has shown oxidation of the ferrocenyl fragment.<sup>331</sup> The carbonylation of the hydroxy derivatives of PCP-complexes results in CO insertion into the Pd–O bond to give  $\mu$ -COO dimers.<sup>343</sup> The main impetus for the development of the chemistry of phosphapalladacycles is still the design of new efficient homogeneous (pre)catalysts based on the PC-<sup>336,337,344,345</sup> and PCP-type<sup>333,346–351</sup> CPCs. Recently, a soluble PC-palladacycle immobilised on polystyrene has been obtained.<sup>345</sup>

In conclusion, note the synthesis of new phosphapalladacyclic structures containing a carbene carbon atom instead of the carbanionic atom present in the classical CPCs.<sup>352</sup> The first imidazol-2-ylidene ligand functionalised by a phosphine fragment was synthesised in 2002.<sup>353</sup> A dozen palladium complexes with chelating carbene P $\curvearrowright$ C:-ligands have now been reported,<sup>354–357</sup> at least three pincer complexes with tridentate carbenes of the P $\curvearrowright$ C:P type have been obtained.<sup>357–359</sup> In all cases, the chelate carbene complexes were meant for being tested in catalysis; the brilliant future of this line of research is beyond doubt.

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<sup>c</sup> — *Russ. J. Org. Chem. (Engl. Transl.)*

# Benzo[*b*]naphthyridines

A S Ivanov, N Z Tugusheva, V G Granik

## Contents

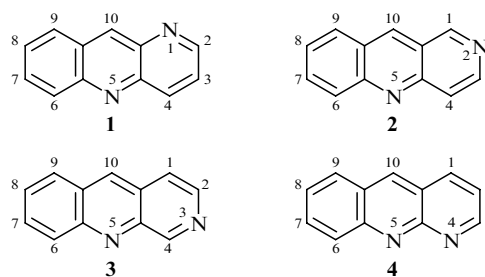
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**Abstract.** The published data on the methods for the synthesis, properties and applications of benzo[*b*]naphthyridines are analysed and generalised. The main attention is focused on biologically active compounds of the benzo[*p*]naphthyridine series. The bibliography includes 140 references.

## I. Introduction

Benzo[*b*]naphthyridines **1–4** can be regarded as aza derivatives of acridines. By virtue of their planar linear structures, benzo[*b*]naphthyridines attract keen attention of investigators as promising antitumour agents, *viz.*, intercalators.<sup>†</sup> The number of publications devoted to the synthesis and analysis of biochemical and pharmacological properties of representatives of this class of heterocycles is steadily increasing. However, no reviews specially devoted to benzo[*b*]naphthyridines exist so far. Several papers published before 1986 were considered in a review.<sup>1</sup> Some novel data on benzonaphthyridines were included into more recent reviews<sup>2–4</sup> devoted to naphthyridines. In this study, we made an attempt to generalise and systematise all published data on the methods for the synthesis and properties of benzo[*b*]naphthyridines (hereinafter referred to for the sake of brevity as benzonaphthyridines). The review encompasses the literature published in the period from 1980 to 2004. Wherever necessary, some earlier papers are included for a more logical and consistent presentation of the material. Special attention is given to the description of methods for the synthesis of benzonaphthyridine derivatives which present interest for medicinal chemistry with due regard to the state-of-the-art and trends.

The structural formulas of all the four isomeric benzo[*b*]naphthyridines **1–4** containing 1,5-, 1,6-, 1,7- or 1,8-naphthyridine skeletons are given below.



## II. Physicochemical properties

Relative nucleophilicities of the nitrogen atoms in the peripheral pyridine ring of 6-methylbenzo[*b*]naphthyridines **5–8** upon their interactions with MeI in DMSO have been studied.<sup>5</sup> To this end, the relative methylation rates of compounds **5–8** with respect to pyridine ( $k_1/k_{Py}$ ) were measured by the competitive reaction method (Table 1). The presence of a methyl group in the benzene ring near the nitrogen atom in the central ring in the compounds under study prevents the reaction from occurring at the acridine nitrogen atom; the reactivities of compounds **5–8** decrease in the following order: 1,8-naphthyridine > 1,6 > 1,7 > 1,5 (see<sup>‡</sup>).<sup>5,6</sup> High reactivity of benzo[*b*][1,8]naphthyridine (**5**) is attributed<sup>5</sup> to the proximity of the lone pairs of the N(1) and N(10) atoms involved in transition state **9** upon quaternisation of N(1). However, in the case of the benzo[*b*][1,5]-isomer **8** the reaction at N(1) is hindered by the H(10) atom in the *peri*-position.<sup>6,7</sup>

Such an interpretation seems to be reasonable enough, but it fails to provide an explicit answer to the question why the methylation rates of all benzonaphthyridines fit in the above-mentioned series. In our opinion, this problem requires an analysis of all initial and hypothetical transition states realised in the processes under consideration. For compound **5**, stabilised hypothetical transition state **9** is rather plausible despite certain instability of the initial state resulting from the interaction of the electron pairs at N(4) and N(5). A combination of these two factors leads to a general decrease in the free activation energy and

A S Ivanov, N Z Tugusheva, V G Granik Federal State Unitary Enterprise 'State Scientific Centre on Antibiotics', ul. Nagatinskaya 3a, 117105 Moscow, Russian Federation. Fax (7-495) 231 42 38, tel. (7-495) 231 42 93, e-mail: a.ivanov@mail.ru (A S Ivanov), tel. (7-495) 231 42 84 (N Z Tugusheva), (7-495) 231 42 83, e-mail: vggranik@mail.ru (V G Granik)

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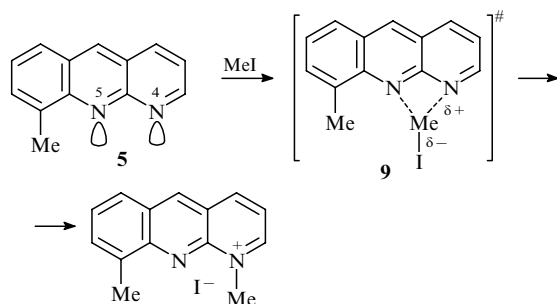
<sup>†</sup> Intercalation entails insertion of compounds between base pairs of DNA; the complex formed is stabilised by van der Waals forces. Intercalation prevents unwinding of DNA chains and, as a consequence, their normal functioning.

<sup>‡</sup> Hereinafter, the isomers bear the numbers corresponding to those used to denote naphthyridines.

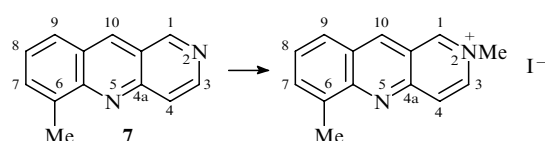
**Table 1.** Relative methylation rates of compounds **5–8** in comparison with pyridine.

| Compound | Isomer | $k_1/k_{Py}$ | Compound | Isomer | $k_1/k_{Py}$ |
|----------|--------|--------------|----------|--------|--------------|
|          | 1,8    | 0.325        |          | 1,6    | 0.265        |
|          | 1,7    | 0.169        |          | 1,5    | 0.010        |

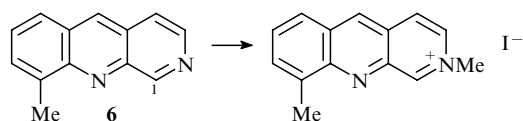
thus determines the highest methylation rate of this particular isomer.



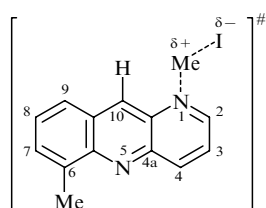
The methylation rate of the 1,6-isomer **7** is comparable with that of the isomer **5**.



The absence of conjugation between the electron-withdrawing double bond C(4a)=N(5) and the nitrogen atom at position 2 of compound **7** favours the electrophilic attack at this nitrogen atom in comparison with other benzonaphthyrindines (except for compound **5**). Neither stabilisation of the initial state nor destabilisation of the transition state take place in this case. The methylation rate of the 1,7-isomer **6** is even lower, since the conjugation between two double bonds C=N results in stabilisation of the initial state and destabilisation of the transition state.



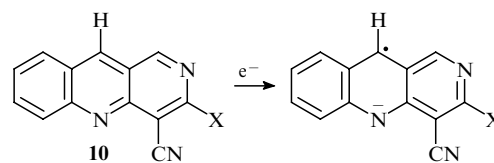
This finding provides a rationale for the decrease in the methylation rate of compound **6** in comparison with other isomers considered above. Methylation of the tricycle **8** is controlled by the same factors. There exists yet another factor responsible for the lowering of the reactivity of 1,5-naphthyrindine (**8**) in comparison with the isomer **6**. The transition state of compound **8** can be presented as follows:



Apart from destabilisation induced by the electron-withdrawing effect (conjugation) of the C(4a)=N(5) bond, the stability of

the transition state is adversely affected by yet another factor, *viz.*, the nonbonding interaction between the N(1)⋯Me and C(10)–H bonds in *peri*-positions. It is this contributing evidence that sheds additional light on the lower (in comparison with the isomeric compound **6**) methylation rate of the tricycle **8**.

The electroreduction of 3-substituted 4-cyanobenzo[*b*][1,6]-naphthyrindine derivatives **10** in DMF was studied by polarography.<sup>8</sup> It was found that the first step of this reaction includes transfer of one electron to position 10 (analogously to reduction of acridine), which is consistent with the appearance of one-electron waves on the polarograms. It was found also that an increase in the electron-donor properties of the substituents at position 3 causes a shift of polarographic half-wave reduction potentials to negative values, *i.e.*, hinders reduction of the tricycles **10**.



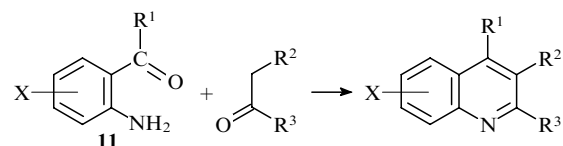
X = NR<sup>1</sup>R<sup>2</sup>, SR<sup>1</sup>; R<sup>1</sup>, R<sup>2</sup> = Alk, Ar.

### III. Methods for synthesis

The most general approaches to the synthesis of benzonaphthyrindines are based on the methods used for the closure of the pyridine ring in the course of quinoline synthesis. The use of the Friedlander and Pfitzinger reactions and the synthesis based on arylaminopyridines enable the preparation of derivatives with functional groups at different positions of the tricyclic system.

#### 1. Friedlander reaction and its modifications

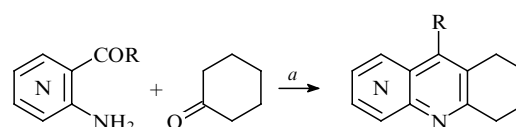
The Friedlander reaction is the most general and well-developed approach to the synthesis of various benzo[*b*]naphthyrindines. It is based on the reaction of *o*-aminoaryl(hetaryl)carbonyl compounds with methylene ketones.<sup>9</sup>

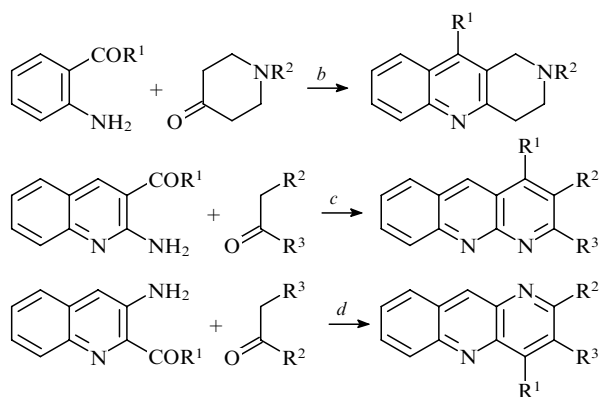


The Niementowski (R<sup>1</sup> = OH) and Pfitzinger (R<sup>1</sup> = CO<sub>2</sub>H) reactions are essentially very similar to the Friedlander reaction (the Pfitzinger reaction is more extensively used for the preparation of benzo[*b*][1,6]naphthyrindines).

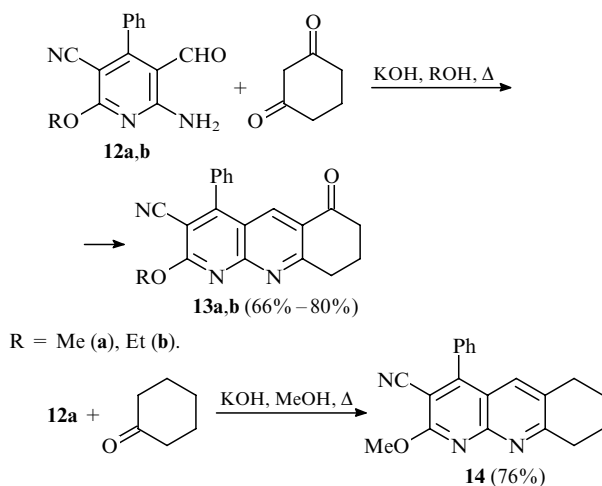
The classical variant of the Friedlander reaction makes use of *o*-aminobenzaldehydes and basic catalysts (KOH, NaOH, piperidine, *etc.*), but this reaction can also be carried out in the absence of these catalysts. However, attempts to synthesise quinolines from less reactive *o*-aminobenzophenones under alkaline conditions are not always successful. In this case, the carbonyl group is activated by acids [HCl, H<sub>2</sub>SO<sub>4</sub>, TsOH, polyphosphoric acid (PPA), *etc.*]. Very often, the reaction is carried out by refluxing in AcOH in the presence of catalytic amounts of H<sub>2</sub>SO<sub>4</sub> (the so-called Fehnel modification<sup>10</sup>).

The formation of a pyridine ring in this reaction enables the synthesis of tricyclic benzonaphthyrindines. This can be accompanied by the closure of both the central (routes *a* and *b*) and peripheral pyridine rings (routes *c* and *d*).

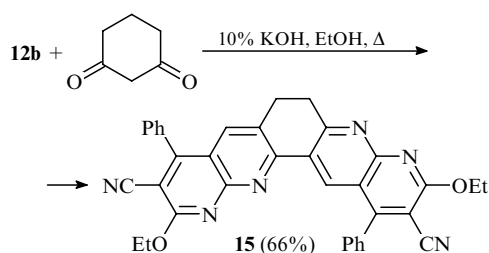




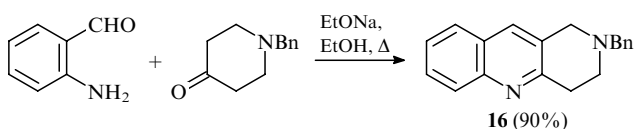
Substituted 2-amino-3-formylpyridines **12a,b** are involved in the Friedlander reaction with cyclohexane-1,3-dione and cyclohexanone under conditions of basic catalysis giving rise to the 1,8-naphthyridine derivatives **13a,b** and **14**. Cyclisation of cyclohexane-1,3-dione occurs much more smoothly due to higher CH-acidity of the methylene fragment.<sup>11, 12</sup>



If *o*-aminoaldehyde is used in excess, the reaction with cyclohexane-1,3-dione does not stop at the formation of benzonaphthyridine **14**, but proceeds further eventually resulting in the pentacyclic product **15**.<sup>12</sup>

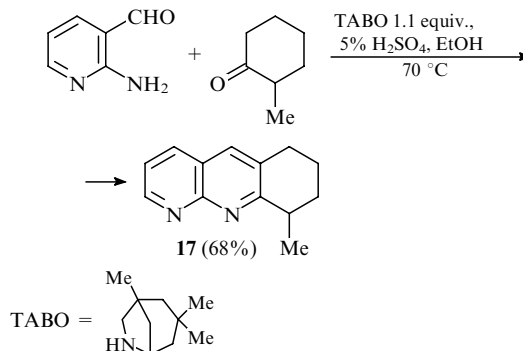


Shiozawa *et al.*<sup>13</sup> used 4-piperidones as ketone components in the synthesis of 2-benzyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine (**16**).

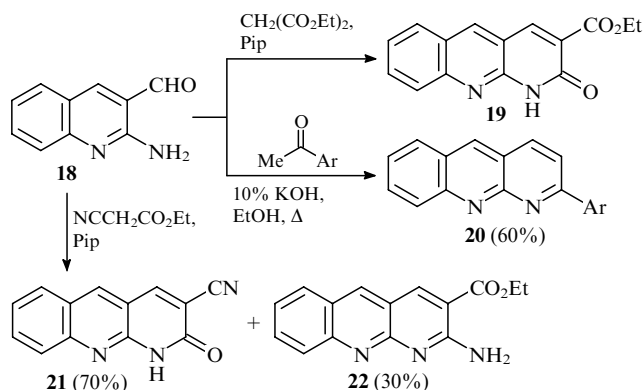


The reaction of 2-amino-3-formylpyridine with 2-methylcyclohexanone in the presence of 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (TABO) as the basic catalyst produced tetrahydrobenzo[*b*][1,8]naphthyridine **17**.<sup>14</sup> In earlier studies,<sup>15</sup> such conversion has been achieved by heating the reactants with sodium *tert*-butoxide in *tert*-butyl alcohol; the yield of naphthyridine **17** was 84%. Apparently, TABO is the catalyst of choice for the Friedlander reaction both by virtue of its high catalytic activity and optimum selectivity. This circumstance is of special importance in those cases where unsymmetrical ketones are used.<sup>14</sup>

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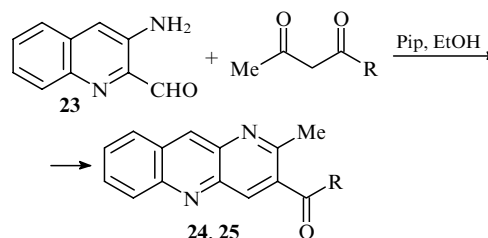


The Friedlander synthesis based on aminoformylquinolines was successfully used for the preparation of benzo[*b*][1,5]naphthyridines and benzo[*b*][1,8]naphthyridines.<sup>16</sup> Thus 2-amino-3-formylquinoline **18** was introduced into base-catalysed cyclocondensation with diethyl malonate and aryl methyl ketones to give the corresponding benzo[*b*][1,8]naphthyridines **19** and **20** in good yields. The reaction with ethyl cyanoacetate gave a mixture of naphthyridines **21** and **22**.



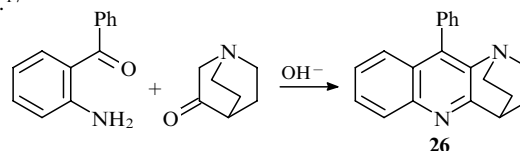
Pip is piperidine.

3-Aminoquinoline-2-carbaldehyde (**23**) reacts with acetylacetone in the presence of piperidine to give 3-acetyl-2-methylbenzo[*b*][1,5]naphthyridine (**24**). The condensation of compound **23** with ethyl acetoacetate under identical conditions involves only the ketone carbonyl group, 3-ethoxycarbonyl-2-methylbenzo[*b*][1,5]naphthyridine (**25**) being the only reaction product.<sup>16</sup>

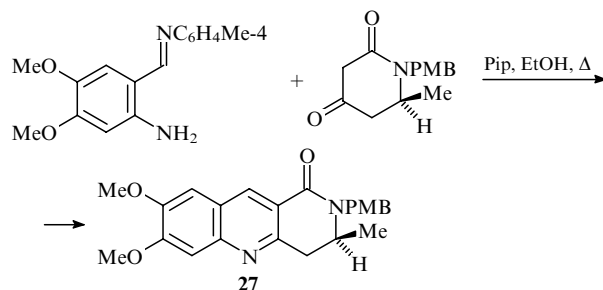


R = Me (**24**, 74%), OEt (**25**, 70%).

2-Aminobenzophenone reacts with quinuclidin-3-one under basic catalysis to give the benzo[*b*][1,5]naphthyridine derivative **26**.<sup>17</sup>

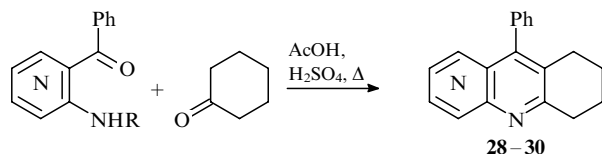


The Borsche modification of the Friedlander synthesis<sup>18</sup>, *i.e.*, the replacement of the aldehyde group with the azomethine fragment, enables the reaction to occur without complications due to low stability of substituted 2-aminobenzaldehydes at elevated temperatures. This reaction was used in the synthesis of benzonaphthyridine **27**.<sup>19</sup>



PMB is  $\text{CH}_2\text{C}_6\text{H}_4\text{OMe-4}$ .

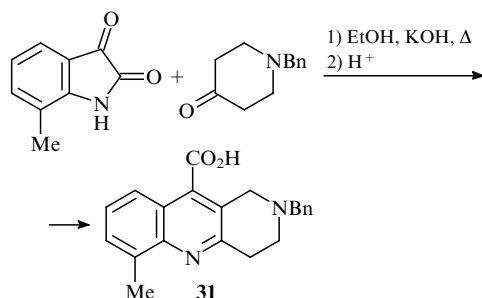
The reactions of *vic*-aminobenzoylpyridines or *vic*-(pivaloyl-amino)benzoylpyridines with cyclohexanone were used in the synthesis of the corresponding tricyclic derivatives of 1,6- (**28**), 1,7- (**29**) and 1,8-naphthyridine (**30**) (70%–99% yields).<sup>20–22</sup>



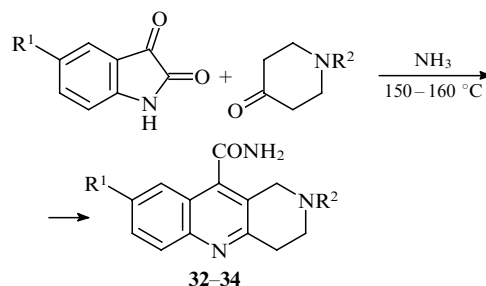
R = H,  $\text{Bu}^t\text{CO}$ .

The Pfitzinger reaction<sup>23</sup> involves condensation of isatine and its derivatives with methylene ketones in the presence of bases (KOH, NaOH, *etc.*), which convert isatine into isatinates. The latter, being *o*-aminocarbonyl compounds, react further with ketones according to the Friedlander reaction.

Thus the use of 4-piperidone derivatives as a carbonyl component in the Pfitzinger reaction enables the one-pot synthesis of 1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines in good yields. For example, refluxing of 7-methylisatine with 1-benzylpiperidin-4-one in ethanolic KOH affords 1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine-10-carboxylic acid (**31**).<sup>24</sup>



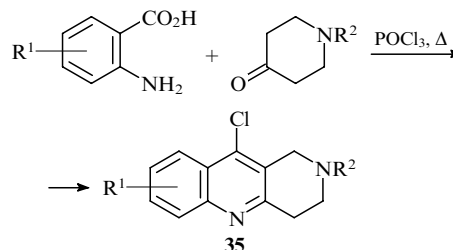
The synthesis of benzo[*b*][1,6]naphthyridine derivatives containing an amide group at position 10 by the Pfitzinger reaction is carried out in the presence of ammonia or ammonium salts. Thus derivatives of 2-benzyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine-10-carboxamide (**32**) and 1,2,3,4-tetrahydro-2-ethoxycarbonylbenzo[*b*][1,6]naphthyridine-10-carboxamide (**33**) were prepared by passing ammonia through the reaction mixture containing 5-substituted isatines and 1-benzylpiperidin-4-one or 1-ethoxycarbonylpiperidin-4-one, respectively, in ethylene glycol at 150–160 °C.<sup>25</sup> The reaction of isatine with 1-*tert*-butoxycarbonylpiperidin-4-one proceeds in a similar fashion: heating in DMF with ammonium acetate affords 2-*tert*-butoxycarbonyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine-10-carboxamide (**34**) in 50% yield.<sup>26</sup>



R<sup>1</sup> = H, Cl, F, OMe; R<sup>2</sup> = Bn (**32**), CO<sub>2</sub>Et (**33**), CO<sub>2</sub>Bu<sup>t</sup> (**34**).

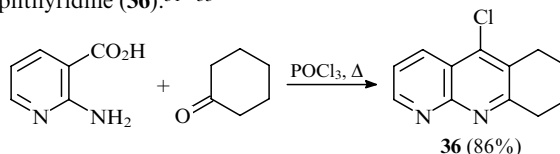
The approach employed in the synthesis of benzonaphthyridines, *i.e.*, reactions of substituted anthranilic acids and *o*-aminonitriles with cyclic ketones, is very similar to that underlying the Friedlander reaction. It is noteworthy that cyclisation reactions involving nitrile groups produce various amino derivatives of benzonaphthyridines (*i.e.*, aza analogues of 9-aminoacridines) that present substantial interest for biological investigations.

Heating of substituted anthranilic acids with *N*-alkyl- and *N*-arylpiperidin-4-ones in POCl<sub>3</sub> gave 2-substituted 10-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines **35**.<sup>27–30</sup>

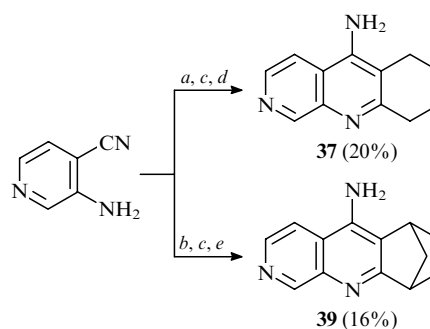


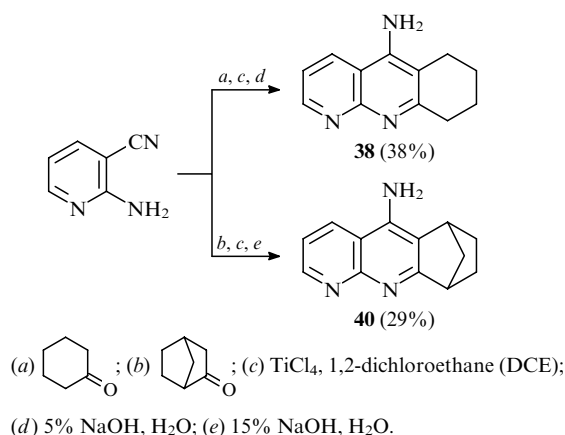
R<sup>1</sup> = H, Alk, NO<sub>2</sub>, Hal; R<sup>2</sup> = Alk, Ar.

Analogously, heating of 2-aminonicotinic acid with cyclohexanone and POCl<sub>3</sub> affords 5-chloro-6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridine (**36**).<sup>31–33</sup>



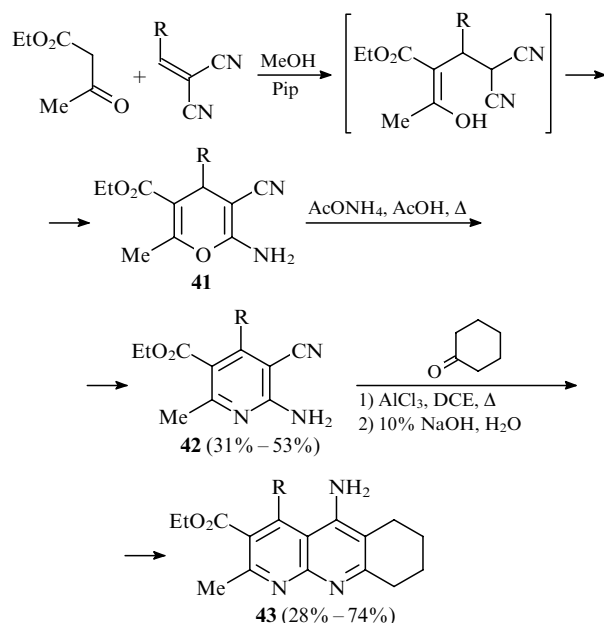
The synthesis of aminobenzonaphthyridines by reactions of *vic*-aminonitriles with cyclic ketones is of importance because it provides an approach to tetrahydro derivatives of 9-aminoacridine (aza analogues of the pharmaceutical tacrine). Heating of the reactants with Lewis acids (ZnCl<sub>2</sub>, AlCl<sub>3</sub>, TiCl<sub>4</sub>) affords complexes, which are decomposed by treatment with bases (NH<sub>4</sub>OH, aqueous NaOH). Thus reactions of 3-amino-4-cyanopyridine and 2-amino-3-cyanopyridine with cyclohexanone and TiCl<sub>4</sub> in dichloroethane give the corresponding 5-amino-6,7,8,9-tetrahydrobenzo[*b*]naphthyridines **37** and **38**. The tetracyclic 1,7- and 1,8-naphthyridine derivatives **39** and **40** were successfully synthesised,





although in lower yields, by the reactions of these compounds with norcamphor, which has a more rigid (in comparison with cyclohexanone) carbon skeleton.<sup>34</sup>

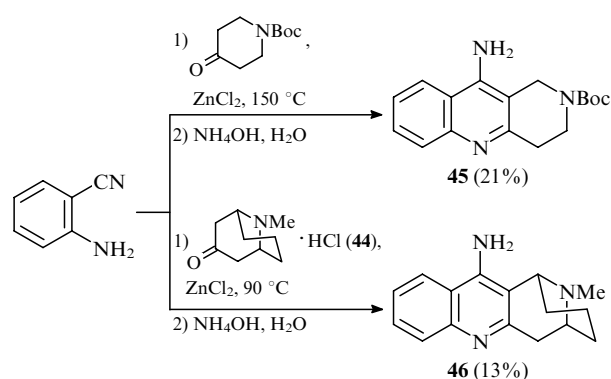
Pyrans **41** derived from ethyl acetoacetate and arylmethylidenemalononitriles underwent recyclisation under the action of ammonium acetate in acetic acid to yield the pyridine derivatives **42**. The resulting compounds containing cyano and amino groups in *vic* positions are involved in cyclocondensation with cyclohexanone in refluxing dichloroethane in the presence of  $\text{AlCl}_3$  to give the tricyclic 1,8-naphthyridine derivatives **43**.<sup>35,36</sup>



R = Ph,  $\text{C}_6\text{H}_4\text{OMe-4}$ ,  $\text{C}_6\text{H}_4\text{OMe-3}$ ,  $\text{C}_6\text{H}_3(\text{OMe})_2\text{-3,4}$ ,  
 $\text{C}_6\text{H}_4\text{F-4}$ ,  $\text{C}_6\text{H}_4\text{Cl-4}$ ,  $\text{C}_6\text{H}_4\text{NO}_2\text{-3}$ .

Cyclocondensation of 2-amino-4,6-diaryl nicotinonitriles with cyclohexanone in the presence of  $\text{ZnCl}_2$  gave 10-amino-1,3-diaryl-6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridines in 57%–65% yields.<sup>37</sup>

In the presence of  $\text{ZnCl}_2$ , anthranilonitrile reacts with cyclic ketones, such as 1-*tert*-butoxycarbonylpiperidin-4-one and pseudopelletierine hydrochloride (**44**), to give the corresponding 1,6-naphthyridine derivatives **45** and **46**.<sup>26,30</sup>



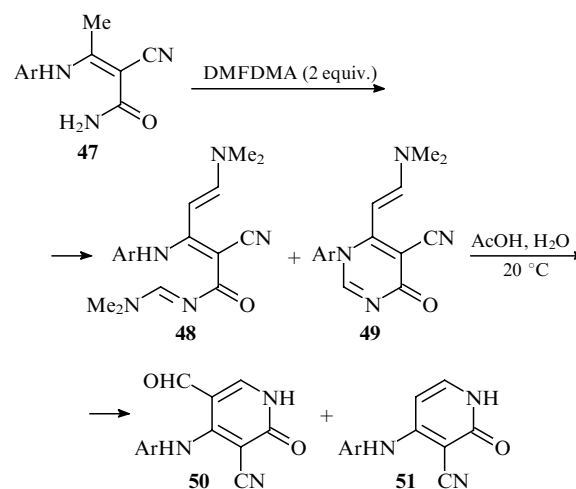
Boc =  $\text{CO}_2\text{Bu}^t$ .

## 2. Cyclisation of arylaminopyridines

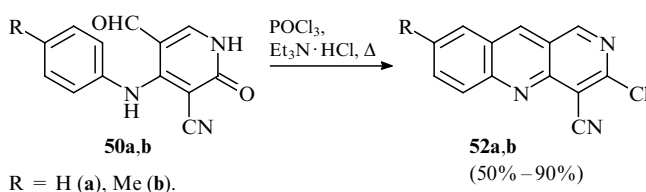
An efficient approach to the design of the benzonaphthyridine system is based on the synthesis involving arylaminopyridines whose aryl rings (less frequently, the pyridine ring) contain a group capable of providing intramolecular cyclisation. Arylaminopyridines are usually prepared by the replacement of good leaving groups in pyridine derivatives with arylamines as well as by the Ullman reaction.

### a. Cyclisation involving carbonyl groups of aldehydes, ketones and esters

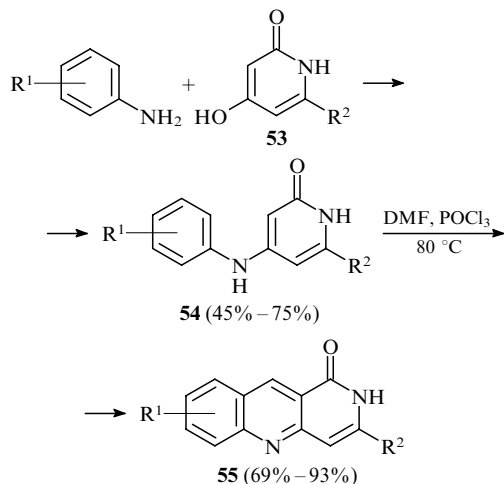
*N,N*-Dimethylformamide dimethyl acetal (DMFDMA) reacts with *N*-aryleneamines **47** involving both the amide and reactive methyl groups to give mixtures of dieneamidines **48** and 1-arylpyrimidinones **49**.<sup>38</sup> Because of low stability of dieneamidines **48**, the resulting mixtures are subjected to acid hydrolysis in aqueous AcOH without separation; this resulted in mixtures of the corresponding formylpyridones **50** and pyridones **51**. The former can be easily isolated due to their lower solubility. Special studies have demonstrated that formylpyridones can be produced only from dieneamidines **48**, whereas hydrolysis of pyrimidinones **49** yields exclusively pyridones **51**.



Cyclisation of 4-arylamino-3-cyano-5-formylpyridones **50a,b** under the action of  $\text{POCl}_3$  in the presence of  $\text{Et}_3\text{N} \cdot \text{HCl}$  afforded 3-chloro derivatives of benzo[*b*][1,6]naphthyridine **52a,b**.<sup>38,39</sup>

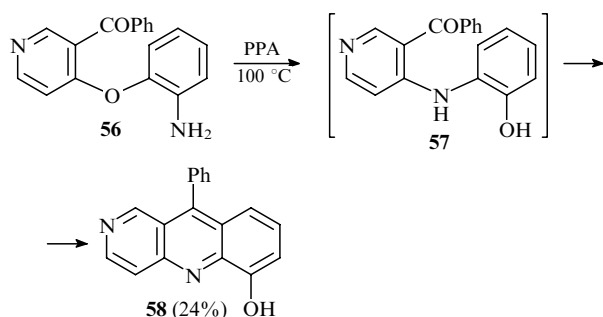


The reactions of arylamines with pyridones **53** give the corresponding 4-arylaminopyridones **54**. These reactions can be performed in the presence of the corresponding arylamine hydrochloride.<sup>40,41</sup> Compounds **54** undergo regioselective formylation at position 3 activated by the arylamino group followed by cyclisation to give the corresponding benzo[*b*][1,6]naphthyridines **55** substituted in the benzene ring and at position 3.<sup>40,42</sup>

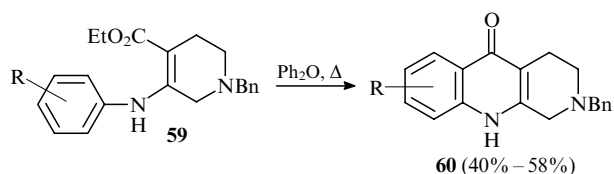


$R^1 = \text{H, 3-Cl, 3-OMe, 2,5-Me}_2$ ;  $R^2 = \text{H, Me}$ .

4-(2-Aminophenoxy)-3-benzoylpyridine (**56**) is unstable in both the solid state and in solution and is gradually isomerised into anilinyridine **57** as a result of the  $\text{O} \rightarrow \text{N}$ -Smiles rearrangement.<sup>43</sup> Heating of compound **56** in PPA leads to the rearrangement and subsequent cyclisation to give 6-hydroxy-10-phenylbenzo[*b*][1,6]naphthyridine (**58**).<sup>44</sup>



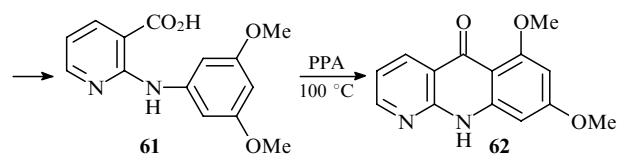
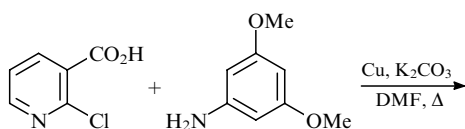
Heating of compounds **59** in diphenyl ether leads to its cyclisation to form benzo[*b*][1,7]naphthyridines **60**.<sup>45</sup>



$R = 2\text{-Cl (59), 4-OMe (59); 6-Cl (60), 8-OMe (60)}$ .

#### b. Cyclisation involving the carboxy group

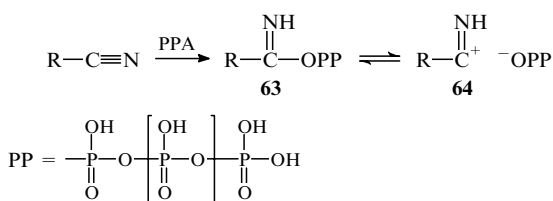
The Ullman reaction was used in the synthesis of 2-(3,5-dimethoxyphenyl)aminonicotinic acid (**61**), which underwent cyclisation to form benzo[*b*][1,8]naphthyridinone **62** as a result of heating in PPA.<sup>46</sup>



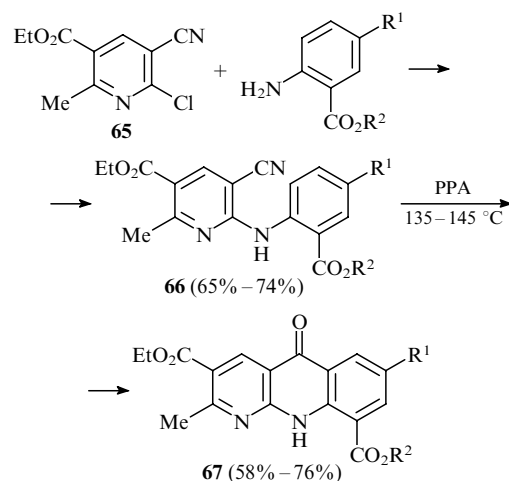
Other benzo[*b*][1,8]naphthyridinone derivatives were prepared analogously from arylaminonicotinic acids.<sup>47,48</sup>

#### c. Cyclisation involving the nitrile group

Heating of starting compounds with strong acids is one of the most efficient procedures for the closure of the pyridine ring involving the nitrile group. Thus PPA can add to the nitrile group to give compounds **63**.<sup>49</sup> The latter can exist in equilibrium with iminocarbenium ions **64**, which are much more electrophilic than the starting imidoyl polyphosphates **63**.<sup>50</sup>



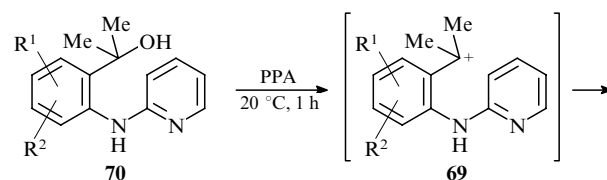
Concentrated  $\text{H}_2\text{SO}_4$  and  $\text{H}_3\text{PO}_4$  capable of activating the nitrile group through protonation can be used instead of PPA. However, the disadvantage of the use of PPA and  $\text{H}_2\text{SO}_4$  is that protonated amino derivatives produced upon cyclisation often undergo hydrolysis to give the corresponding oxo derivatives. Thus the reaction of substituted 2-chloro-3-cyanopyridine **65** with arylamines gives the corresponding 2-arylmino-3-cyanopyridines **66**. Heating of the latter in PPA leads to their cyclisation to form benzo[*b*][1,8]naphthyridinones **67**.<sup>51</sup>

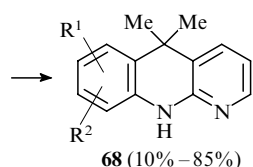


$R^1 = \text{H, Me; } R^2 = \text{H, Me, Et}$ .

#### d. Cyclisation involving carbocations

5,10-Dihydro-5,5-dimethylbenzo[*b*][1,8]naphthyridine derivatives (**68**) were prepared by intramolecular cyclisation of the carbocations **69** generated *in situ* from alcohols **70** under the action of PPA.<sup>52</sup>



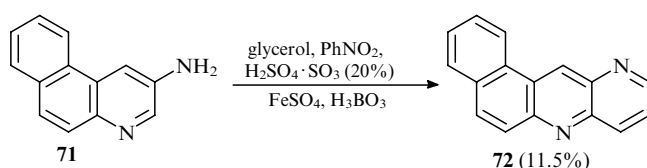


$R^1 = \text{H, Hal, OMe, OEt}; R^2 = \text{H, Cl, Me}.$

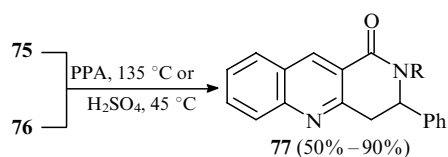
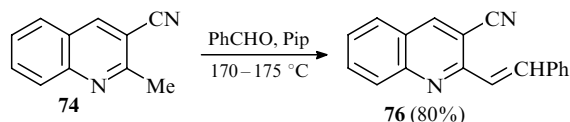
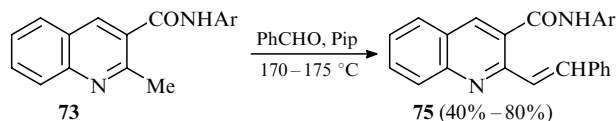
### 3. Annulation of the pyridine ring to the quinoline system

Annulation of the pyridine ring to substituted quinolines can be used as an alternative approach to the design of the benzonaphthyridine system.

Benzonaphthyridines can be prepared by the Skraup synthesis.<sup>53</sup> Thus annulated benzonaphthyridine **72** was synthesised starting from 2-aminobenzo[*f*]quinoline **71**. This reaction was carried out in the presence of an oxidant (nitrobenzenesulfonic acid) formed *in situ* upon the reaction of nitrobenzene with oleum.<sup>54</sup>



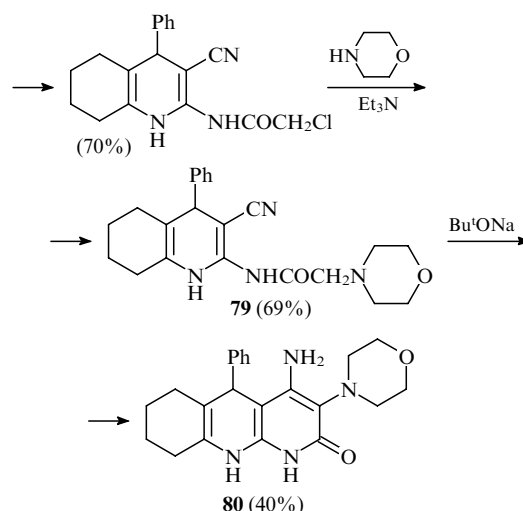
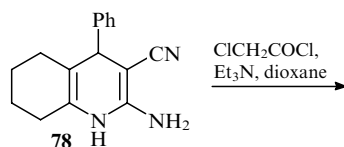
*N*-Arylamides (**73**) and nitriles (**74**) of 2-methylquinoline-3-carboxylic acid reacted with aromatic aldehydes on heating in *p*-xylene in the presence of piperidine as a base.<sup>55,56</sup> The  $\beta$ -aryl-vinyl derivatives **75** and **76** formed upon heating in PPA underwent cyclisation to form 3-phenyl-1-oxo-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines **77**.<sup>55,56</sup>



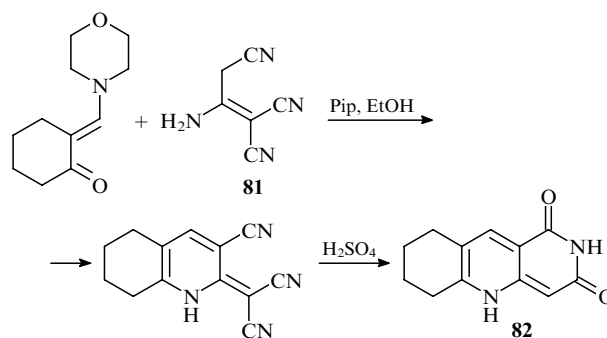
$R = \text{Ar, H}.$

Analogous cyclisation of 8-benzylidene-2-styryl-5,6,7,8-tetrahydroquinoline-3-carboxanilide giving rise to 6-benzylidene-2,3-diphenyl-1-oxo-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridine was performed by heating in PPA (80%–84%  $\text{P}_2\text{O}_5$ ) at 135 °C.<sup>57</sup>

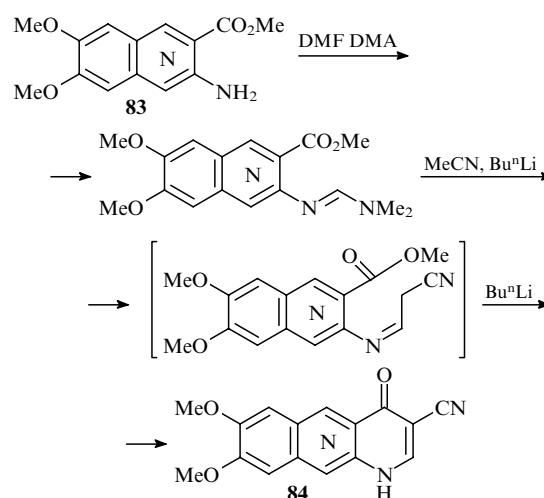
Acylation of 2-amino-3-cyano-6,7,8,9-tetrahydroquinoline (**78**) with chloroacetyl chloride followed by the reaction with morpholine affords the morpholinoacetyl derivative **79**. Cyclisation of the latter under the action of sodium *tert*-butoxide yields benzo[*b*][1,8]naphthyridinone **80**.<sup>58</sup>



The piperidine-catalysed reaction of morpholinomethylene-cyclohexanone with the malononitrile dimer **81** and subsequent heating of the product in concentrated  $\text{H}_2\text{SO}_4$  gave the benzo[*b*][1,6]naphthyridine derivative **82**.<sup>59</sup>



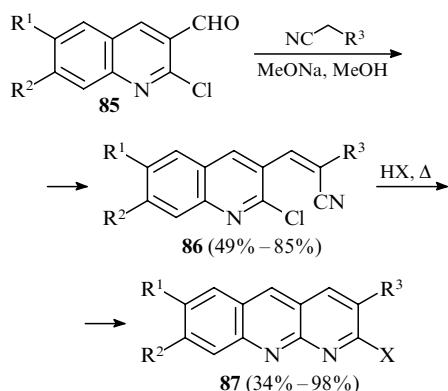
Dimethoxyquinolines **83** containing the *vic*-amino and methoxycarbonyl groups were transformed into benzo[*b*][1,5]- and benzo[*b*][1,8]naphthyridinone derivatives **84** in two steps. The reactions of quinolines **83** with the DMF acetal gave amidines whose reactions with acetonitrile and *n*-butyllithium include nucleophilic substitution of the dimethylamino group for the acetonitrile anion and the Thorpe–Ziegler cyclisation. Butyllithium acted as a base abstracting the proton from the reactive methylene group and thus providing the closure of the pyridine ring.<sup>60</sup>



Condensation of 2-chloro-3-formylquinolines **85** with substituted acetonitriles in MeOH in the presence of MeONa yields the 2-chloro-3-cyanovinyl derivatives **86**.<sup>61</sup> The latter react with



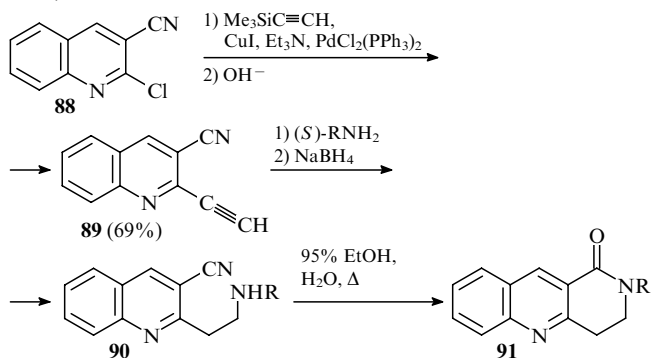
secondary amines resulting in smooth cyclisation giving rise to the 2-aminobenzo[*b*][1,8]naphthyridine derivatives **87**.



$R^1 = R^2 = \text{H, OMe}$ ;  $R^3 = \text{C}_6\text{H}_4\text{Cl-4, SC}_6\text{H}_4\text{Cl-4}$ ;

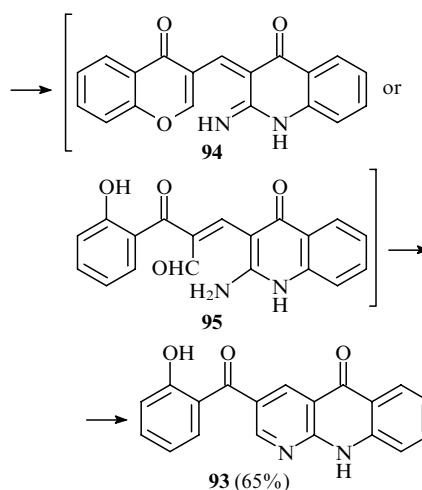
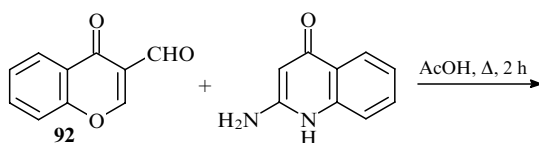
$X = -\text{N}(\text{CH}_2)_2\text{CH}_2\text{CH}_2\text{N}-, -\text{N}(\text{CH}_2)_2\text{CH}_2\text{CH}_2\text{N}(\text{Me})-$

2-Chloro-3-cyanoquinoline (**88**) and trimethylsilylacetylene are involved in the Sonogashira reaction catalysed by  $\text{Pd}^0$  that is generated from  $\text{PdCl}_2(\text{PPh}_3)_2$  during the reaction. Subsequent elimination of the trimethylsilyl group in an alkaline medium gives rise to 3-cyano-2-ethynylquinoline **89**. The addition of (*S*)-phenylalaninol to the latter compounds and subsequent reduction of the double bond yield the amine **90**, whose refluxing in aqueous ethanol results in intramolecular cyclisation at the nitrile group and hydrolysis to give lactam **91** (the yield over two steps is 52%).<sup>62</sup>

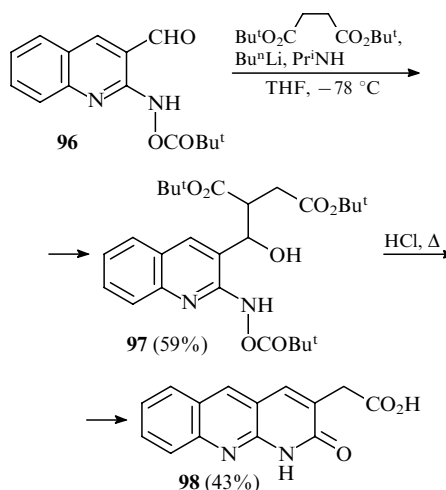


$R = \text{CH}(\text{CH}_2\text{OH})\text{CH}_2\text{Ph}$ .

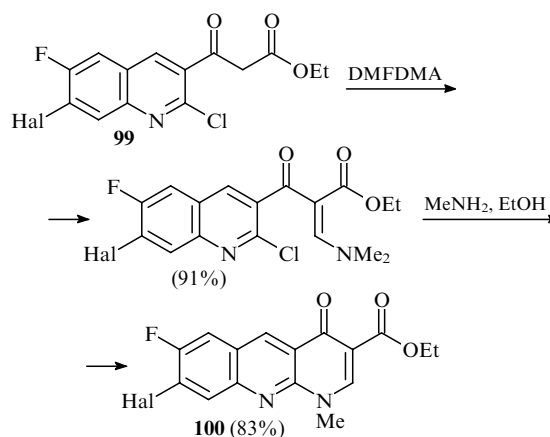
3-Formylchromone (**92**) containing three electrophilic centres, *viz.*, C(2), C(4) and CHO, reacts with 2-amino-1*H*-quinolin-4-one to give benzo[*b*][1,8]naphthyridinone **93**.<sup>63</sup> It is suggested<sup>63</sup> that 2-aminoquinolin-4-one in which position 3 is activated by the electron-donating amino group similarly to the  $\beta$ -position in enamines can undergo condensation at both the aldehyde group (which seems to be a more preferable route) and the C(2) atom of chromone **92** to give the intermediates **94** or **95**, respectively. In both cases, cyclisation of the addition products **94** and **95** gives benzonaphthyridinone **93**.<sup>63</sup>



Condensation of compound **96** with di-*tert*-butyl succinate in the presence of  $\text{Bu}^n\text{Li}$  yields a mixture of the corresponding diastereomeric alcohols **97** in 59% yield. Refluxing of these alcohols with HCl in dioxane leads to elimination of the protective *tert*-butoxycarbonyl group and cyclisation to form 3-carboxymethylbenzonaphthyridine **98**.<sup>64</sup>



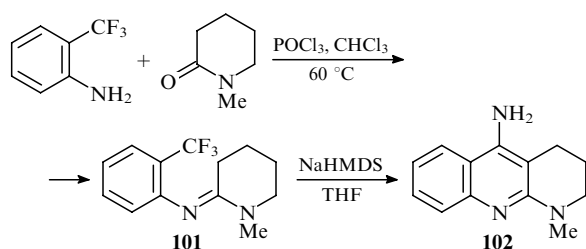
Condensation of compounds **99** with dimethylformamide dimethyl acetal gave enamine. Transamination of the latter with methylamine resulted in the replacement of chlorine at position 2 of the quinoline ring and cyclisation to form the benzo[*b*][1,8]-naphthyridine derivative **100**.<sup>65–67</sup>



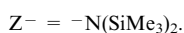
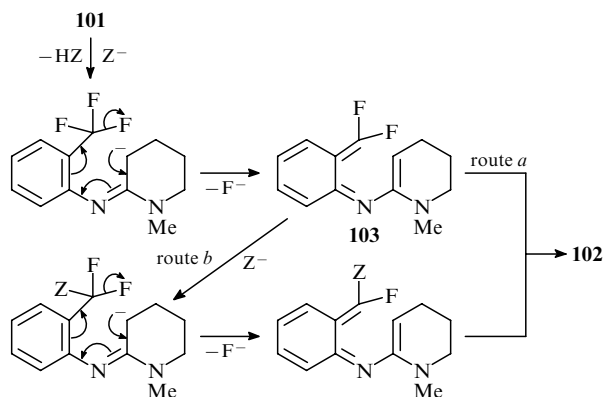
#### 4. Syntheses involving *ortho*-quinomethane intermediates

Syntheses of heterocycles involving intermediates having *o*-quinomethane or *o*-quinomethane imide structures (hereinafter referred to as quinomethanes) offer an original approach to the design of the benzonaphthyridine system. The literature term azaxylenes is, in our opinion, inappropriate as a synonym for *o*-quinomethane imides.

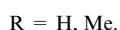
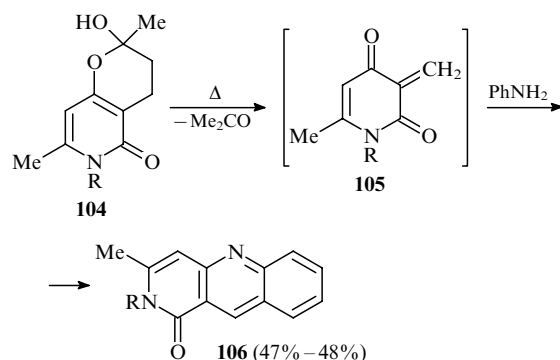
Amidine **101**, which was prepared by the reaction of 2-trifluoromethylaniline and the *N*-methylpiperidin-2-one complex with POCl<sub>3</sub>, reacted with sodium hexamethyldisilazide (NaHMDS) to give the tricyclic product **102**.<sup>68</sup>



In terms of the cyclisation mechanism proposed in,<sup>68</sup> the anion formed as a result of proton abstraction from amidine **101** under the action of a base loses the fluoride anion to give quinomethane **103**. Its cyclisation giving rise to the target tricyclic product **102** can occur by two different pathways: (a) through the electrocyclic reaction with subsequent nucleophilic substitution of fluorine for the amino group followed by aromatisation and elimination of HF; (b) through the addition of the Z<sup>−</sup> anion and elimination of the fluoride anion to give the target product **102**.

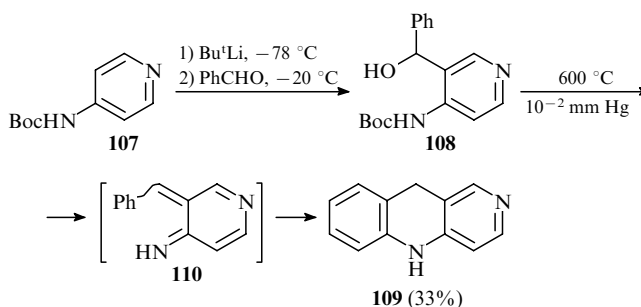


Hemiacetals **104** derived from the corresponding 4-hydroxypyridin-2-ones can be used as a source of quinomethanes.<sup>69, 70</sup> Heating of hemiacetals **104** leads to elimination of acetone to form quinomethane intermediates **105**, which react with aniline to give the tricyclic products **106**.



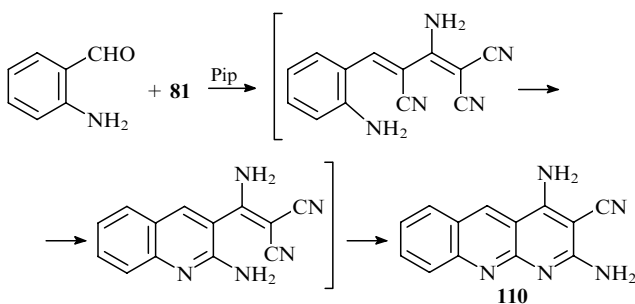
Tetracyclic derivatives of 1,6-naphthyridine were synthesised with the use of hemiacetals derived from 3-hydroxyquinolones as a source of quinomethanes. Elimination of acetone in this reaction was confirmed by the formation of the corresponding 2,4-dinitrophenylhydrazone.

Directed *ortho*-lithiation of 4-*tert*-butoxycarbonylamino-pyridine (**107**) and subsequent reactions of the lithium derivative with aldehydes yield alcohol **108**, which is further transformed into the benzo[*b*][1,6]naphthyridine derivative **109** by flash vacuum pyrolysis (FVP). Apparently, quinomethane intermediate **110** is involved in the formation of tricyclic product **109**.<sup>71</sup>

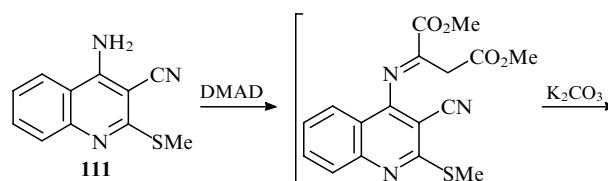


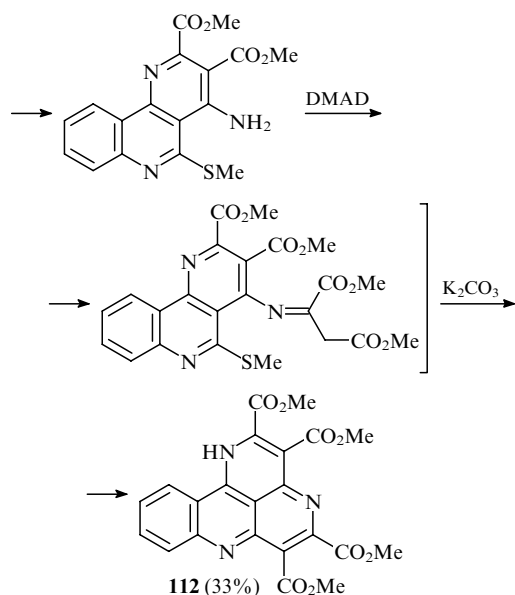
#### 5. Domino reactions

Domino reactions involve two or more transformations giving rise to new bonds (as a rule, C–C bonds). These reactions proceed under identical conditions without the addition of supplementary reagents or catalysts. Noteworthy, each subsequent reaction is triggered by a functional group generated in the previous step.<sup>72</sup> Only a few examples of the synthesis of benzonaphthyridines by domino reactions are known. Thus the piperidine-catalysed reaction of 2-aminobenzaldehyde with the malononitrile dimer **81** gives 1,3-diamino-2-cyanobenzo[*b*][1,8]naphthyridine (**110**).<sup>73</sup>



4-Amino-3-cyano-2-methylthioquinoline (**111**) reacts with two molecules of dimethyl acetylenedicarboxylate (DMAD) in the presence of K<sub>2</sub>CO<sub>3</sub> or K<sub>3</sub>PO<sub>4</sub>·H<sub>2</sub>O to give tetramethyl 1*H*-quinolino[2,3,4-*de*][1,6]naphthyridine-2,3,5,6-tetracarboxylate (**112**).<sup>74</sup> The mechanism of this reaction can be presented as follows: the addition of DMAD to the amino group, proton abstraction from the activated methylene group under the action of a base and, finally, cyclisation involving the nitrile group. The addition of the second DMAD molecule to the amino group of the naphthyridine derivative thus formed is followed by cyclisation involving the activated methylene group and the replacement of the good leaving group MeS.

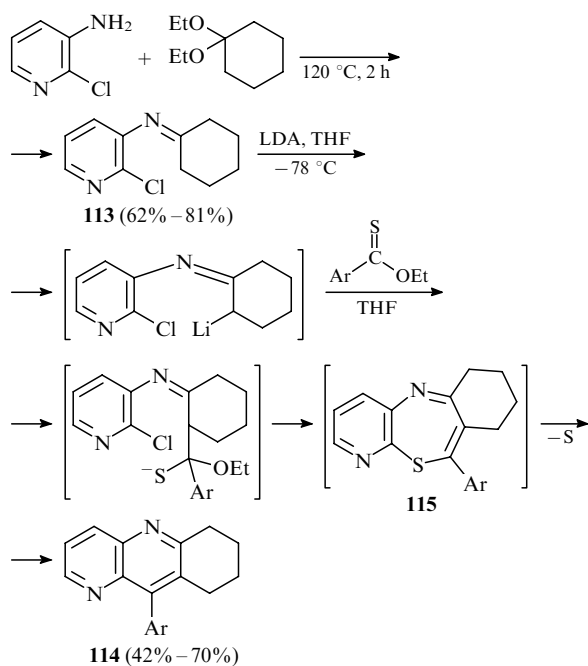




## 6. Other transformations of heterocycles producing benzo[b]naphthyridines

The synthesis of benzonaphthyridine derivatives by recyclisation of other heterocyclic systems is an efficient approach to the synthesis of compounds many of which are otherwise inaccessible.

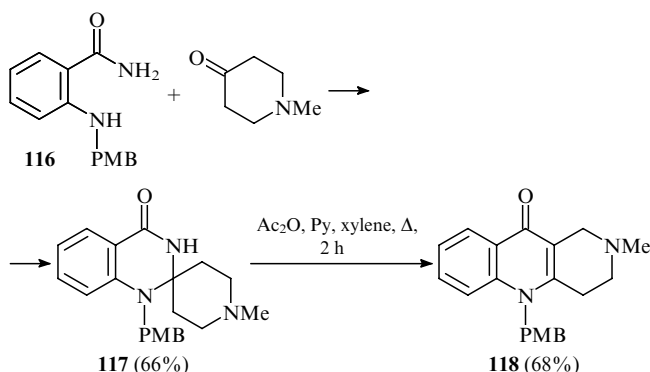
The ability of  $8\pi$ -electron systems containing divalent sulfur to be transformed into more stable aromatic compounds in the course of thermal rearrangement accompanied by the removal of sulfur from the ring is well known.<sup>75</sup> This principle underlies the synthesis of benzo[b][1,5]naphthyridine derivatives generated *in situ* from the corresponding fused 1,4-thiazepines. Thus the reaction of 3-amino-2-chloropyridine with cyclohexanone diethyl ketal gives imine **113**. Lithiation of the latter with lithium diisopropylamide (LDA) and subsequent treatment with  $\text{ArC(S)OEt}$  afford 10-aryl-6,7,8,9-tetrahydrobenzo[b][1,5]naphthyridines **114**. In all probability, this reaction entails sequential addition of the lithiated imine to  $\text{ArC(S)OEt}$ , closure of the 1,4-



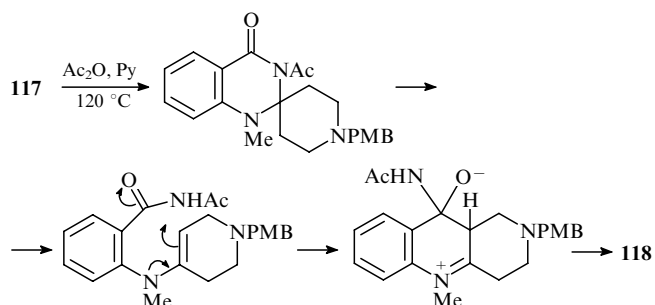
$\text{Ar} = 4\text{-XC}_6\text{H}_4$  ( $\text{X} = \text{Cl}, \text{MeO}, \text{Me}$ );

thiazepine ring and extrusion of sulfur from the  $8\pi$ -electron system of the intermediate **115** giving finally benzonaphthyridines **114**.<sup>76</sup> Apparently, this approach can be used in the synthesis of both 1,5-naphthyridines and other isomers.

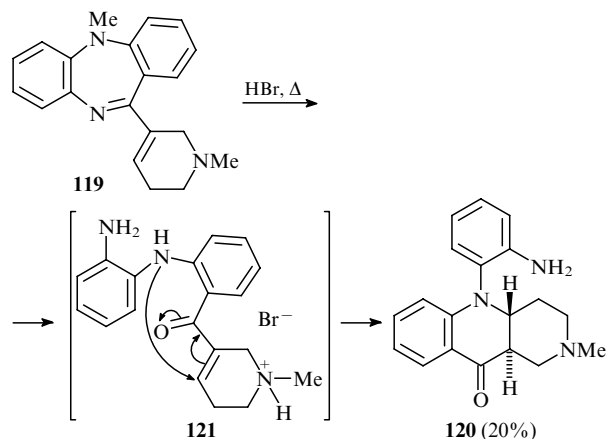
The reaction of *N*-(4-methoxybenzyl)anthranilamide (**116**) with *N*-methylpiperidin-4-one yielded spiro[piperidine-4,2'-(1',2',3',4'-tetrahydroquinazolinone)] (**117**), whose refluxing with acetic anhydride and pyridine in xylene led to recyclisation to form benzonaphthyridine **118**.<sup>77</sup>



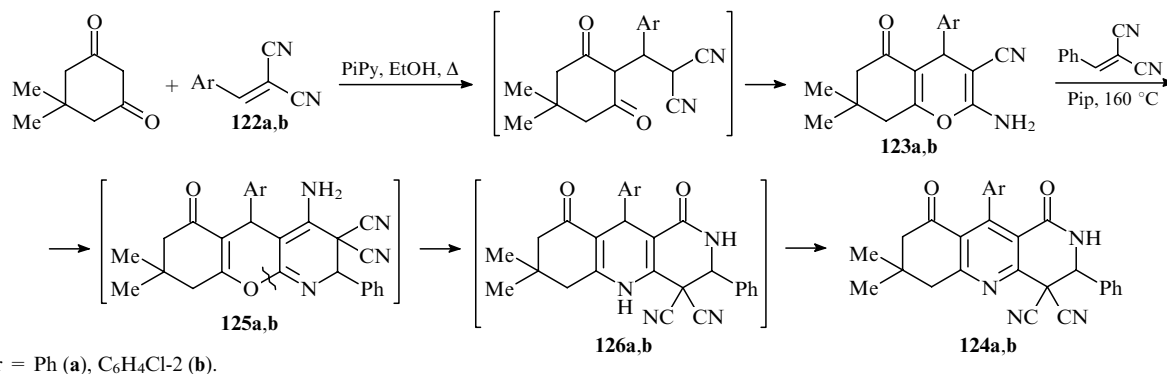
Earlier study has shown<sup>78</sup> that *N*(3)-substituted and *N*(1),*N*(3)-disubstituted spiro compounds that are structurally similar to quinazoline **117** do not react under these conditions. At the same time, the spiro compound in which both atoms in the quinazoline ring are devoid of substituents was transformed into quinazolinone. The benzonaphthyridine structure was prepared exclusively from *N*(1)-substituted compounds.<sup>78</sup> Based on these findings, a mechanism for the rearrangement of compounds **117** into **118** has been proposed. Its first step involves acylation of the lactam NH group.



Heating of diazepine **119** in 40% HBr leads to demethylation along with recyclisation to give benzo[b][1,6]naphthyridinone **120**. It may be assumed that hydrolytic cleavage of the diazepine ring in acidic media affords the intermediate **121** which contains an  $\alpha,\beta$ -



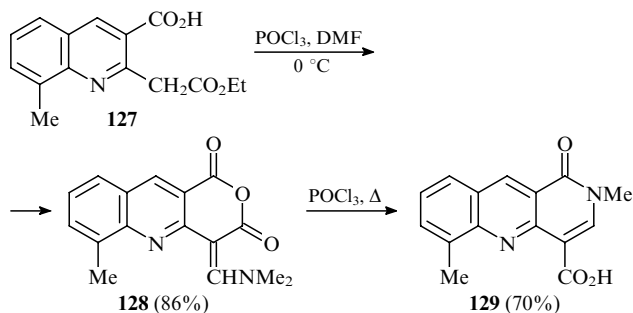
Scheme 1



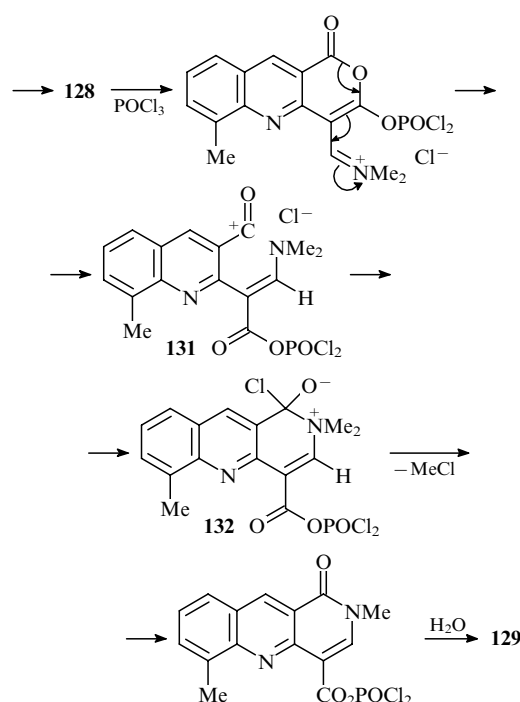
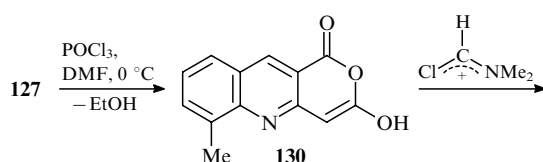
unsaturated ketone fragment. This compound is transformed into the *trans*-isomer **120** through the intramolecular Michael addition involving the NH group and the  $\beta$ -carbon atom of the acryloyl fragment.<sup>79</sup>

Arylmethylidenemalononitriles **122a,b** react with dimedone to give Michael addition products which undergo spontaneous cyclisation to form 4*H*-pyrans **123a,b**. Reactions of the latter with benzylidenemalononitrile in the presence of catalytic amounts of piperidine at 160 °C afforded benzonaphthyridines **124a,b**.<sup>80</sup> In the authors' opinion, this reaction proceeds *via* the intermediate formation of compounds **125a,b** and **126a,b**. An analogous rearrangement concomitant with the formation of 1,6-naphthyridine derivatives has been reported.<sup>81</sup> It is noteworthy that this reaction is accompanied by aromatisation of the 1,4-dihydropyridine fragment (Scheme 1).

Ethyl (3-carboxy-8-methylquinolin-2-yl)acetate (**127**) undergoes cyclisation to form 4-dimethylaminomethylidene-6-methyl-4*H*-pyrano[4,3-*b*]quinoline-1,3-dione (**128**) by the Vilsmeier reaction. Heating of the latter with POCl<sub>3</sub> results in its transformation into 1,2-dihydro-2,6-dimethyl-1-oxo-benzo[*b*][1,6]naphthyridine-4-carboxylic acid (**129**).<sup>82</sup>

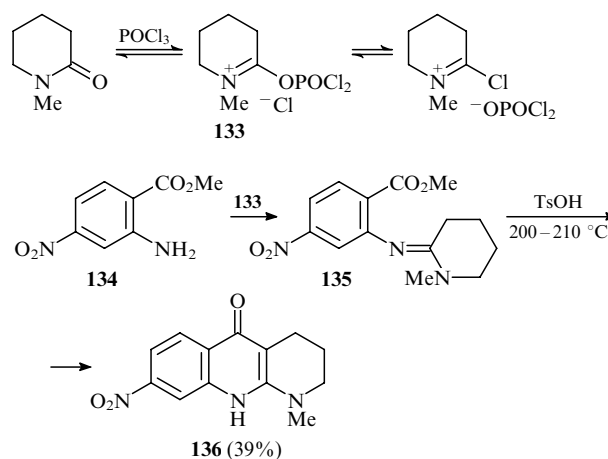


An analogous POCl<sub>3</sub>-induced transformation has been described for homophthalic acid and its methyl ester.<sup>83</sup> Based on these data, the following reaction mechanism for the synthesis of benzonaphthyridine **129** can be proposed. Cyclisation of dicarboxylic acid **127** into anhydride **130** is followed by electrophilic addition of the Vilsmeier reagent to form enamino anhydride **128**. *o*-Acylation of the latter with POCl<sub>3</sub> and cleavage of the C–O bond yield the acylium cation **131**, which can undergo cyclisation involving the dimethylamino group to give the intermediate **132**. Subsequent elimination of MeCl and hydrolysis afford benzonaphthyridine **129**.



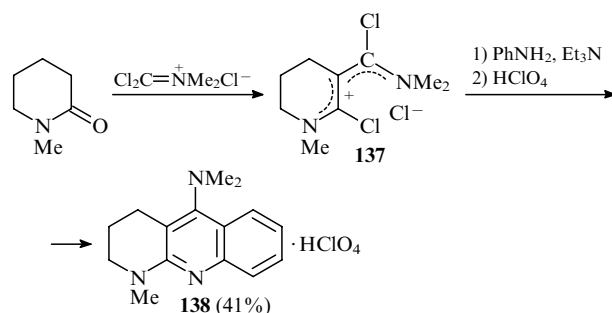
## 7. Other methods

The reaction of the *N*-methylpiperidin-2-one–POCl<sub>3</sub> complex (**133**) with the methyl 4-nitroanthranilate (**134**) gives amidine **135**. Heating of the latter in the presence of TsOH results in cyclisation to form benzonaphthyridinone **136**. Analogous cyclisation takes place in the Friedlander reaction.<sup>84</sup>

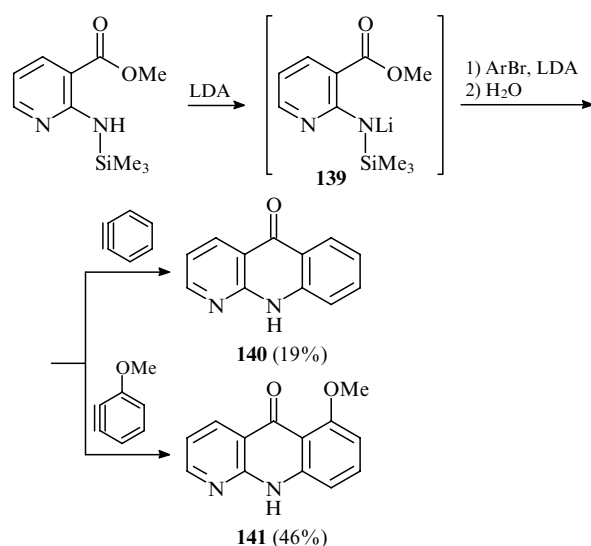


The addition of *N,N*-dimethyldichloromethyleneimmonium chloride to *N*-methylpiperidin-2-one gives the salt **137**. The reaction of the latter with aniline proceeds selectively and is

accompanied by the replacement of chlorine at the C(2) atom followed by cyclisation to form benzonaphthyridine **138**.<sup>85, 86</sup>

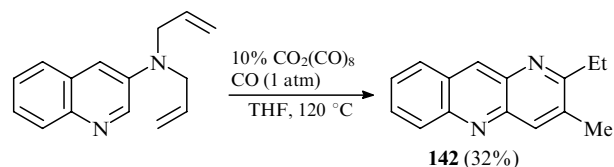


A procedure for the synthesis of benzonaphthyridines based on cycloaddition of arynes to 1,4-dipolar compounds was developed. The *N*-lithium derivative of methyl 2-(trimethylsilylamino)-nicotinate **139** reacts with dehydrobenzene, which is generated *in situ* from bromobenzene in the presence of a base, under mild conditions to give benzo[*b*][1,8]naphthyridinone **140**. 6-Methoxybenzonaphthyridinone **141** was isolated as the only product from 3-methoxydehydrobenzene derived from 3-bromoanisole.<sup>87</sup> High regioselectivity of this reaction testifies that the process occurs by a concerted mechanism.<sup>88</sup>

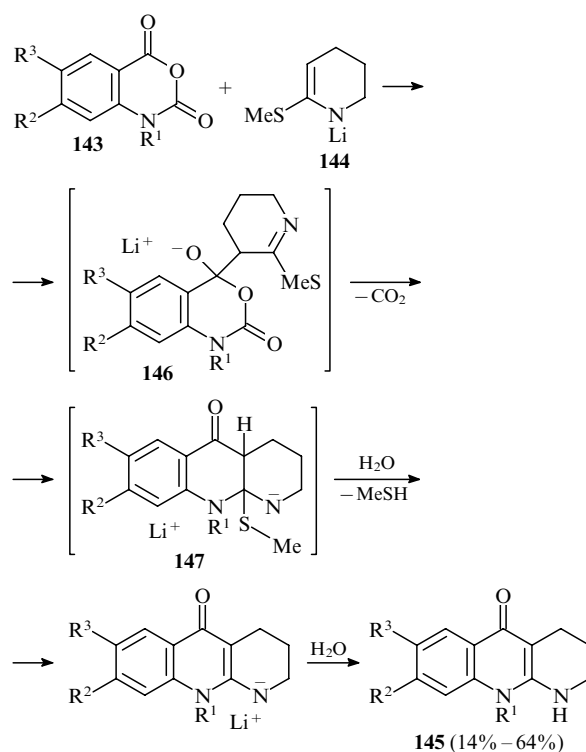


Ar = Ph, MeOC<sub>6</sub>H<sub>4</sub>Br-3.

The conversion of 3-(*N,N*-diallylamino)quinoline into the benzo[*b*][1,5]naphthyridine derivative **142** was carried out under a CO atmosphere using Co<sub>2</sub>(CO)<sub>8</sub> as a catalyst. Analogously, *N,N*-diallylaniline is transformed under the action of CO and Co<sub>2</sub>(CO)<sub>8</sub>, the mechanism of transfer of the allylic groups between the substrate molecules being confirmed for this process.<sup>89</sup>

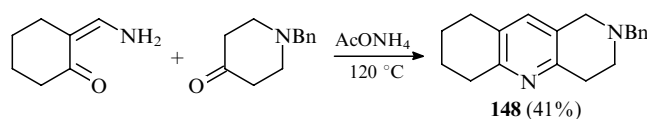


The reaction of *N*-alkylisatin anhydrides **143** with the lithium derivative of enamine **144** was used for the preparation of benzo[*b*][1,8]naphthyridinones **145**.<sup>90</sup> Presumably, the addition of enamine **144** to the C(4)-carbonyl group of isatin anhydride derivatives gives the intermediates **146**, which can be further transformed into the tricyclic derivatives **147** with elimination of the CO<sub>2</sub> molecule. After elimination of MeSH, these compounds are transformed into benzonaphthyridinones **145**.<sup>90</sup>

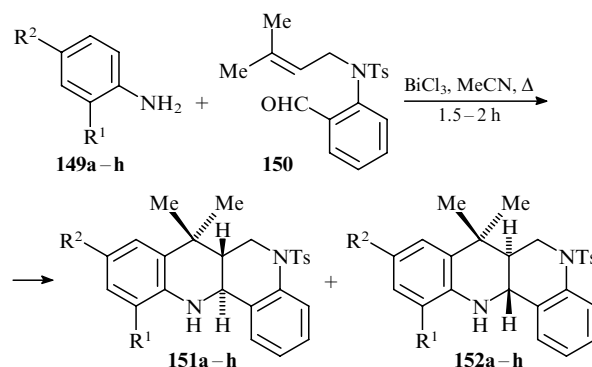


R<sup>1</sup> = Me, Bn; R<sup>2</sup> = H, Cl; R<sup>3</sup> = H, Me.

1,2,3,4,6,7,8,9-Octahydrobenzo[*b*][1,6]naphthyridine (**148**) was synthesised starting from 2-aminomethylidenecyclohexanone, 1-benzylpiperidin-4-one and ammonium acetate.<sup>13</sup>



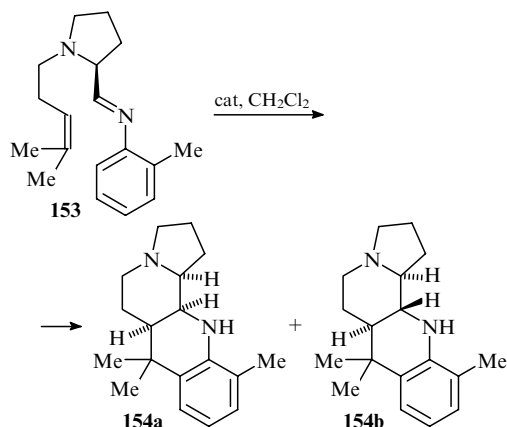
A procedure was proposed for the synthesis of dibenzo[*b,h*]-[1,6]naphthyridines based on the BiCl<sub>3</sub>-catalysed hetero-Diels–Alder reaction involving the aryl ring as a component of the diene system.<sup>91</sup> Cyclisation of aldimines generated *in situ* from anilines **149a–h** and the *N*-allylic derivative of *o*-aminobenzaldehyde **150** affords a mixture of the diastereomers **151a–h** and **152a–h** in a 1 : 1 ratio in 90%–96% yields.<sup>92</sup>



R<sup>1</sup> = R<sup>2</sup> = H (**a**); R<sup>1</sup> = Me, R<sup>2</sup> = H (**b**); R<sup>1</sup> = Br, R<sup>2</sup> = Me (**c**);  
R<sup>1</sup> = H: R<sup>2</sup> = OMe (**d**), Cl (**e**), F (**f**), Me (**g**);  
R<sup>1</sup> = OH, R<sup>2</sup> = H (**h**).

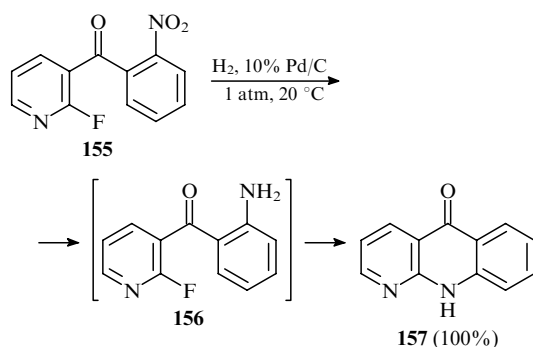
Cyclisation of (*S*)-*N*-(1-(4-methylpent-3-enyl)pyrrolidin-2-yl)methylidene)toluidine (**153**), which is catalysed by Lewis and Brønsted acids (FeCl<sub>3</sub>, SnCl<sub>4</sub>, BF<sub>3</sub>·Et<sub>2</sub>O, TsOH, CF<sub>3</sub>CO<sub>2</sub>H, SnCl<sub>4</sub>, AlCl<sub>3</sub>, EtAlCl<sub>2</sub>, Et<sub>2</sub>AlCl, MeAlCl<sub>2</sub>, Me<sub>2</sub>AlCl), yields tetracyclic decahydro-7,7,4-trimethylindolizino[3,4-*b*]quinolines **154a,b** (79%–84% total yields). Only two out of four possible

isomers are formed under these conditions. The ratios of the isomeric products depend on the coordination number of the acidic catalyst. Monodentate Brønsted and Lewis acids as well as octahedral bidentate Lewis acids yield predominantly the *trans,trans*-product **154b**, whereas tetrahedral aluminium Lewis acids give the *cis,cis*-product **154a**.<sup>93</sup>

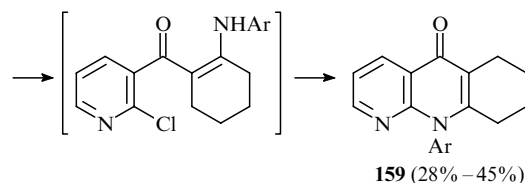
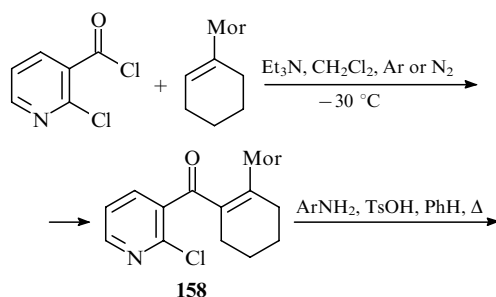


A stepwise mechanism involving the imino group was proposed for cyclisation of compound **153**. Within the framework of this mechanism, complete inversion of the configuration occurs due to the presence of the nitrogen atom in the pyrrolidine ring capable of complex formation.<sup>93</sup>

Reduction of 2-fluoro-3-(2-nitrobenzoyl)pyridine (**155**) by hydrogen over Pd/C yields the amino derivative **156**, which undergoes spontaneous cyclisation to give benzonaphthyridinone **157**.<sup>22</sup>

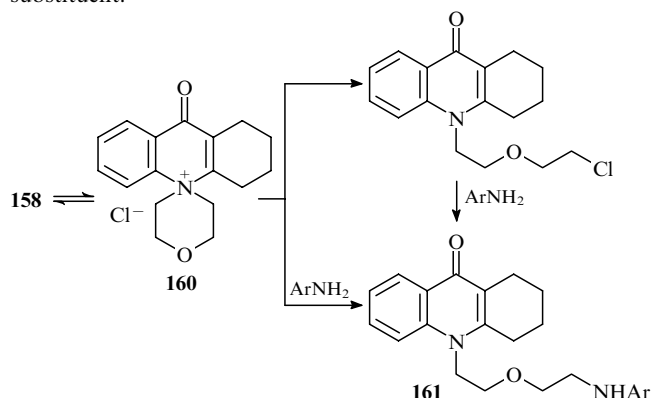


Addition of 2-chloronicotinoyl chloride to morpholinocyclohexene yields enamino ketone **158**, which is involved in the reactions with arylamines accompanied by cyclisation to form the 1,8-naphthyridine derivatives **159**.<sup>94</sup> It is of note that this process occurs both through transamination of the enamino ketone **158** with arylamine followed by cyclisation and replacement of chlorine at position 2 of the pyridine ring and through the primary replacement of chlorine by the arylamine fragment with subsequent intramolecular transamination and elimination of morpholine.



Mor is ; Ar = XC<sub>6</sub>H<sub>4</sub> (X = 3-MeO, 3-Cl, 2-Cl, 3-NO<sub>2</sub>), 3-Py.

Moderate yields of the target products **159** are partly due to hydrolysis of enamines and a side process involving cyclisation of enamino ketone **158** to give the spiro intermediate **160**. Treatment of the latter with nucleophilic reagents eventually results in its conversion into the acridine derivatives **161** containing an *N*-alkyl substituent.<sup>94</sup>



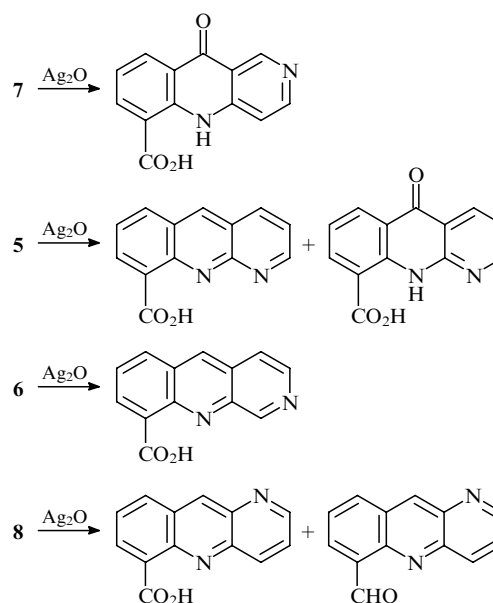
#### IV. Chemical properties

The chemical properties manifested by benzonaphthyridines are equally characteristic of acridine derivatives and the corresponding naphthyridines.

## 1. Oxidation and dehydrogenation

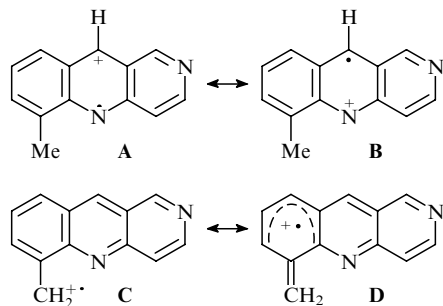
This section contains information concerning oxidation of benzonaphthyridines and their di- and tetrahydro derivatives that yields fully aromatic tricycles.

Four isomeric 6-methylbenzo[*b*]naphthyridines **5–8** were treated with a basic solution of silver oxide at 20 °C for 30 min. The structures of the reaction products were established by <sup>1</sup>H NMR spectroscopy. The processes associated with such



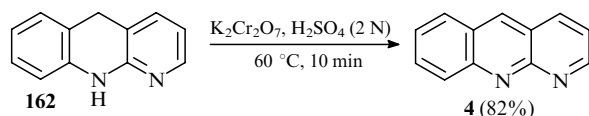
oxidation were found to depend on the structures of isomeric substrates. The methyl group can be oxidised to the formyl group (compound **8**) or the carboxy group (for all isomers).

The abilities of compounds **5–8** to be oxidised can be compared using oxidation at position 10 as a criterion. The reactivities of the isomeric compounds change in the following order: **7** (1.6) > **5** (1.8) > **6** (1.7) > **8** (1.5).<sup>5</sup> The difference in stability of the radical cations **A–D** generated upon oxidation of the isomeric compounds **5–8** can in principle be regarded as the determining factor.

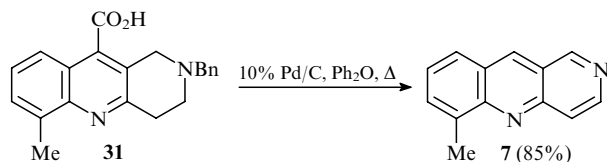


However, this experimental material is insufficient for adequate interpretation of the available data.<sup>5</sup> Therefore, in this review we simply cite the results of investigations.

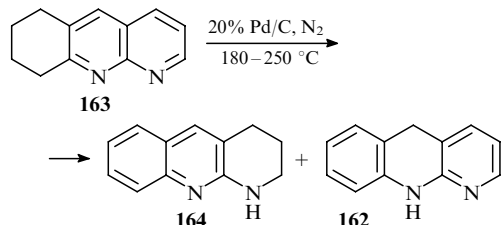
5,10-Dihydrobenzo[*b*][1,8]naphthyridine (**162**) is rapidly oxidised under the action of a chromic mixture to give benzo[*b*][1,8]-naphthyridine (**4**).<sup>24</sup>



Debenzylation, decarboxylation and dehydrogenation of benzonaphthyridine **31** were successfully combined by refluxing with 10% Pd over activated carbon in diphenyl ether.<sup>24</sup>

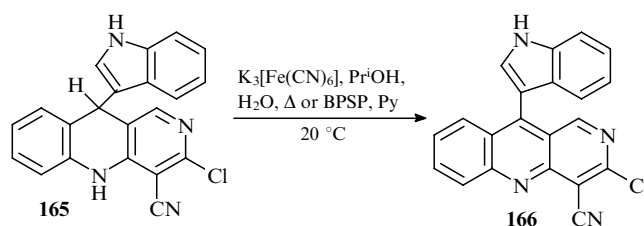


However, an attempt to perform dehydrogenation of 6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridine (**163**) by heating over 20% Pd/C gave a mixture of compounds **164** and **162**. The product **162** was obtained as the major one at higher temperatures.<sup>95</sup>

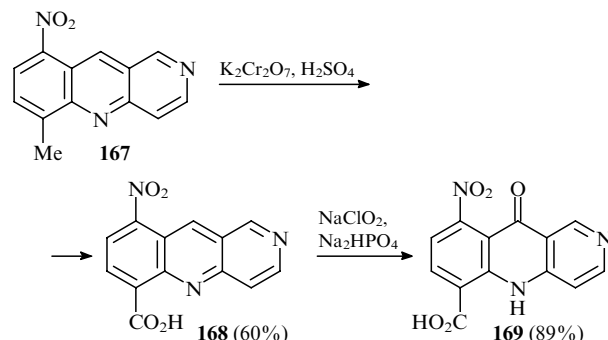


Dehydrogenation of 6-methyl-6,7,8,9-tetrahydrobenzo[*b*]-[1,5]naphthyridine achieved by heating with 10% Pd/C in biphenyl afforded a fully aromatic tricycle in 76% yield.<sup>15</sup>

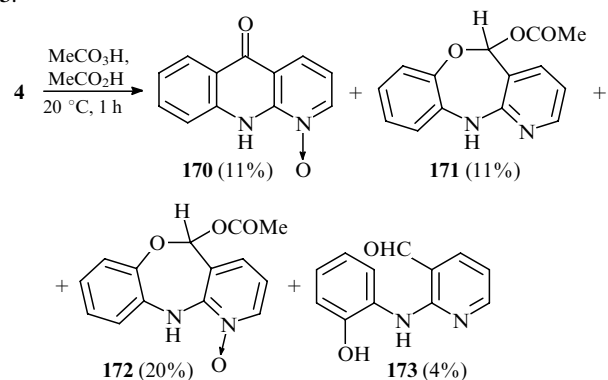
Potassium ferricyanide or bispyridine silver(I) permanganate (BPSP) was used as an oxidant for the transformation of 5,10-dihydrobenzo[*b*][1,6]naphthyridine **165** into the corresponding aromatic heterocycle **166**.<sup>96</sup>



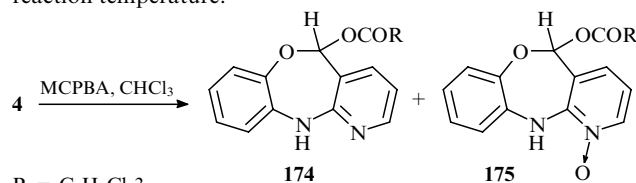
Oxidation of 6-methyl-9-nitrobenzo[*b*][1,6]naphthyridine (**167**) by a chromic mixture occurred at the methyl group without affecting position 10 and yields 9-nitrobenzo[*b*][1,6]naphthyridine-6-carboxylic acid (**168**). The latter was oxidised with sodium chlorite at 20 °C for 4 days to give the 10-oxo derivative **169**.<sup>24</sup>



Oxidation of benzonaphthyridines by peroxy acids is often accompanied by transformations of the heterocyclic system. Thus oxidation of benzo[*b*][1,8]naphthyridine (**4**) with peracetic acid occurred at the nitrogen atom of the peripheral pyridine ring to yield *N*-oxide **170**.<sup>93</sup> This was concomitant with competitive reactions yielding the oxazepine derivatives **171** and **172** and aldehyde **173**. The latter seems to be formed as a result of opening of the oxazepine ring in the compound **171**.<sup>93</sup> The reactions of 1,8-naphthyridine<sup>97</sup> and acridine<sup>98</sup> with peroxy acids were not accompanied by expansion of the pyridine ring to the oxazepine ring. However, oxidation of acridine by perbenzoic and *m*-chloroperbenzoic (MCPBA) acids yielded a mixture of acridine *N*-oxide and 2-(2-hydroxyanilino)benzaldehyde analogous to compound **173**.

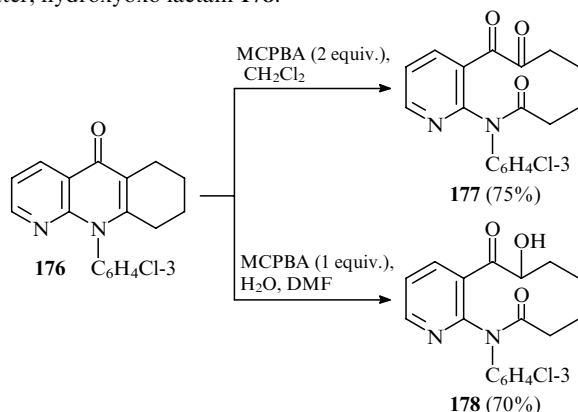


Oxidation of benzo[*b*][1,8]naphthyridine (**4**) by MCPBA gives a mixture of the products **174** and **175**; their ratio depends on the reaction temperature.

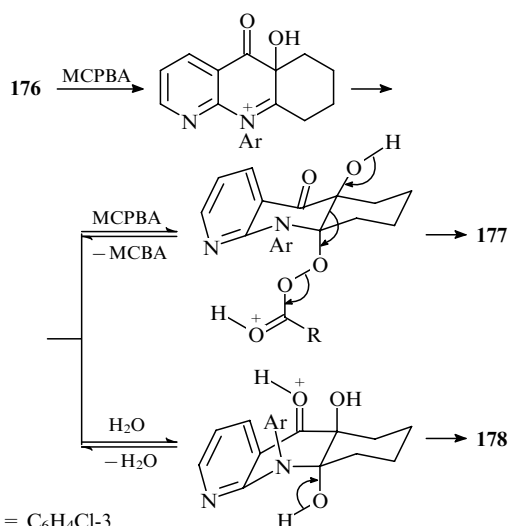


R = C<sub>6</sub>H<sub>4</sub>Cl-3.

Benzonaphthyridinone **176** is oxidised by MCPBA in non-aqueous media to give dioxo lactam **177** or, in the presence of water, hydroxyoxo lactam **178**.<sup>99</sup>

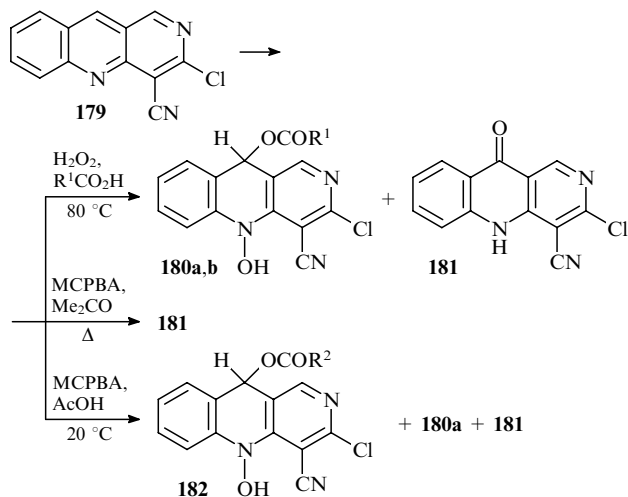


A mechanism for oxidative cleavage of benzonaphthyridinone **176** has been proposed that involves the formation of lactams **177** and **178** in the presence and absence of water.<sup>99</sup>



Ar = C<sub>6</sub>H<sub>4</sub>Cl-3.

Oxidation of 3-chloro-4-cyanobenzo[*b*][1,6]naphthyridine (**179**) by hydrogen peroxide in acetic or propionic acid afforded the corresponding ethers **180a,b** and a small amount of the 10-oxo derivative **181**.<sup>100</sup> Oxidation of the compound **179** by MCPBA in aqueous AcOH at 20 °C gave the acyloxy derivative **182** and trace amounts of the products **180a** and **181**. This reaction performed in



R<sup>1</sup> = Me (**a**), Et (**b**); R<sup>2</sup> = C<sub>6</sub>H<sub>4</sub>Cl-3.

refluxing acetone gave the 10-oxo derivative **181** as the only product.<sup>96</sup>

Most probably, the transformation of the starting compound **179** into the acyloxy derivatives **180a,b** and **182** under the action of MCPBA occurs *via* N(5)-oxidation (oxidation of the nitrogen atom in the peripheral pyridine ring is hindered due to the presence of electron-withdrawing substituents). The resulting N(5)-oxide intermediate readily add acyloxy anions and water to give the products **180a,b**, **181** and **182**.

The mechanisms of action of NADH-containing coenzymes in stereospecific biochemical reactions formed the basis of the biomimetic approach to the design of novel chiral NADH mimetic agents of the benzo[*b*][1,6]naphthyridine series. The derivatives **183a–f** (Table 2) were used for stereoselective reduction of the oxo groups of methyl mandelate and 2-benzoylpyridine.<sup>101</sup>

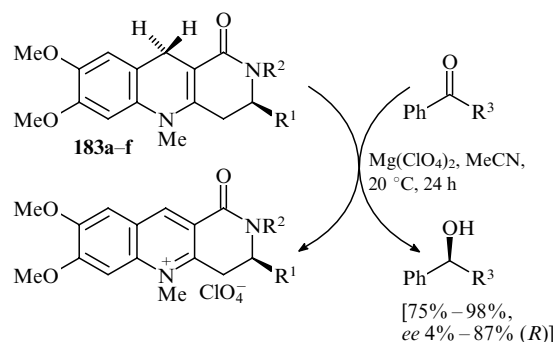
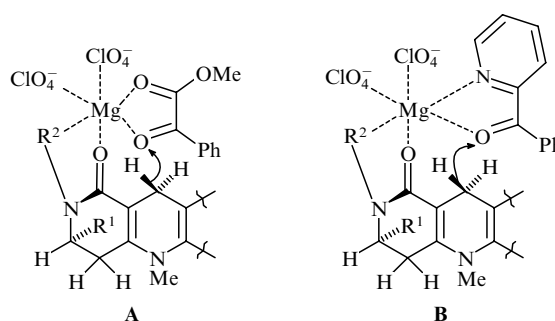


**Table 2.** Reduction of the oxo groups of methyl mandelate and 2-benzoylpyridine by compounds **183a–f**.<sup>101</sup>

| Reagent     | R <sup>1</sup> | R <sup>2</sup>                                       | R <sup>3</sup>     | Yield (%) | ee (R) (%) |
|-------------|----------------|------------------------------------------------------|--------------------|-----------|------------|
| <b>183a</b> | Me             | Bn                                                   | CO <sub>2</sub> Me | 95        | 4          |
| <b>183b</b> | Me             | (CH <sub>2</sub> ) <sub>2</sub> OMe                  | CO <sub>2</sub> Me | 98        | 71         |
| <b>183c</b> | Me             | (CH <sub>2</sub> ) <sub>3</sub> OH                   | CO <sub>2</sub> Me | 90        | 81         |
| <b>183d</b> | Me             | (CH <sub>2</sub> ) <sub>2</sub> OH                   | CO <sub>2</sub> Me | 81        | 86         |
| <b>183e</b> | Ph             | (CH <sub>2</sub> ) <sub>2</sub> OH                   | CO <sub>2</sub> Me | 90        | 84         |
| <b>183f</b> | Me             | (CH <sub>2</sub> ) <sub>2</sub> PO(OEt) <sub>2</sub> | CO <sub>2</sub> Me | 91        | 87         |
| <b>183b</b> | Me             | (CH <sub>2</sub> ) <sub>2</sub> OMe                  | 2-Py               | 90        | 30         |
| <b>183c</b> | Me             | (CH <sub>2</sub> ) <sub>3</sub> OH                   | 2-Py               | 95        | 84         |
| <b>183d</b> | Me             | (CH <sub>2</sub> ) <sub>2</sub> OH                   | 2-Py               | 85        | 35         |

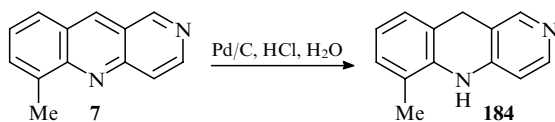
The data listed in Table 2 suggest that the compounds **183f** (*ee* 87%) and **183c** (*ee* 84%) are stereoselective reagents of choice for reduction of methyl mandelate and 2-benzoylpyridine, respectively. Both reactions were carried out in the presence of Mg(ClO<sub>4</sub>)<sub>2</sub>, which is thought to be involved in the formation of the triple **183a–f**–Mg<sup>2+</sup>–substrate complexes (**A** and **B**).<sup>101</sup>



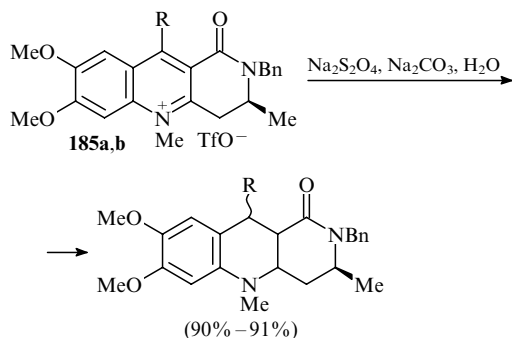
## 2. Reduction and hydrogenation

Treatment of 6-methylbenzo[*b*][1,6]naphthyridine (**7**) with hydrochloric acid in the presence of Pd/C is accompanied by reduction of the central ring to form the derivative **184**.<sup>24</sup>





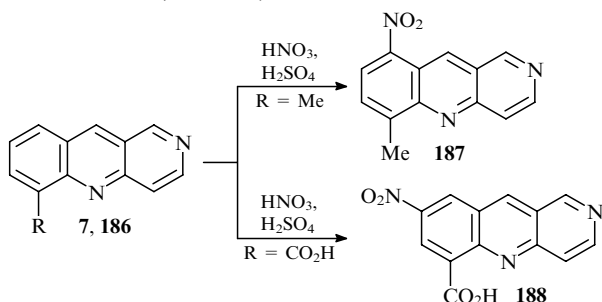
As expected, reduction of benzonaphthyridinium salts occurs more smoothly than reduction of the corresponding bases. Sodium dithionite was used for reduction of the benzonaphthyridinium salts **185a,b** at 20 °C.<sup>62, 101</sup>



$\text{R} = \text{H}$  (**a**),  $\text{Me}$  (**b**).

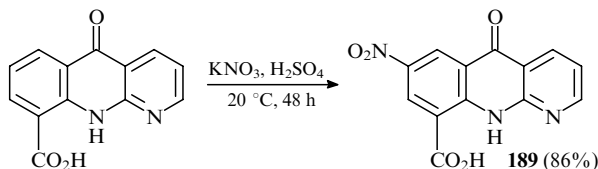
### 3. Substitution reactions

Data on the electrophilic substitution in benzonaphthyridines are scarce. It is known that nitration of benzonaphthyridines by a  $\text{HNO}_3$ – $\text{H}_2\text{SO}_4$  mixture occurs exclusively in the benzene ring. Thus nitration of 6-methyl-(**7**) and 6-carboxybenzo[*b*][1,6]naphthyridines (**186**) gives the corresponding 9-nitro (**187**, 78%) and 8-nitro derivatives (**188**, 82%).<sup>24</sup>

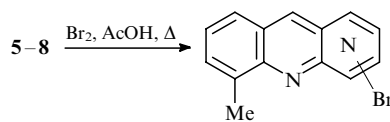


Nitration of 9-methylbenzo[*b*][1,8]naphthyridine (**5**) and 6-methylbenzo[*b*][1,5]naphthyridine (**8**) occurs analogously. In these reactions, the nitro group is also attached to the benzene ring in the *para* position with respect to the methyl substituent.<sup>15</sup>

Nitration of 5,10-dihydro-9-carboxy-5-oxobenzo[*b*][1,8]naphthyridine by a nitrating mixture at 20 °C gave the 7-nitro derivative **189**.<sup>102</sup>



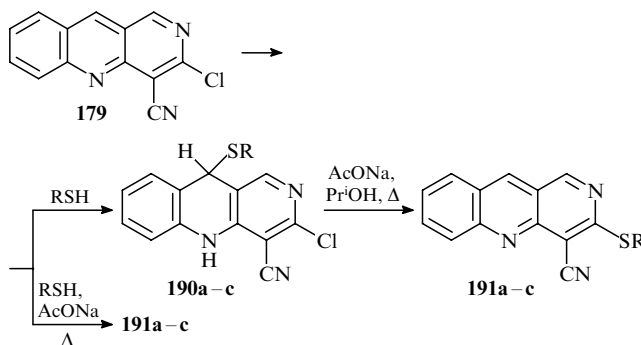
At the same time, isomeric 6-methylbenzo[*b*]naphthyridines **5–8** are brominated at the peripheral pyridine ring in the  $\beta$ -position with respect to the nitrogen atom (rather than at the benzene ring).<sup>5</sup>



This reaction pathway cannot be explained in terms of the electrophilic substitution mechanism [aromatic  $\text{S}_\text{E}(\text{AE})$ ]. In this case, the behaviour of benzonaphthyridines **5–8** is similar to that of quinoline and isoquinoline. Bromination of the latter in weakly acidic media also occurs at the pyridine ring in the  $\beta$ -position with respect to the nitrogen atom rather than at the benzene ring. The mechanism for bromination of these compounds, which entails nucleophilic addition–elimination [ $\text{S}_\text{N}(\text{AE})$ ], was proposed.<sup>103</sup>

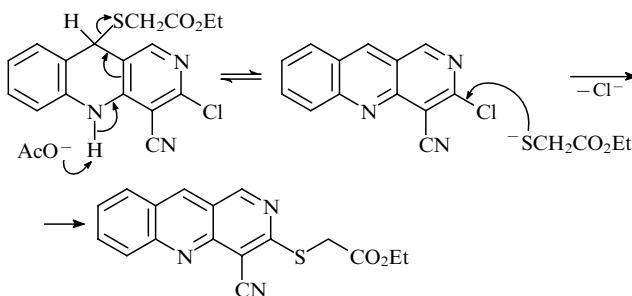
Nucleophilic substitution of hydrogen ( $\text{S}_\text{N}^\text{H}$ ) is widely used in the synthesis of heterocycles and for the introduction of various substituents into  $\pi$ -electron-deficient heterocycles.<sup>104–107</sup> The  $\text{S}_\text{N}^\text{H}$  reactions were well studied for benzo[*b*][1,6]naphthyridine derivatives in which position 10 is depleted of electrons as a result of the unidirectional electron-withdrawing effect of both nitrogen atoms. The latter created a prerequisite for the nucleophilic addition at this position.

In the absence of bases, 3-chloro-4-cyanobenzo[*b*][1,6]naphthyridine (**179**) adds thiols at position 10 to give stable products **190a–c** even at 20 °C. The reaction of the compound **179** with thiols in the presence of a basic catalyst ( $\text{AcONa}$ ) yields sulfides **191a–c**.<sup>100</sup> Reversibility of the addition of thiols to the tricyclic compound **179** can be illustrated by the following experiment. Heating of compound **190b** with sodium acetate as a base in isopropyl alcohol resulted in its conversion into sulfide **191b**.



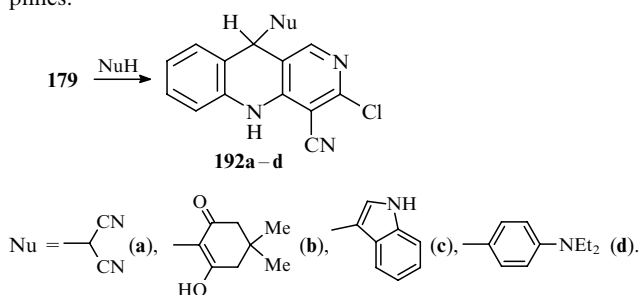
$\text{R} = \text{Ph}$  (**a**),  $\text{CH}_2\text{CO}_2\text{Et}$  (**b**),  $\text{CH}_2\text{CONHPh}$  (**c**).

Evidently, the reaction involves abstraction of the NH proton and elimination of the thiolate anion under the action of a base followed by slower, albeit irreversible substitution of chlorine at position 3 for the thiol residue.<sup>100</sup>

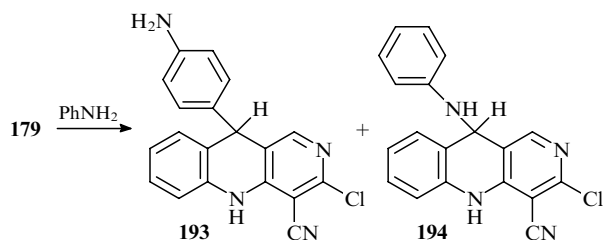


The reaction of benzonaphthyridine **179** with various C-nucleophiles yielded the addition products **192a–d** at position 10. Compounds with strong C–H-acidic properties, such as malononitrile and dimedone, and electron-rich aromatic compounds,

such as indole and *N,N*-diethylaniline, were used as C-nucleophiles.

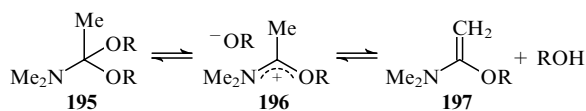


The reaction of benzonaphthyridine **179** with aniline gave a mixture of C–C- (**193**) and C–N-addition (**194**) products. Thus aniline manifested dual reactivity by reacting with the substrate both as a C- and N-nucleophile.



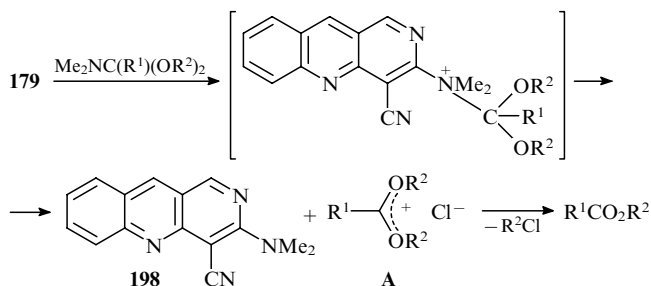
At the same time, reactions of compound **179** with more basic arylamines, *e.g.*, *p*-toluidine and *p*-anisidine, and aliphatic alkyl- and dialkylamines were accompanied by the replacement of chlorine at position 3.<sup>8, 100</sup>

Dimethylacetamide acetals, which can act as C-nucleophiles due to equilibrium between amidoacetals **195**, their ionised forms **196** and  $\alpha$ -alkoxy enamines **197**, were studied as nucleophilic reagents in a reaction with the tricyclic compound **179**.



R = Me, Et.

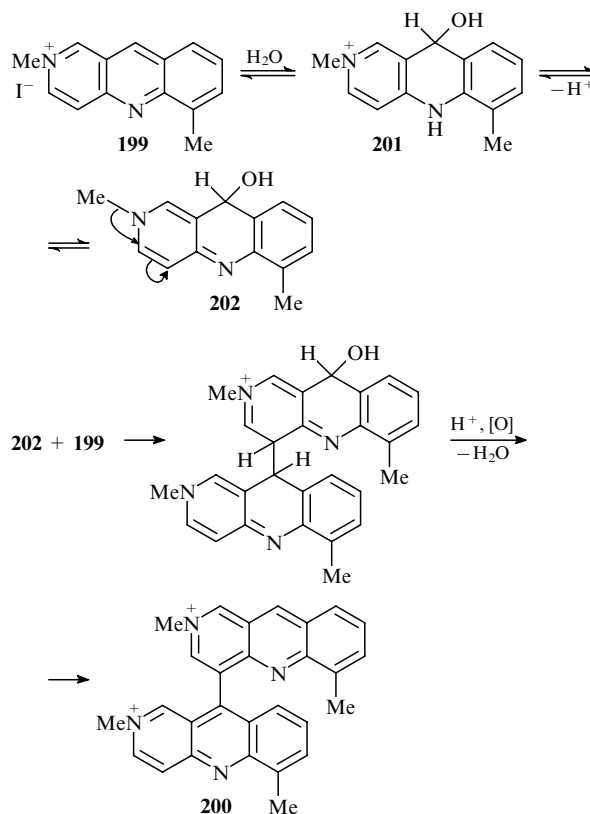
However, the reactions of compound **179** with acetals **195** gave the 3-dimethylamino derivative **198** as the only product.<sup>96</sup> The latter was also synthesised by the reaction of the chloro derivative **179** with dimethylformamide dimethyl acetal, which excludes its involvement in the reactions with  $\alpha$ -alkoxy enamine **197**. Evidently, the latter reaction involves hetarylation of amidoacetals by the compound **179**. The reaction of enamine **197** with DMF diethyl acetal results in elimination of ethyl acetate (identified by GLC) due to dealkylation of the diethoxycarbenium ion A, which is produced upon arylation and then easily splits the corresponding alkyl halide.



R<sup>1</sup> = H, Me; R<sup>2</sup> = Me, Et.

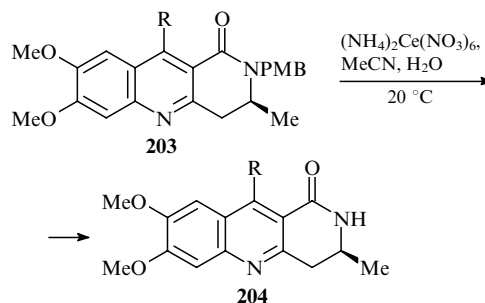
2,6-Dimethylbenzo[*b*][1,6]naphthyridinium iodide (**199**) in DMSO is easily dimerised to form compound **200**. The structure

of the latter was established by X-ray diffraction analysis. Dimerisation is markedly accelerated in the presence of water. Apparently, water can add to the cation **199** to give pseudobase **201**. The latter can be deprotonated to give the intermediate **202**. The dimer is formed through the addition of the intermediate **202** at electron-deficient position 10 of the cation **199**. Subsequent elimination of water and oxidation afford the dication **200**.<sup>5</sup>



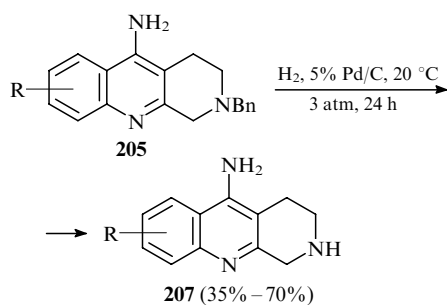
#### 4. Deacylation and dealkylation

Considering that many synthetic processes produce benzonaphthyridines containing alkyl or acyl substituents at the pyridine nitrogen atom, it is necessary to get a better insight into the mechanism of their elimination. Thus the acyl group of tetrahydrobenzo[*b*][1,6]naphthyridines is easily eliminated under conditions of acid or alkaline hydrolysis to give deacylation products in nearly quantitative yields.<sup>30</sup> The protective 4-methoxybenzyl group in compounds **203** can smoothly be removed under oxidative conditions; this affords debenzilation products **204** in good yields.<sup>19</sup>

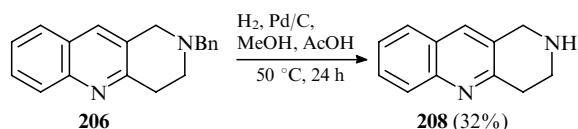


R = H (72%), Me (67%).

The benzyl group in compounds **205** and **206** is not activated by electron-donating substituents and it was removed by hydrogenation over Pd/C. This approach was used for the preparation of the debenzylated tetrahydro derivatives of benzo[*b*][1,7]-(**207**) (see Ref. 45) and benzo[*b*][1,6]naphthyridines **208**.<sup>30</sup>



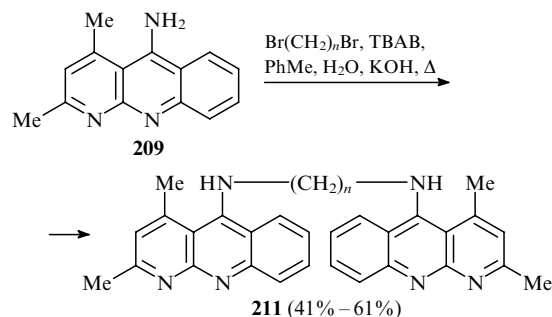
R = 7-F, 7-OMe, 8-F, 8-OMe.



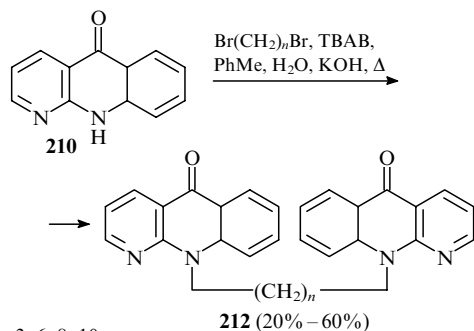
### 5. Synthesis of bis(benzo[b]naphthyridines)

Biological (mostly antitumour and antiacetylcholinesterase) properties of dimeric derivatives of acridine and its aza analogues, *viz.*, benzo[b]naphthyridines, have been studied extensively in the past decade. Reactions of the corresponding 10(5)-chlorobenzonaphthyridines with alkylenediamines or reactions of alkylene dihalides with the corresponding 10(5)-aminobenzonaphthyridines are used in the synthesis of bis(aminobenzonaphthyridines). However, the yields of the target products are rather low.

The tricyclic compounds **209** and **210** were used as the starting reagents in the synthesis of *N,N'*-bis(benzo[b][1,8]naphthyridin-5-yl)- $\alpha,\omega$ -alkylenediamines **211** and  $\alpha,\omega$ -bis(5,10-dihydro-5-oxo-benzo[b][1,8]naphthyridin-10-yl)alkanes **212**. These reactions were carried out under phase-transfer catalysis conditions using tetrabutylammonium bromide (TBAB) as a catalyst.<sup>108</sup>



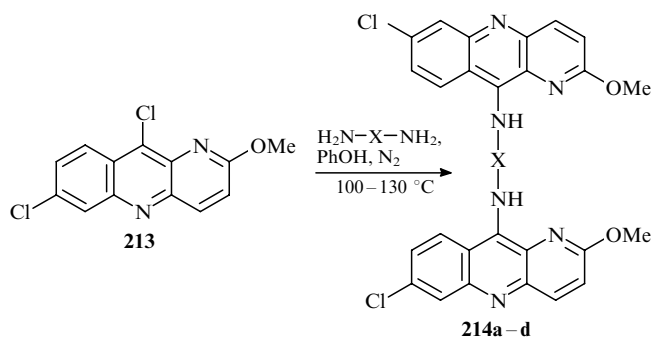
$n = 3, 6, 8, 10$ .



$n = 3, 6, 8, 10$ .

The synthesis of a series of *N,N'*-bis(6,7,8,9-tetrahydrobenzo[b][1,8]naphthyridin-5-yl)- $\alpha,\omega$ -alkylenediamines containing polymethylene chains of different length was also documented.<sup>31–33</sup>

Dimeric benzo[b][1,5]naphthyridines **214a–d** were synthesised by the reactions of 7,10-dichlorobenzonaphthyridine **213** with di- and polyamines.<sup>109</sup>



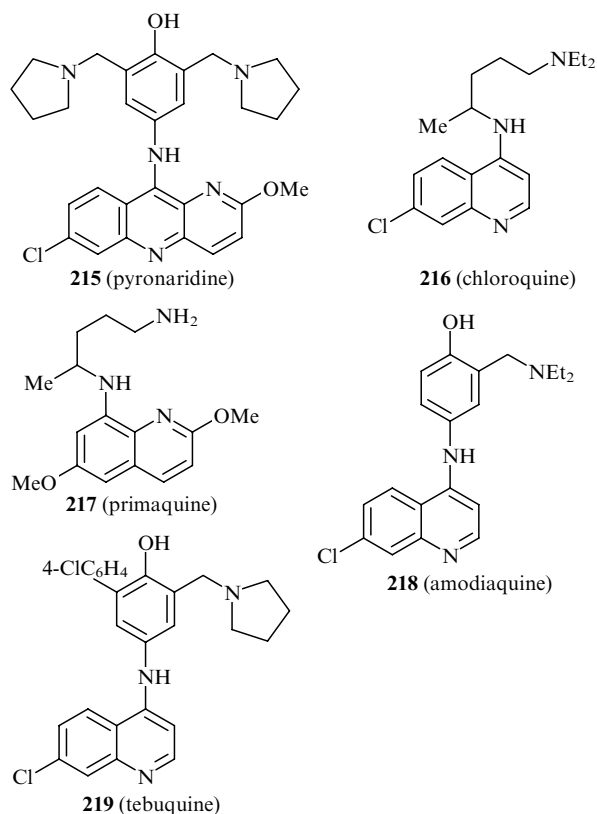
X = CH<sub>2</sub>CH(OH)CH<sub>2</sub> (**a**), (CH<sub>2</sub>)<sub>3</sub>NH(CH<sub>2</sub>)<sub>3</sub> (**b**), (CH<sub>2</sub>)<sub>4</sub>NH(CH<sub>2</sub>)<sub>3</sub> (**c**), (CH<sub>2</sub>)<sub>3</sub>NH(CH<sub>2</sub>)<sub>4</sub>NH(CH<sub>2</sub>)<sub>3</sub> (**d**).

Aminobenzonaphthyridines linked to other heterocycles through a flexible chain are synthesised in a similar way.<sup>26, 110</sup>

## V. Biological activity

### 1. Antimicrobial activity

The Chinese antimalarial drug pyronaridine (**215**) is related to the class of benzo[b][1,5]naphthyridine derivatives. Its preclinical trials demonstrated its safety and high activity against *Plasmodium falciparum* and *P. vivax*.<sup>111, 112</sup> The clinical efficiency of pyronaridine against the chloroquine (**216**) resistant strain of *P. falciparum*, *P. ovale* and *P. malariae* was established in studies with human volunteers from Thailand and Cameroon.<sup>113–115</sup> The antimalarial activities of pyronaridine and other drugs were compared in *vitro* studies on clinically isolated malarial strains obtained from Cameroon, Gabon and Senegal.<sup>116–120</sup> An HPLC procedure for measuring pyronaridine levels in human blood plasma samples and in different drug forms has been developed.<sup>121</sup> *In vitro* studies demonstrated synergism between pyronaridine **215** and primaquine **217**.<sup>116</sup>

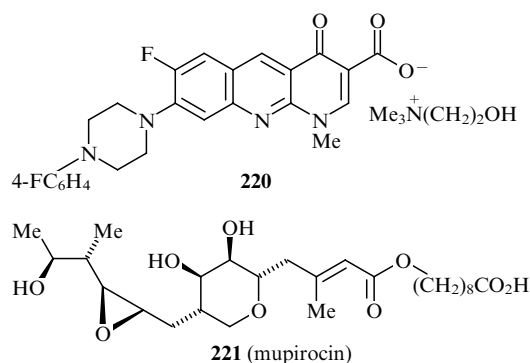


A more long-lasting pharmacological effect of pyronaridine in comparison with amodiaquine (**218**), tebuquine (**219**) and other antimalarial drugs related to the group of Mannich monobases

can be attributed to its higher lipophilicity and, as a consequence, higher ability to be accumulated in tissues.<sup>122</sup>

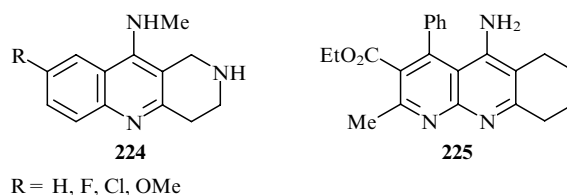
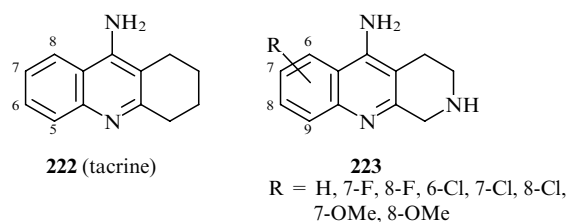
| Drug         | Distribution coefficient<br>in octanol–water (log <i>P</i> ) |        |
|--------------|--------------------------------------------------------------|--------|
|              | pH 5.0                                                       | pH 7.4 |
| Pyronaridine | −0.88                                                        | 0.34   |
| Amodiaquine  | −1.16                                                        | 0.93   |
| Tebuquine    | 0.99                                                         | 1.08   |

A series of benzo[*b*][1,8]naphthyridine-based antimicrobial agents highly active against multiresistant Gram-positive pathogens, including *Staphylococcus aureus* (MRSA), have been synthesised. These substances did not exhibit cross-resistance against the major classes of antimicrobial drugs (quinolones,  $\beta$ -lactams, *etc.*). The 50% inhibitory concentration ( $IC_{50} = 0.25–2$  mg litre<sup>−1</sup>) was established *in vitro* for the most reactive compound, RP60556A (**220**); its *in vivo* activity upon topical use in a model of skin infection (*Staphylococcus aureus*) in guinea pigs was found to be similar to that of mupirocin (**221**).<sup>65</sup>



## 2. Anticholinesterase activity

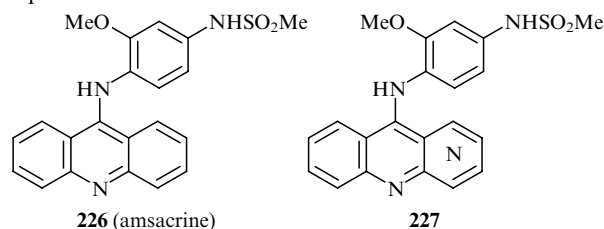
The use of drugs related to the class of acetylcholinesterase inhibitors (tacrine, amiridine) is chronologically the earliest and most well-developed approach to the use of adjuncts to control an attack of neurodegenerative diseases (*e.g.*, Alzheimer's disease).<sup>123, 124</sup> The disadvantage of this class of medicinal drugs is that they are low selective acetylcholinesterase (AChE) inhibitors (compared to butyrylcholinesterase (BChE) inhibition), which evokes undesirable side effects. A series of investigations are devoted to the synthesis of tricyclic aza analogues of tacrine (**222**) and analysis of their anticholinesterase properties. 1,7-Naphthyridine **223**,<sup>34, 45, 125</sup> 1,6-naphthyridine **224** (see Ref. 25) and 1,8-naphthyridine **225** derivatives were synthesised and studied.<sup>35</sup> The  $IC_{50}$  values of compounds **223** lie in the range 0.06 ( $R = 8\text{-Cl}$ )–0.5 ( $R = 8\text{-OMe}$ ) mM, the tacrine activity being 0.19 mM. The presence of a substituent at position 8 (corresponding to position 6 of tacrine) improves the inhibiting properties.<sup>45</sup> 1,6-Naphthyridines **224** have much lower affinity for the enzyme in comparison with tacrine. The  $IC_{50}$  of the most efficient of those, *viz.*, ( $R = H$ ), was = 0.86 mM, *i.e.*, about four times lower in comparison with tacrine.<sup>25</sup> Naphthyridine **225** approached tacrine in terms of anti-AChE activity, but strongly exceeded it in selectivity (AChE/BChE).<sup>35, 36</sup> Compounds of the type **225** also manifested the properties of L-type calcium channel blockers.<sup>36</sup>



Compounds exhibiting a higher AChE inhibition level *in vitro* and higher [in comparison with tacrine (**222**)] anti-AChE selectivity with respect to butyrylcholinesterase (BChE) were identified among other dimeric tetrahydroacridine derivatives (tacrine analogues) and 5,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridine derivatives. The optimum length of the polymethylene bridge was 7 methylene units.<sup>31</sup>

## 3. Antitumour activity

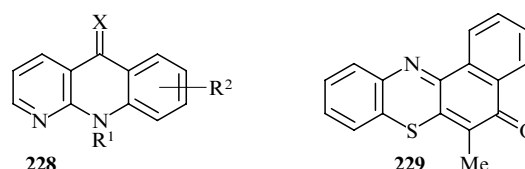
Antitumour activity of 9-aminoacridine derivatives is closely connected with the intercalation characteristic of many planar ionisable systems. The drug amsacrine (**226**) (see Ref. 126) is an example.



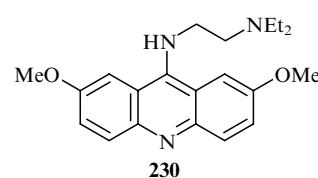
A series of compounds the acridine system in which was modified by the insertion of an additional nitrogen atom into the benzene ring have been synthesised in an attempt to search for novel promising medicinal drugs endowed with antitumour activities. The same approach was used in the synthesis of amsacrine aza analogues **227**.<sup>127</sup>

The antitumour properties of benzonaphthyridines have also been studied. Some of these compounds manifested antitumour properties *in vitro*<sup>32, 47, 102, 109, 127</sup> and *in vivo*.<sup>102</sup> Dimeric intercalators based on *N,N'*-bis(benzonaphthyridine)- $\alpha,\omega$ -alkylenediamines manifested higher (in comparison with mono-intercalators) DNA binding constants.<sup>108, 109</sup> If the chains contained 7–10 methylene fragments, double intercalation took place.

The benzo[*b*][1,8]naphthyridine derivatives **228** were studied as modulators of multidrug resistance (MDR). These compounds were tested *in vitro* on mouse T-lymphoma cells after transfection (artificial transfer of genetic information) of the MDR1 gene into eukaryotic cells with the help of purified DNA. The effects of compounds **228** were compared to those of 6-methyl-5-oxobenzo[*a*]phenolthiazine (**229**) and 9-[2-(diethylamino)ethylamino]-2,7-dimethoxyacridine (**230**). The majority of the tested substances killed MDR tumor cells more effectively than the reference compounds **229** and **230**.<sup>128</sup>



$X = O, NH$ ;  $R^1 = OMe$ ;  
 $R^2 = R^3N(CH_2)_n$  ( $R^3 = Alk, Ar$ ;  $n = 2, 3$ ).



#### 4. Anti-inflammatory activity

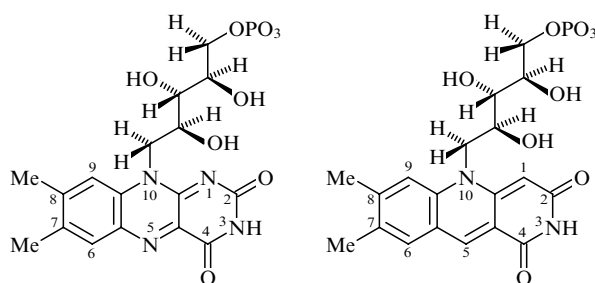
10-Substituted 1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines manifested remarkable activities as interleukin-1 inhibitors and were patented as anti-inflammatory drugs.<sup>28, 29</sup>

Several neurokinin A antagonists, which represent 1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine derivatives, were patented as remedies against diseases associated with tachykinin receptors and as preventives.<sup>30</sup>

3-Amino derivatives of 4-cyanobenzo[*b*][1,6]naphthyridine relieved the spasmogenic effect of bradykinin in experiments with isolated segments of guinea pig ileum; however, these compounds manifested significantly lower activities when the experiments were carried out on whole animals.<sup>129</sup>

#### 5. Other biological characteristics

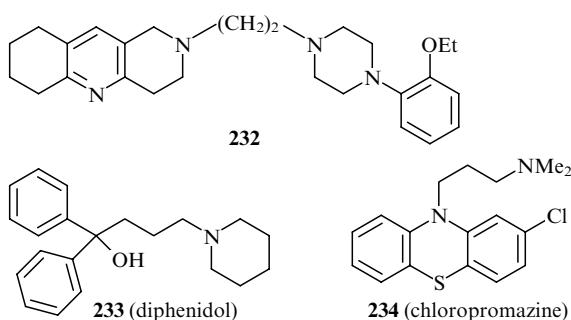
In some papers devoted to the study of the cofactor properties of modified flavins, benzo[*b*][1,6]naphthyridine derivatives were considered as 1,5-dideaza analogues of alloxazine and isalloxazine. Bio-isomers of flavins, such as compound **231**, were used to simulate the activities of flavin-dependent enzymes and to elucidate the structural properties essential for the manifestation of cofactor effects.<sup>130, 131</sup>



Flavin mononucleotide (FMP)

**231**

6-[ω-(4-Aryl-1-piperazinyl)alkyl]-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridines **232** manifested high antivertigo and anti-emetic activities.<sup>132–135</sup> A close QSAR – activity relationship was established for *ortho*-substituted arylpiperazine derivatives.<sup>135</sup> Compound **232** (NK 422; difumarate) was chosen as a promising antivertigo drug<sup>134</sup> and manifested a stronger (in comparison with diphenidol<sup>136</sup> and chlorpromazine<sup>137</sup>) anti-emetic effect.



**233** (diphenidol)

**234** (chlorpromazine)

A series of acridines and their aza derivatives (in total, 71 compounds) were tested as  $\text{Ca}^{2+}$ -dependent inhibitors of protein kinase from wheat embryos. Benzo[*b*][1,5]naphthyridine derivatives containing basic and neutral substituents at position 4 manifested the highest activity.<sup>138</sup>

The ability of the 10-aminobenzo[*b*][1,5]naphthyridine compounds, fragments in which are linked together through flexible chains, to inhibit replication of the prions  $\text{PrP}^{\text{Sc}}$  was studied.<sup>§</sup>

However, the activities of such bisbenzonaphthyridines appeared to be lower than those of the corresponding bisacridines.<sup>140</sup>

#### VI. Conclusion

This review is a generalisation of the published data on the synthesis and properties of benzo[*b*]naphthyridines. The data reviewed suggest that a search for novel compounds endowed with unique biological properties is the main trend of research in this area. Indeed, some experimental findings corroborate the conclusion that such a search can be both successful and constructive. The discovery of pyronaridine, the first representative of this class of compounds manifesting high clinical efficiency, is the first step in this direction. In-depth studies into antitumour activities of some benzo[*b*]naphthyridine derivatives, their ability to inhibit acetylcholinesterase and to suppress replication of prions are currently of paramount importance. The search for novel biologically active substances among compounds of the benzo[*b*]naphthyridine series demands additional experiments aimed at the functionalisation of this type of tricyclic compound through the insertion of various pharmacophores able to enhance their biological properties.

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§ Prions are abnormal forms of ordinary cellular proteins that are thought to be causatives of many severe infectious diseases, e.g., Creutzfeldt–Jacob's disease (degenerative neurological disorder).<sup>139</sup>

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<sup>a</sup> — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*

<sup>b</sup> — *Chem. Heterocycl. Compd. (Engl. Transl.)*

<sup>c</sup> — *Pharm.-Chem. J. (Engl. Transl.)*

# Topological structure and relaxation properties of polymers<sup>†</sup>

V I Irzhak

## Contents

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**Abstract.** The experimental data and theoretical views on the relations between the relaxation properties and structure of polymers are generalised. The attention is focused on the topological structural level, in particular, characteristics including the molecular mass, the molecular mass distribution, the degree of branching, and the covalent and equilibrium network parameters. In relation to the discussion of the relaxation spectrometry concept, the physical meaning of the kinetic parameters of local transitions and the nature of  $\beta$ -relaxation are considered. Methods of calculation of the continuous and discrete relaxation spectra from the results of relaxation and rheological experiments are described. Data establishing the relation between the relaxation spectrum and the topological structure of a polymer are analysed. The bibliography includes 282 references.

## I. Introduction

The relaxation properties of polymeric materials determine the possibility of using them in practice.<sup>1,2</sup> Of course, the nature and character of relaxation processes depend on the polymer structure. However, the concept of polymer structure requires a clear definition.

A feature of high-molecular-mass compounds is that their complex structure cannot be described in a certain single fashion. Conditionally, it is possible to consider three interrelated structural levels, namely, a molecular, a topological and a supra-molecular level.<sup>3</sup> Characterisation of each level requires the use of a specific approach.

The molecular level covers the chemical and isomeric structure, *i.e.*, all aspects that can be described by structural formulae accepted in chemistry. On this level polymers are not basically different from low-molecular-mass compounds (of course, if we are dealing with rather complex molecules). While on the subject of chemical structure, the case in point is mainly the local organisation of compounds (at least on the length scale of a unit). At the same time introduction of the notion of sequences (blocks) comprising units of different chemical structure (including isomeric states) (copolymers) is due to the chain nature of

high-molecular-mass compounds. Besides, chain molecules (in contrast to the molecules of low-molecular-mass compounds) can have stereoisomers, *i.e.*, include isotactic and syndiotactic groups and correspondingly, blocks comprised of them. Therefore, characterisation of the molecular structure of a polymer requires the use of not only 'chemical language' but also complex concepts, which provide a quantitative description of sequences comprising different types of units.

The second, topological, level is immediately related to the concept of polymer chains. Here, we abstract from particular chemical meaning and consider polymers as sets of chains. Chains can have different lengths and different molecular mass distributions (MMDs), be linear or branched or have a complex cyclic structure (including chemically nonbonded molecules, *e.g.*, catenanes); they can also form a continuous three-dimensional network. It is the topological structure that is responsible for many physical properties of polymeric materials.<sup>1,3–5</sup> The concept of local structural organisation of molecules is insufficient for an understanding of the polymer structure on the topological level. Apparently, the chemical notation is inappropriate for the description of the topological structure, which has a particular geometrical meaning. The topological structure is characterised by graphs which include such elements as vertices (branching points), edges (chains), *etc.* The graph theory ignores the edge length, but the chain length and the chain length distribution are quite important for the topological structure of polymers.

The topological structural level 'abstracts' from the spatial arrangement of macromolecules, which characterises the supra-molecular structure of the polymer. In essence, this is a macroscopic level; nevertheless, the local structural organisation is an important factor. For instance, the local density strongly depends on the energy of intermolecular interaction (chemical nature of the polymer units). The topology also plays a significant role; for instance, the degree of polymer crystallinity is very responsive to the degree of chain branching, *i.e.*, to the structural level in question.

The chemical level of the polymer structure is basic (eventually, chain formation involves formation of chemical bonds; the possibility or impossibility of ring formation or branching in macromolecules is essentially a chemical problem). However, when considering the relations between the structure and properties of a polymer, it is convenient to discuss the effect of each level separately.

V I Irzhak Institute of Problems of Chemical Physics, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation. Fax (7-496) 515 32 44, tel. (7-496) 522 21 63, e-mail: irzhak@icp.ac.ru



The relaxation properties characterise the ability of a compound disturbed from the equilibrium state to return to the equilibrium state. They are determined by the sum of all types of motions of molecular groups, chain fragments and macromolecules, that is, rotational, vibrational and translational motions. Representation of a relaxation process by the sum of such motions makes it possible to obtain an idea of a spectral characteristic of the compound.

If a process can be expressed by the sum of  $n$  independent elementary relaxation transitions, the kinetics of the process can formally be expressed as follows:

$$g(t) = \sum_{i=1}^n h_i e^{-t/\lambda_i},$$

where  $g(t)$  is the kinetic modulus,  $t$  is the running time,  $h_i$  is the relaxation spectrum and  $\lambda_i$  is the relaxation time.

In the continuous case one has

$$g(t) = \int_0^{\infty} h(\lambda) e^{-t/\lambda} d\lambda. \quad (1)$$

Sometimes the relaxation spectrum  $h_i$  or  $h(\lambda)$ , as a function of the relaxation time  $\lambda_i$  (or  $\lambda$ ), is denoted as  $H(\lambda) = \lambda h(\lambda)$ . A very broad range of relaxation times can be described in a more compact form, namely, in the logarithmic scale

$$g(t) = \int_{-\infty}^{\infty} H(\lambda) e^{-t/\lambda} d \ln \lambda. \quad (1a)$$

The frequency dependence of a relaxation process is represented by a Fourier transform of expression (1), namely

$$G^*(\omega) = i\omega \int_0^{\infty} g(t) e^{-i\omega t} dt, \quad (2)$$

where  $G^*(\omega)$  is the complex frequency modulus and  $\omega$  is the frequency.

As can be seen, there is a one-to-one correspondence between  $G^*(\omega)$  and  $g(t)$ , *i.e.*, knowledge of one parameter permits determination of the other. Since expression (1) is an integral Laplace transform of the spectrum  $h(\lambda)$ ,<sup>‡</sup> there is also a one-to-one correspondence between these quantities. A difficulty consists in that the experimentally measured  $G^*(\omega)$  and  $g(t)$  values (i) usually include random (noise) or systematic errors and (ii) are obtained within limited time and frequency intervals. The integral operator on the right side of equality (1) is a smoothing operator, *i.e.*, intensive perturbations in the  $h(\lambda)$  function are considerably smoothed in the  $g(t)$  function. But this also means that minor disturbances (*e.g.*, errors) in experimental data can introduce a large uncertainty into solution of the problem of determination of the relaxation spectrum  $h(\lambda)$ . Cutting off the integration limits due to limitations imposed by experimental techniques can also be a source of errors introduced into the results of the inverse Laplace transform and Fourier transform.

The complex frequency modulus  $G^*(\omega)$  is usually expressed through its real and imaginary components

$$G^*(\omega) = G'(\omega) + iG''(\omega), \quad (3)$$

$$G'(\omega) = \int_0^{\infty} h(\lambda) \frac{\omega^2 \lambda^2}{1 + \omega^2 \lambda^2} d\lambda,$$

$$G''(\omega) = \int_0^{\infty} h(\lambda) \frac{\omega \lambda}{1 + \omega^2 \lambda^2} d\lambda,$$

<sup>‡</sup> Strictly speaking, the Laplace integral transform of the function  $h(1/s)/s^2$ , where  $s = \lambda^{-1}$ .

Their ratio, called the (mechanical, dielectric, *etc.*) loss factor and given by

$$\tan \delta = \frac{G''(\omega)}{G'(\omega)}, \quad (4)$$

is often used for the determination of individual relaxation transitions. In this case the amplitude (intensity) of a peak in the  $\tan \delta$ -vs.-temperature ( $T$ ) or in the  $\tan \delta$ -vs.-frequency plots is usually related to the content of the relaxing element (relaxer).

## II. Relaxation spectrometry

In order to describe and classify local relaxation transitions, G M Bartenev put forward a concept of relaxation spectrometry.<sup>1,2,5</sup> As it was written in a monograph<sup>1</sup> that 'relaxation spectrometry itself, as a specific kind of kinetic spectroscopy,... is in the early stage of its development and at present not all principles of relaxation spectrometry can be considered rigorously substantiated'.<sup>§</sup>

In fact, local character of relaxation processes means that each process occurs (and, correspondingly, can be considered) independently. Parameters of each process (in particular, the relaxation times) are determined by the local polymer structure, which in turn can be characterised by these parameters. This is a distinctive feature of relaxation spectrometry as a method for studying the polymer structure.

A more or less broad spectrum of local relaxation times is due to the fact that even in the simplest macromolecules (such as polyethylene, polyethylene oxide and polystyrene molecules) one can select a set of relaxers. Torsional motions of atoms and side groups and crankshaft rotations of various intrachain atomic groups are characterised by different relaxation times. Complication of the molecular structure leads to broadening of the relaxation spectrum.

Structural description of local relaxation transitions is usually performed by relating the position of the maximum in the temperature dependence of loss factor, at a given frequency or temperature scan rate, to the presence of particular molecular groups in the polymer chain. At the point of maximum, the condition  $\omega\lambda = 1$  or  $W(T)\lambda = 1$  is met, where  $W(T)$  is the temperature scan rate. This makes it possible to determine the relaxation time  $\lambda$ .

According to Bartenev,<sup>2</sup> a relaxation transition can be represented by a jump of a relaxer through an activation barrier, *i.e.*, the temperature dependence of relaxation time obeys an Arrhenius equation

$$\lambda = B \exp \frac{E}{RT}.$$

The barrier height is governed by the activation energy  $E$  while the pre-exponent  $B$  characterises the volume of the relaxing element (relaxer)

$$B = \frac{v^{5/6}}{(6kT/\rho)^{1/2}}, \quad (5)$$

where  $v$  is the volume and  $\rho$  is the relaxer density.

Processes due to motions of small molecular groups (group size is much less than the size of a chain segment) belong to the smallest-scale  $\gamma$ -processes. Typical values of the kinetic parameters characteristic of this type of motion are as follows:  $B \approx 10^{-9} - 10^{-12}$  s and  $E_\gamma = 10 - 20$  kJ mol<sup>-1</sup>.

Larger-scale  $\beta$ -relaxation is characterised by  $B$  values of the order of  $2 \times 10^{-13}$  s and  $E_\beta$  values lying between 30 and 70 kJ mol<sup>-1</sup>.  $\alpha$ -Relaxation also belongs to local processes. Usually, the temperature dependence of the  $\alpha$ -relaxation time does not obey the Arrhenius equation. However, in a limited temperature

<sup>§</sup> See page 297 in Ref. 1.

interval it is characterised by the parameters  $B \sim 5 \times 10^{-12}$  s and  $E_\alpha = 50-70$  kJ mol $^{-1}$ .

It should be noted that almost all local transitions can be detected by both high-frequency (NMR, EPR, acoustic, dielectric and various mechanical dynamical methods) and low-frequency [the same mechanical dynamical methods in the low-frequency range, thermomechanical analysis (TMA), differential scanning calorimetry (DSC), *etc.*] methods.<sup>1,2,6</sup> For instance, knowledge of the temperature dependence of the damping constant or of the mechanical loss factor at a frequency of about 1 Hz (or fractions of a Hertz) makes it possible to find out all these transitions.<sup>2,5</sup>

As a rule, local relaxation transitions correspond to structural transitions. For instance, it was shown<sup>7</sup> that the thermal expansion coefficients of the polymers listed below change stepwise at the following temperatures (°C):

|                             |                   |
|-----------------------------|-------------------|
| poly(methyl methacrylate)   | 15, 100           |
| poly(methacrylate)          | -115, -15, 25, 60 |
| poly(n-propyl methacrylate) | -85, -35, 15, 30  |
| poly(n-butyl methacrylate)  | -95, -55, -25, 20 |

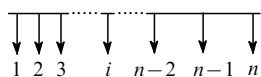
The last-mentioned temperatures correspond to  $\alpha$ -transitions and the lower temperatures correspond to small-scale local transitions.

### 1. Model of coupled rotators

The Frenkel–Eyring discrete model of activated diffusion provides the basis for relaxation spectrometry. According to this model, a diffusion act involves three consecutive stages. These are (i) reorganisation of the environment of the diffusing species involving formation of a ‘hole’ of comparable volume, (ii) the jump of the particle through the activation barrier to the ‘hole’ formed and (iii) reorganisation of the environment to remove the ‘hole’.

According to modern concepts of the diffusion mechanism (see, *e.g.*, Ref. 2), the motion of a particle occurs simultaneously with local reorganisation of the environment. The particle moves gradually by ‘elbowing’ particles of the environment rather than by hopping over distances of the order of the particle size. According to this continuous model, the particle executes a number of steps during the hopping time and thus travels a distance comparable with the particle size. Thus, formally both models lead to the same results. However, the kinetic parameters of the process (‘hole’ volume, energy of ‘hole’ formation, activation energy for hopping) and, correspondingly, the parameters  $B$  [see Eqn (5)] and  $E$  in the Arrhenius equation have a different physical meaning.<sup>8-10</sup>

The model of elastically coupled rotators<sup>11,12</sup> was first proposed by Mansfield.<sup>13</sup> It is based on the physically more substantiated mechanism of local relaxation.



Rotators (asterisked) execute torsional motions near the equilibrium positions in the plane normal to the axis. The character of motion is determined by the local (torsional) friction coefficient  $\zeta_i$  and by the rigidity,  $K_i$ , of the bond being twisted (rotators are enumerated from the left, so the bonds are enumerated from zero to  $n$ ). The two outermost bonds can have a zero rigidity (free chain) or a finite rigidity (chain is embedded into a framework, *e.g.*, a network).

The equations describing relaxation of this system, have the form

$$\begin{aligned}\dot{x}_1 &= -K_0x_1 - K_1(x_1 - x_2) - \tau_1^{-1}x_1 = \\ &= -x_1(K_0 + K_1 + \tau_1^{-1}) + K_1x_2, \\ \dot{x}_2 &= K_1(x_1 - x_2) - K_2(x_2 - x_3) - \tau_2^{-1}x_2 = \\ &= K_1x_1 - x_2(K_1 + K_2 + \tau_2^{-1}) + K_2x_3,\end{aligned}\quad (6)$$

$$\begin{aligned}\dot{x}_3 &= K_2(x_2 - x_3) - K_3(x_3 - x_4) - \tau_3^{-1}x_3 = \\ &= K_2x_2 - x_3(K_2 + K_3 + \tau_3^{-1}) + K_3x_4, \\ &\dots\dots\dots \\ \dot{x}_i &= K_{i-1}x_{i-1} - x_i(K_{i-1} + K_i + \tau_i^{-1}) + K_ix_{i+1} \\ &\dots\dots\dots \\ \dot{x}_{n-1} &= K_{n-2}x_{n-2} - x_{n-1}(K_{n-2} + K_{n-1} + \tau_{n-1}^{-1}) + K_{n-1}x_n, \\ \dot{x}_n &= K_{n-1}x_{n-1} - x_n(K_{n-1} + K_n + \tau_n^{-1}),\end{aligned}$$

where  $x_i$  is the angle of deviation of the dipole from its equilibrium position and  $\tau_i$  is treated as the effective relaxation time of the  $i$ th dipole, which is proportional to the friction coefficient  $\zeta_i$ .

The solution is written as expansion into a series

$$x_i = \sum_{j=1}^n a_{ij} \exp(-p_j t). \quad (7)$$

The relaxation time  $\lambda_i = p_i^{-1}$  is determined by the equation

$$D_n = \begin{vmatrix} \varphi_{11} & \varphi_{12} & 0 & 0 & \dots & 0 & 0 \\ \varphi_{21} & \varphi_{22} & \varphi_{23} & 0 & \dots & 0 & 0 \\ 0 & \varphi_{32} & \varphi_{33} & \varphi_{34} & \dots & 0 & 0 \\ \dots & \dots & \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \varphi_{i,i-1} & \varphi_{i,i} & \dots & 0 & 0 \\ \dots & \dots & \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & \dots & \dots & \varphi_{n,n-1} & \varphi_{n,n} \end{vmatrix} = 0 \quad (8)$$

where  $\varphi_{11} = z_1 - (\tau_1^{-1} + K_0 + K_1)$ ;  $\varphi_{12} = K_1$ ;  $\varphi_{21} = K_1$ ;  $\varphi_{22} = z_2 - (\tau_2^{-1} + K_1 + K_2)$ ;  $\varphi_{23} = K_2$ ;  $\varphi_{i,i-1} = K_{i-1}$ ;  $\varphi_{i,i} = z_i - (\tau_i^{-1} + K_{i-1} + K_i)$ ;  $\varphi_{i,i+1} = K_i$ ;  $\varphi_{n,n-1} = K_{n-1}$ ;  $\varphi_{n,n} = z_n - \tau_n^{-1} + K_{n-1} + K_n$ ;  $z_i = 1/\lambda_i$ .

Analysis of the solution of Eqn (8) showed that if  $K_i \ll 1$  for any  $i$ , the elements relax independently with  $\lambda_i = \tau_i$ . In other words, in this case the relaxation is governed solely by the physical nature and by the magnitude of the local friction coefficient  $\zeta_i$ , *i.e.*, by the level of local intermolecular interaction. If  $K_i \gg 1$  for any  $i$ , the structure of the  $D_n$  matrix will be identical to the structure of the Rouse matrix for a free chain (at  $K_0 = K_n = 0$ ) or for an end-to-end cross-linked chain (at  $K_0$  and  $K_n \neq 0$ ). However, in this case the relaxation times increase by a factor of  $K$ . Thus, intrachain interaction causes relaxation of each element to be characterised by a spectrum of relaxation times.

To obtain a detailed description of the relaxation kinetics of the system in the framework of the model of coupled rotators, one should allow for the Brownian force<sup>11</sup> exerted on each element in the system. Therefore, each equation in system (6) should be augmented with the corresponding term.

Analysis of the solution of the modified system (6) showed<sup>12</sup> that, at times shorter than  $\lambda_{\min}$  (minimum relaxation time of the chain of rotators), the correlator  $\langle \cos x_j(t) \cos x_j(0) \rangle$  decreases exponentially with the characteristic time  $\lambda_1$ . In this region the effect of the neighbours of a given rotator can be ignored and the motion occurs as rotational diffusion, which is not affected by chain rigidity

$$\lambda_{\min} = \frac{\zeta^{\text{rot}}}{4K^{\text{rot}}}, \quad \lambda_1 = \frac{\zeta^{\text{rot}}}{4kT} = \frac{1}{4D}.$$

Here  $\zeta_1 = \zeta_2 = \dots = \zeta_i = \dots = \zeta^{\text{rot}}$  is the torsional friction coefficient,  $K_1 = K_2 = \dots = K_i = \dots = K^{\text{rot}}$  is the twisting rigidity of the chain and  $D$  is the rotational diffusion coefficient.

At times longer than  $\lambda_{\min}$ , relaxation is described by a ‘stretched’ exponent:  $\sim \exp[-(t/\lambda_2)^{1/2}]$ , where

$$\lambda_2 = \frac{\pi \zeta^{\text{rot}} K^{\text{rot}}}{(4kT)^2}.$$

In this time interval the motion of a rotator is strongly affected by the neighbouring rotators (manifestation of chain rigidity), the

length scale of the motion being equal to the length of the rigid chain fragment.

Note that the relations given above are valid for an infinite chain where the effect of the end groups can be ignored. Finite chains have also been studied.<sup>12</sup>

Thus, the character of local relaxation transitions is first of all determined by the local viscosity. An important additional factor is intrachain interaction, which manifests itself as the twisting rigidity of the chain. In all cases the activation model is inadequate.

## 2. On the nature of $\alpha$ - and $\beta$ -relaxation

At present there are two antipodes of opinion of the nature of  $\alpha$ - and  $\beta$ -relaxation. On the one hand, it is traditionally accepted (see references cited in Ref. 2) that different molecular groups are responsible for these transitions. Namely,  $\alpha$ -transition is due to segmental motion while  $\beta$ -transition is due to a smaller-scale motion of relaxers (here, the molecular mass of the relaxer is five to ten times smaller than that of a chain segment).

According to the other point of view (see Refs 14, 15), relaxation in the corresponding temperature and frequency ranges is due to the same chain fragments, namely, chain segments. This is reasoned by the following:

1. Amorphous low-molecular-mass glasses with rigid molecules (in *e.g.*, solutions of chlorobenzene, *o*-dichlorobenzene and 1-chloronaphthalene in decalin, blends of chlorobenzene with pyridine, blends of tetrahydrofuran with bromobenzene and 1-chloronaphthalene, *etc.*) exhibit not only the  $\alpha$ -transition but also a low-temperature transition, which can be associated with  $\beta$ -relaxation.<sup>16–23</sup> The systems in question contain no other relaxers, except for the rigid molecules, capable of moving as a whole. Therefore, both relaxation transitions are due to the same structural elements. Characteristics of the low-temperature transition are similar to those of  $\beta$ -relaxation in polymeric systems, namely, it obeys an Arrhenius-type temperature dependence with an activation energy lying in the range 17–33 kJ mol<sup>−1</sup>. As the temperature increases, both transitions approach each other. Finally, both relaxation processes in the system including low-molecular-mass components are also observed in the polymeric reaction product, but here the relaxation times are longer, which is quite natural.<sup>22</sup>

2. Bershtein *et al.*<sup>15, 24–26</sup> showed that for certain polymers the dependences of the heats of the  $\beta$ - and  $\alpha$ -transitions on the number,  $n$ , of monomer units are given by similar curves that reach the plateau zone at the same  $n$  value. This is indicative of the identity of the  $\beta$ - and  $\alpha$ -relaxers in polymeric systems.

3. Liquid systems characterised by one relaxation transition, namely, the glass transition, show a second low-temperature transition upon compression.<sup>27</sup> Apparently, new relaxers cannot appear under these conditions. A possible reason is an increase in the density of the system and, as a consequence, an increase in the concentration of high-density fluctuations.

4. Theoretical analysis<sup>14, 28, 29</sup> of the relaxation of bulk amorphous systems that show a unique structural feature (density fluctuations) showed the following.

The temporal correlation function  $\psi(t)$  is given by the Kohlrausch – Williams – Watts (KWW) formula

$$\psi(t) = \alpha_1 \exp \left[ - \left( \frac{t}{\tau_1} \right)^{\beta_1} \right] + \alpha_2 \exp \left[ - \left( \frac{t}{\tau_2} \right)^{\beta_2} \right], \quad (9)$$

where  $\alpha_1$  and  $\alpha_2$  are the pre-exponents,  $\beta_1 = 0.33$  and  $\beta_2 = 0.14–0.27$ .

Analysis of expression (9) revealed the existence of two relaxation regions. The first region corresponds to a short relaxation time, being almost temperature independent, while the second region corresponds to a long relaxation time and extends with temperature. The temperature dependence of  $\tau_1$  obeys an Arrhenius relationship while that of  $\tau_2$  is described by the Williams – Landell – Ferry (WLF) equation, which is typical of

$\alpha$ -relaxation. It was also found that the activation energy for the first region  $E_1 = 35$  kJ mol<sup>−1</sup> and  $80 \leq E_2 \leq 139$  kJ mol<sup>−1</sup> for the second region.

The frequency dependence of the imaginary component of the bulk modulus exhibits two maxima. The temperature dependence of the high-frequency peak obeys an Arrhenius relation and that of the low-frequency peak obeys the WLF equation.

These processes,  $\alpha$ - and  $\beta$ -relaxations, are characteristic of all amorphous systems and both transitions can be initiated by the same elements. The appearance of two regions is due to a nonuniform density distribution, *viz.*,  $\alpha$ -relaxation occurs in the high-density fluctuations while  $\beta$ -relaxation occurs in the low-density ones. The former process is essentially a co-operative one for which an important role is played by structural rearrangements in the environment; as a consequence, the temperature dependence is of the WLF type. The latter process is non-co-operative; therefore it is described by the Arrhenius equation.

Recent studies of the structure and properties of thin polymer films (see, *e.g.*, Ref. 30) showed that the glass transition temperature decreases appreciably if the thickness of the polymer film approaches the diameter of the unperturbed coil. It was assumed that this effect is due to violation of the co-operative character of molecular motion in thin films (namely,  $\alpha$ -transition manifests itself as a  $\beta$ -transition). If by this is understood a known decrease in the packing density in near-surface layers and thin films, this assumption can be considered quite reasonable.

The aforesaid does not mean that  $\beta$ -relaxation in polymeric systems always has segmental character. Some other mechanism, which is due to the presence of other molecular groups, *i.e.*, a complex structure of polymer chains, can also be involved in addition to the mechanism described above.

## III. Manifestation of the topological structure of polymers in their relaxation properties

Certain structural meaning can be assigned with ease to local relaxation transitions that are mainly responsible for the level of internal friction in a polymeric material. This level governs, *e.g.*, the brittleness of the material. At the same time the relaxation properties in a broad sense determine the deformability, long-term strength and other characteristics related to the conformational rearrangements and motions of macromolecules. Apparently, the topological structure plays the key role in this case. But it is a rather complicated task to relate the topological structure to the relaxation behaviour of the polymer, although this problem is undoubtedly topical. In addition it is the relaxation techniques that can become basic to the development of non-destructive methods of structural characterisation of polymeric materials.<sup>31–34</sup>

### 1. Molecular mass

For linear polymers the dependence of the melt viscosity,  $\eta$ , on the average molecular mass ( $\bar{M}$ ) has the form<sup>4</sup>

$$\eta = K \bar{M}^\nu, \quad (10)$$

where  $\nu = 1$  at  $\bar{M} \leq 2 M_e$ ,  $\nu = 3.5 \pm 0.2$  at  $\bar{M} > 2 M_e$  and  $M_e$  is the molecular mass of the chain between entanglements in terms of the Doi – Edwards theory.<sup>11, 34</sup>

Expression (10) is a particular case of a more general dependence<sup>3, 35, 36</sup>

$$\eta \propto [\eta]^\nu$$

or

$$\eta \propto R^\nu,$$

where  $[\eta]$  is the characteristic viscosity, the exponent  $\nu$  lies between 6 and 7 and  $R$  is the coil radius. Validity of these relationships was shown for various types of polymers, *viz.*, linear polymers of different rigidity; cyclic, star-branched with different numbers of arms and comb-like polymers, randomly branched chains and

highly cross-linked polymer globules.<sup>3,37–42</sup> Therefore, the viscosity cannot serve as a unique characteristic of the molecular mass of a polymer. Other parameters of the topological structure, namely, the molecular mass distribution and the degree of branching also play a significant role.

The flow curves obtained for linear monodisperse polymers exhibit a specific shape.<sup>43,44</sup> At relatively low shear rates  $\dot{\gamma}$  (and, correspondingly, strain  $\tau$ ), one deals with a Newtonian flow, *i.e.*,  $\tau = \eta_0 \dot{\gamma}$ , where  $\eta_0 = KM^v$ . However, at a certain critical shear strain,  $\tau_c$ , the flow character changes. Here, flow breakdown occurs or the strain abruptly decreases with an increase in the shear rate (the former is characteristic of monodisperse polymers while the latter is typical of polydisperse polymers). The  $\tau_c$  value is independent of the molecular mass of the polymer. At the same time the shear rate corresponding to the  $\tau_c$  value can serve as a measure of the molecular mass of monodisperse polymers

$$\dot{\gamma}_c(M) = \frac{\tau_c}{KM^v}.$$

Knowing the temperature dependence of the stress,  $\varepsilon$ , of linear polymers (TMA method), it is possible to relate the molecular mass to the relaxation properties. Kargin and Slonimskii<sup>45</sup> first showed that the extension of a portion of the  $\varepsilon(T)$  curve, which is nearly parallel to the temperature axis (rubbery plateau zone,  $\Delta T = T - T_g$ , where  $T$  is the flow onset temperature and  $T_g$  is the glass transition temperature) is related to the molecular mass as follows

$$\log\left(\frac{M}{M_s}\right) \propto \frac{\Delta T}{C + \Delta T}, \quad (11)$$

where  $M_s$  is the molecular mass of the chain segment and  $C$  is a constant.

It should be noted that determination of the parameter  $\Delta T$  faces some difficulties, which are due to the diffuse character of the transition from the glassy to the rubbery state and from the rubbery state to a melt flow. The character of these transient regions depends on the width of the MMD. The validity of relationship (11) was confirmed<sup>46–48</sup> for a broad range of polymers. The authors studied narrow-MMD polymers, which made it possible to attain abrupt glass–elastomer and elastomer–melt transitions. The plot of the dependence (11) is shown in Fig. 1.

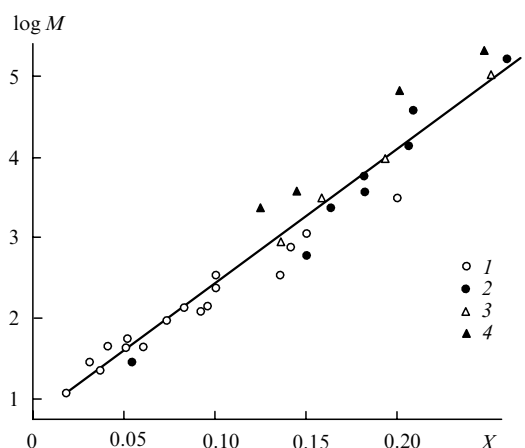


**Figure 1.** Correlation between the temperature interval corresponding to the rubbery plateau and the molecular mass of polymers plotted in the coordinates of Eqn (11) [ $X$  is the numerical value of the right side of Eqn (11),  $C = T_g$ ].<sup>48</sup> Polymers: polybutadiene (1), polyurethane-based polymers (2, 3) at  $T_g = 215$  (2) and 250 K (3) and polyacrylonitrile (4).

Using the temporal and the frequency dependences of the elastic modulus, one can also relate the relaxation properties of polymers to their molecular masses. Since the rubbery plateau zone extends from the minimum ( $\lambda_{\min}$ ) to the maximum ( $\lambda_{\max}$ ) relaxation time (see Refs 1, 24, 34), the  $\lambda_{\min}$  value being independent of the molecular mass and much shorter than  $\lambda_{\max}$ , the extension of the plateau zone is nearly equal (in time or frequency units) to  $\lambda_{\max}$ . But

$$\lambda_{\max} \propto M^v,$$

where the exponent  $v$  can take different values. Usually, it is assumed that  $v = 3.4$ . At the same time analysis of strain relaxation data showed<sup>49</sup> that  $v \approx 4$ . From the shift of the relaxation curves as functions of the molecular mass of the polymer (Fig. 2, lines 1, 2), *i.e.*, based on the estimate of the extension of the rubbery plateau zone, it was found that the  $v$  value lies between 3.3 and 3.5. Analysis of the frequency dependence of the elastic modulus revealed a similar  $v$  value ( $v = 3.5$  from the real component of the modulus, see Fig. 2, line 3, data were taken from Ref. 50). It should be noted that the maximum in the  $G''(\omega)$  plot correlates with the critical shear strain  $\tau_c$  (see Ref. 44), *i.e.*, it also characterises the molecular mass of linear monodisperse polymers, namely,  $v \approx 3.3$  (from the position of the maximum  $G''$  value).

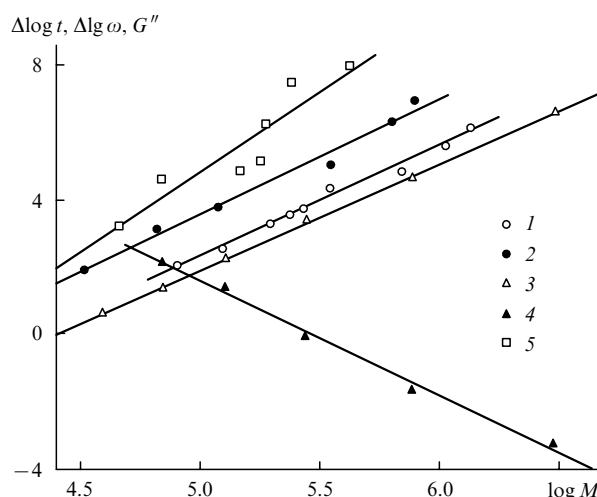


**Figure 2.** Relaxation parameters of linear polymers (1–4) and a four-arm star-branched polymer (5) plotted vs. molecular mass using the data taken from different studies.

Parameter:  $\Delta \log t$  (1, 2),  $\Delta \log \omega$  (3, 5) and  $G''_{\max}$  (4); the plateau extension is denoted by  $\Delta$ ; *e.g.*,  $\Delta \log t = \log t_{\max} - \log t_{\min}$ .

The molecular mass is closely related to parameters of the terminal zone of the complex frequency modulus curves  $G^*(\omega)$ .<sup>4,51–54</sup> The effective relaxation time

$$\lambda_{\text{ef}, w}(\omega) = \frac{G'(\omega)}{\omega G''(\omega)} \quad (12)$$

in the terminal zone takes the limiting value, which is frequency independent and equals the ratio of the second to the first moment of the relaxation time distribution, *i.e.*, is the weight-average relaxation time

$$\langle \lambda \rangle_w = \frac{\sum_i h_i(\lambda) \lambda_i^2}{\sum_i h_i(\lambda) \lambda_i}. \quad (13)$$

At  $\omega \rightarrow 0$ , the effective relaxation time given by

$$\lambda_{\text{ef}, n}(\omega) = \frac{G''(\omega)}{\omega[G_N^0 - G'(\omega)]}, \quad (14)$$

is the number-average relaxation time, which is also frequency independent ( $G_N^0$  is the modulus corresponding to the rubbery plateau zone),

$$\langle \lambda \rangle_n = \frac{\sum_i h_i(\lambda) \lambda_i}{\sum_i h_i(\lambda)}. \quad (15)$$

It is well known that the average relaxation times in the terminal zone correlate with the rheological properties of polymers, namely, the number-average relaxation time correlates with viscosity and the product of the viscosity and the compliance correlates with the weight-average relaxation time. From here it follows that these relaxation times depend on the molecular mass. The data for a number of monodisperse polymers are listed in Table 1.

**Table 1.** Dependence of the average relaxation times in the terminal region on the molecular mass of polymers.

| Polymer                               | $\langle \lambda \rangle_n$ | $\langle \lambda \rangle_w$ | Ref.   |
|---------------------------------------|-----------------------------|-----------------------------|--------|
| Polystyrene                           | $M^{3,4}$                   | $M^{3,7}$                   | 50     |
| Poly(methyl methacrylate)             | $M^{3,4}$                   | $M^{3,65}$                  | 53     |
| <i>cis</i> -Polyisoprene <sup>a</sup> | $M^{3,62}$                  | $M^{3,69}$                  | 54     |
| 1,4-Polybutadiene                     | $M^{3,37}$                  | $M^{3,52}$                  | 55, 56 |

<sup>a</sup> Data from dielectric measurements.

The parameters of dielectric relaxation are related to the molecular masses of polymers in a similar way. Here one should keep in mind that this can concern only those polymers in which the dipoles and chains are aligned (A-type polymers according to Stockmayer<sup>57</sup>).

The effective dielectric relaxation times are defined as follows:

$$\langle \lambda_e \rangle_w = \frac{\varepsilon_0 - \varepsilon'(\omega)}{\omega \varepsilon''(\omega)}, \quad \langle \lambda_e \rangle_n = \frac{\varepsilon''(\omega)}{\omega \Delta \varepsilon}, \quad \omega \rightarrow 0, \quad (16)$$

where  $\varepsilon_0$  is the conductivity,  $\varepsilon'$  and  $\varepsilon''$  are the real and imaginary components of the complex dielectric permittivity,  $\Delta \varepsilon$  is the intensity of dielectric relaxation for the motion of the entire chain (analogue of  $G_N^0$  in mechanical relaxation).

The position of the maximum in the  $\varepsilon''(\omega)$  curve on the frequency axis is also related to the molecular mass by a power law (for *cis*-polyisoprene, the exponent is 3.8<sup>58</sup>).

The spin–spin relaxation measured by pulsed NMR spectroscopy is sensitive to the molecular mass of linear polymers.<sup>59–62</sup> At a sufficiently high temperature ( $T > T_g + 100$ ), the free induction decay,  $G(t)$ , is defined by

$$G(t) = \int_1^{N\pi/2} \int_0^{\pi/2} \{ [g(N, \theta, t) P(N) \sin \theta] d\theta \} dN, \quad (17)$$

where

$$g(N, \theta, t) \approx \exp \left[ -\omega_1^2 (3 \cos^2 \theta - 1)^2 t^2 \frac{\ln N}{N^2} \right],$$

$N$  is the number of segments in the chain and  $\theta$  is the angle between the vector connecting the chain ends and the direction of external magnetic field;  $\omega_1$  is the second moment of the free induction decay curve, expressed in frequency units and  $P(N)$  is the numerical MMD function.

However, since NMR spectroscopy is a high-frequency method, Eqn (17) is valid for the macromolecules with molecular masses smaller than  $M_e$ .

## 2. The molecular mass distribution

The problem of establishment of correlations between the MMD and the relaxation properties of polymers has a long history;<sup>2, 4, 34, 63–66</sup> however, no unambiguous solution has been reported so far.<sup>31, 32</sup> Only qualitative dependences were determined. For instance, it is assumed<sup>4</sup> that MMD is correctly allowed for in the following relationship for the viscosity

$$\eta \propto \bar{M}_w^v,$$

where  $\bar{M}_w = \sum_M \omega(M)M$ ,  $\omega(M)$  is the mass fraction of the polymer with molecular mass  $M$  and  $v \approx 3, 4$ . More complicated expressions, which take into account higher moments of the MMD function, are also used. For instance, the following expressions were proposed for creep compliance  $J_e$ :<sup>64–66</sup>

$$J_e \approx \frac{\bar{M}_{z+1} \bar{M}_z}{\bar{M}_w \bar{M}_n}$$

or

$$J_e \approx \left( \frac{\bar{M}_z}{\bar{M}_w} \right)^b,$$

Here  $\bar{M}_n = \mu_1/\mu_0$ ,  $\bar{M}_z = \mu_3/\mu_2$ ,  $\bar{M}_{z+1} = \mu_4/\mu_3$ ,  $\mu_k =$

$\sum_M \omega(M) M^k$  is the  $k$ th distribution moment; and  $b = 3.5–3.7$ .

As an example Fig. 3 presents the dependences of the compliance  $J_e = \langle \lambda \rangle_w / \langle \lambda \rangle_n$  and polydispersity index  $\bar{M}_w / \bar{M}_n$  on the composition of a bidisperse blend of polystyrenes with molecular masses  $4.27 \times 10^5$  and  $3.89 \times 10^4$  (data were taken from Ref. 67).

Because of polydispersity of the polymer the flow curve changes its shape.<sup>31, 68–71</sup> A sharp kink near the critical shear strain disappears and the viscosity gradually decreases from a constant value with an increase in the shear rate. The curves of the temporal and frequency dependences of the relaxation modulus behave analogously.<sup>32–34, 72–78</sup> In the rubbery plateau zone the modulus becomes time (or frequency) dependent; the wider the MMD, the stronger this dependence. Broadening of the MMD

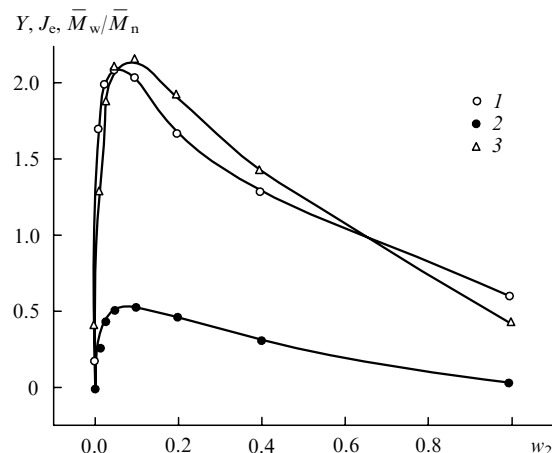


**Figure 3.** Compliance- vs. polydispersity index correlations for polystyrene.<sup>67</sup>

$J_e$  (1) and  $\bar{M}_w/\bar{M}_n$  ratio (2) plotted vs. compositions of bidisperse polystyrene blends with the molecular masses  $M_1 = 3.89 \times 10^4$  and  $M_2 = 4.27 \times 10^5$ , where  $w_2$  is the mass fraction of the second component, and the  $Y = 0.2 + 3.4 \log(\bar{M}_w/\bar{M}_n)$  plot (3).

also leads to fundamental changes in the character of the temperature dependence of strain;<sup>32, 48, 79–82</sup> namely, the wider the MMD of the polymer, the less pronounced the transition from the rubbery state to flow.

Numerous attempts at establishing quantitative relations between the character of the MMD and the relaxation behaviour of polymers are usually based on the assumption of additivity of the contributions of each polymer fraction to the properties. For instance, it was proposed to describe the flow curve of a polydisperse polymer by the following relationship<sup>68, 71</sup>

$$\eta(\dot{\gamma}) = \left[ \int_0^{M_c} \omega(\mu) \mu d\mu + M_c \int_{M_c}^{\infty} \omega(\mu) d\mu \right]^v, \quad M_c = \left( \frac{\tau_c}{K \dot{\gamma}} \right)^{1/v},$$

where  $\mu$  is the integration variable.

The dynamical theory of polymers, which is based on the fixed tube model, predicts<sup>34</sup> that the relaxation modulus of a bidisperse polymer blend equals the weight-average of the relaxation moduli of the components. Correction of the model made it possible to derive much more complicated relationships.<sup>83</sup> Generalisation of various theoretical and experimental approaches led to the following strain relaxation equation<sup>84, 85</sup>

$$G(t) = G_N^0 \left[ \int_{\ln M_c}^{\infty} G^{1/\beta}(t, M) \omega(M) d \ln M \right]^\beta,$$

where  $G(t, M)$  is the function describing the relaxation behaviour of the polymer fraction with molecular mass  $M$  and the parameter  $\beta$  characterises the mixing rule (it allows for the mutual influence of macromolecules of different size).

It is this factor that allows the additivity principle to be used. However, opinions are different as to the mutual influence of macromolecules or its manifestation in the relaxation properties of polydisperse polymers. On the one hand, there is no denying a strong chain–chain interaction in polymeric systems, which is allowed for by the concepts of entanglements<sup>65, 66</sup> or physical networks.<sup>37, 86–89</sup> It was experimentally shown<sup>83, 84, 90–93</sup> that the longest relaxation time depends on the composition of bidisperse polymer blends.

On the other hand it was assumed<sup>52, 94, 95</sup> that the effect of this interaction can be ignored in the case of slow relaxation processes. This was substantiated by the results of IR dichroism studies<sup>96, 97</sup> of chain orientation relaxation in bidisperse blends of ethylene-*co*-propylene copolymers comprised of monodisperse fractions with the molecular masses  $M_S = 5.3 \times 10^4$ ,  $M_M = 1.25 \times 10^5$  and  $M_L = 3.7 \times 10^5$ . It was shown that the maximum effective relaxation time of long chains is virtually independent of the composition of the system (Fig. 4). As can be seen, the presence of shorter chains has almost no effect on the relaxation of long chains (curves 1, 2, 4) if the concentration of the long chains is not too low.<sup>93</sup> At the same time the relaxation times of the chains of different length are significantly different (*cf.* curves 1, 2 and curve 3).

The notion of a ‘low-molecular-mass’ component of a bidisperse blend is conditional. Probably, under certain conditions this component should be considered as a solvent, which dramatically decreases the concentration of entanglements in a physical network. It was suggested<sup>98</sup> that this occurs at  $M_L M_c^2 / M_S^3 < 0.1$ .

As applied to thermomechanical experiments, the additivity principle can be expressed as follows:<sup>48, 81</sup>

$$J_T = J_0 [1 - \omega(M)]^{-1}, \quad \omega(M) = \sum_M \varphi(M) \chi(T, M),$$

where  $J_T$  and  $J_0$  are the compliances of the polydisperse polymer and of a hypothetical polymer with infinite molecular mass (base line),  $\omega(M)$  is the integral MMD function,  $\varphi(M)$  is the differential MMD function and  $\chi$  is the Heaviside step function

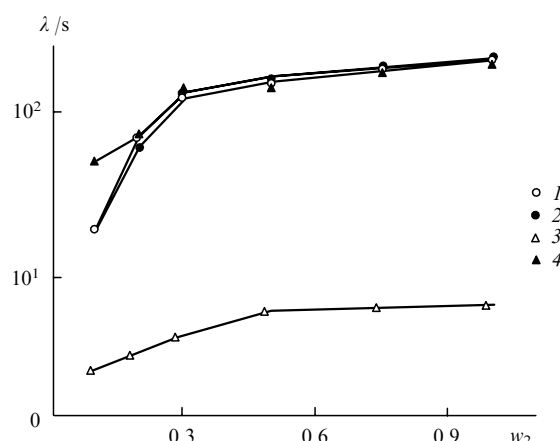


**Figure 4.** Effective long-chain orientation relaxation time plotted vs. volume fraction of long chains in a bidisperse polymer blend.

Molecular mass of the polymer:  $M_S = 5.3 \times 10^4$ ,  $M_M = 1.25 \times 10^5$  and  $M_L = 3.7 \times 10^5$ . Curve 1 was plotted using the data taken from Ref. 97 and curves 2–4 were plotted using the data taken from Ref. 98.

(1, 2)  $M_S + M_L$ , (3)  $M_S + M_M$ , (4)  $M_M + M_L$ .

$$\chi(T, M) = \begin{cases} 0 & \text{for } T < T_{f,M} \\ 1 & \text{for } T \geq T_{f,M} \end{cases},$$

where  $T_{f,M}$  is the temperature at which the transition from the rubbery state to the flow of the polymer fraction with the molecular mass  $M$  occurs.

Only a few studies on relations between the character of dielectric relaxation and the MMD are available (see the bibliography in a review<sup>52</sup>). Probably, this is due to a narrow range of objects (A-type polymers). Studies of (mainly) bidisperse *cis*-polyisoprene blends showed<sup>99–104</sup> that the MMD manifests itself in dielectric and mechanical relaxation in a similar way, *i.e.*,

$$\frac{\varepsilon''(\omega)}{\Delta\varepsilon} \approx \frac{G''(\omega)}{G_N^0},$$

although the mechanisms of these processes are different, namely, dielectric relaxation is governed by orientation correlation of the *i*th and *j*th segments at different time instants while mechanical relaxation is determined by orientation anisotropy of a segment.

NMR experiments showed that the polydispersity of a polymer affects the shape of the free induction decay curve<sup>61, 62</sup> to the extent to which the  $M_c$  parameter limits the chain length.

### 3. Branching

Branching of polymers, as a structural factor, which manifests itself in the relaxation properties, has been much less studied compared to MMD. This problem has attracted attention only recently<sup>105</sup> owing to the extended possibilities of the synthesis of branched chains of a preset topological structure<sup>106</sup> including ‘living’ radical polymerisation techniques.<sup>107, 108</sup>

As mentioned above, the viscosity of polymers is independent of their topological structure. However, the coil size is highly sensitive to the chain structure, namely, the higher the degree of branching of a macromolecule, the smaller the root-mean-square radius of the coil at the same molecular mass.<sup>1, 4, 11</sup> For instance, the characteristic viscosities  $[\eta]$  (THF solution, 30 °C) of polystyrenes of different topological structure are related to their molecular masses by the following expressions:<sup>109</sup>

$$[\eta] = 9.6 \times 10^{-5} \bar{M}_w^{0.73} \text{ for a linear polymer,}$$

$$[\eta] = 1.42 \times 10^{-4} \bar{M}_w^{0.68} \text{ for eight-arm stars and}$$

$$[\eta] = 6.45 \times 10^{-4} \bar{M}_w^{0.39} \text{ for a hyperbranched polymer with}$$

more than twenty arms.

The rheological properties of branched molecules differ from those of linear molecules with the same molecular mass.<sup>109–111</sup> Namely, they show lower viscosities and higher critical shear rates, their melts are characterised by enhanced elasticity, which manifests itself in particular in the magnitude of the first normal stress difference. Branched polymers are characterised by high longitudinal viscosities.

A relation derived in the dynamical reptation theory of star-branched chains<sup>34, 112</sup> has the form

$$\eta \propto \left(\frac{M_a}{M_e}\right)^b \exp\left(\nu \frac{M_a}{M_e}\right),$$

where  $M_a$  is the molecular mass of the arm and  $b$  and  $\nu$  are the parameters of the model. Indeed, experiments<sup>113</sup> showed that the viscosities of star-branched polymers at equal molecular masses are independent of the number of arms, if this number is greater than three, being at the same time dependent on  $M_a$  (see Refs 114 and 115). This also holds for hyperbranched polymers.<sup>116–118</sup> It was also experimentally found<sup>41, 116, 119–121</sup> that  $0.5 \leq b \leq 2$ ,  $\nu < 1$  (theoretical values are  $b = 2$  and  $\nu = 15/8$ ).

A fundamental distinction of branched chains, which is due to a more compact coil structure compared to linear macromolecules, consists in complex thermorheological behaviour.<sup>41, 122–129</sup> Since the key parameter in rheology is the coil size, the effect of temperature on the viscosity is determined by not only the temperature dependence of the friction coefficient but also the thermal coefficient of the coil size<sup>130</sup>

$$\kappa = \frac{d \ln \langle r^2 \rangle}{dT},$$

where  $\langle r^2 \rangle$  is the root-mean-square radius of gyration of the macromolecule. The coefficient  $\kappa$  increases as the degree of branching increases.<sup>41, 125, 126</sup> Because of this the effective activation energy of viscous flow also increases.<sup>†</sup>

According to a hypothesis by Graessley,<sup>123</sup> a fraction of the activation energy, which is due to the branching effect, is related to the arm length as follows

$$E_b = A \frac{M_a}{M_e}. \quad (18)$$

The  $A$  coefficient depends on the chemical structure of the macromolecules and the  $\kappa$  parameter. However, the parameters  $A$  and  $\kappa$  are related in a rather complex fashion and can even not show any correlation (see the data listed in Table 2).

**Table 2.** Parameters of equation (18).

| Polymer                         | $10^3 \kappa \times /K^{-1}$ | $M_a/M_e$ | $A$         |
|---------------------------------|------------------------------|-----------|-------------|
| Hydrogenated polyisoprene       | −1.3                         | 23–33     | 0.169       |
| Hydrogenated polybuta-1,4-diene | −1.05                        | 12–39     | 0.25        |
| Polybuta-1,2-diene              | ~ −1                         | 12        | 0.17        |
| Polybuta-1,4-diene              | 0.39                         | 12–13     | 0.11        |
| Hydrogenated polybuta-1,2-diene | 0.5                          | 5–6       | 0           |
| Polyisoprene                    | 0.3                          | 15–44     | 0.07 ± 0.02 |

The extension of the rubbery plateau zone depends on the molecular mass of the branched polymers more strongly than in the case of the linear polymers. For instance, for linear monodisperse polystyrene<sup>50</sup> the exponent,  $\nu$ , equals 3.5 (cf.,  $\nu = 4.8$  for four-arm star-branched polyisoprene<sup>131</sup>). It was shown<sup>116</sup> that at equal molecular mass, ( $\bar{M}_w \approx 6 \times 10^4$ ), the  $G'(\omega)$  and  $G''(\omega)$

curves plotted for a linear polymer and a three-arm star-branched polymer nearly merge, whereas for an eight-arm star-branched polymer the terminal zone is shifted towards higher frequencies. At the same time the character of the frequency dependence of the relaxation modulus in the terminal zone is retained, namely,  $G'(\omega) \propto \omega^2$  and  $G''(\omega) \propto \omega$ . Hyperbranched polymers (number of arms is about 50) behave in a different fashion, viz., in the terminal zone one has  $G'(\omega) \propto \omega^{1.12}$  and  $G''(\omega) \propto \omega^{0.91}$  ( $\bar{M}_w \approx 2.5 \times 10^5$ );  $G'(\omega) \propto \omega^{1.1}$  and  $G''(\omega) \propto \omega^{0.85}$  ( $\bar{M}_w \approx 5.75 \times 10^5$ ).

An interesting method of classification of manifestations of the topological structure in the relaxation properties of polymers was proposed.<sup>132</sup> The technique is based on the analysis of the frequency dependence of the shear modulus in the  $\delta$ – $G^*$  coordinates [ $\delta$  is the loss angle,  $\delta = \arctan(G''/G')$ ;  $G^*$  is the complex

modulus,  $G^* = \sqrt{(G')^2 + (G'')^2}/G_N^0$ ], the so-called van Gurp–

Palmen plot.<sup>133</sup> Using experimental data for a rather large number of polymers having different topological structures (asymmetrical and symmetrical star-branched, H-shaped and comb-like, linear chains with variable MMD), a topology map was constructed. The  $\delta$ – $G^*$  curves exhibit a characteristic point  $P_c$ , which is assigned a meaning of a characteristic of the topological structure of the polymer. The set of points corresponding to a specific topology forms a particular region in the map. Thus, location of the  $P_c$  point in a certain region allows characterisation of the polymer structure.

It should be noted that this is an essentially empirical and physically unsubstantiated approach. In addition, the authors<sup>132</sup> pointed out that the boundaries between the areas characterising different topologies in the topology map are not sharp.

In some sense branching and polydispersity influence the relaxation properties of polymers in a similar fashion. The difference is that branching in the terminal zone retards the relaxation processes. In contrast to this, relaxation at high frequencies is accelerated.<sup>105, 134</sup>

#### 4. The gel point

The formation of polymer networks in any way (by polycondensation, polymerisation or cross-linking) is accompanied by considerable broadening of the MMD as the gel point is approached.<sup>3, 135</sup> The attainment of a gel point is associated with the formation of an infinite cluster,<sup>136</sup> which then undergoes a transformation into the gel fraction. This is accompanied by narrowing of the MMDs of the constituents of the sol fraction (they have a finite size).<sup>3, 135</sup> Thus, at the gel point a polymer has a specific topological structure, which can be characterised in terms of fractal theory.<sup>137</sup> The fractal dimension,  $D_f$ , of a cluster relates its volume to the mass

$$R \propto M^{1/D_f},$$

where  $R$  and  $M$  are the radius and the mass of the cluster. For linear ‘massless’ chains one has  $D_f = 2$  ( $D_f = 5/3$  with allowance for the excluded volume).<sup>1, 66, 137</sup> In accordance with percolation theory the fractal dimension of clusters in the region of critical conversion is 2.53.<sup>137</sup> Therefore, branched macromolecules in this region are more compact than linear chains.

The relaxation properties of a polymeric system at the gel point are described by a power law rather than an exponential function<sup>138–141</sup>

$$G(t) \propto t^{-n}. \quad (19)$$

The exponent  $n$  is related to the fractal dimension<sup>142</sup>

$$n = \frac{D}{D_f + 2},$$

where  $D$  is the dimension of the space ( $n = 0.66$  for three-dimensional space).

<sup>†</sup> See page 137 in Ref. 4.

If the degree of conversion  $\alpha$  is expressed in the form

$$\varepsilon = \left| \frac{\alpha - \alpha_c}{\alpha_c} \right|,$$

where  $\varepsilon$  is the relative conversion and  $\alpha_c$  is the critical conversion, at  $\alpha < \alpha_c$  the viscosity is given by  $\eta = \eta_0 \varepsilon^{-s}$  and at  $\alpha > \alpha_c$  the shear modulus is given by  $G = G_0 \alpha^r$  (see Refs 143–146). The exponents  $s$  and  $r$  are related to  $n$  as follows:

$$n = \frac{r}{s + r}.$$

A consequence of relationship (19) is that the frequency dependence of the shear modulus obeys a power law

$$G' \propto \omega^n \cos\left(\frac{\pi n}{2}\right), \quad G'' \propto \omega^n \sin\left(\frac{\pi n}{2}\right).$$

Therefore,  $\tan \delta$  is frequency independent

$$\delta = \frac{\pi n}{2}.$$

Theoretical estimates<sup>146</sup> give  $n = 0.706$ .

These relations were repeatedly confirmed by three-dimensional polymerisation of methacrylate-based oligomers<sup>147</sup> and by end-to-end cross-linking of poly(dimethylsiloxane),<sup>148</sup> *i.e.*, for irreversible processes. Similar behaviour is also characteristic of biopolymers;<sup>149,150</sup> here, reversible formation of an equilibrium network is due to a change in the physical conditions, *e.g.*, the temperature, pH value and concentrations of components. For instance, when xanthane interacts with  $\text{Al}^{3+}$  ions, the exponent  $\rho$  in the expression

$$\tan \delta \propto \omega^\rho$$

varies from  $-0.1$  to  $0.08$  depending on the solution temperature and becomes equal to zero at  $32^\circ\text{C}$ .<sup>150</sup> The  $\rho$  value varies within nearly the same limits as the pH value changes (critical pH value is  $2.9$ ).

A decrease in the temperature of spherical particles of *N*-isopropylacrylamide microgel in a water–methanol solution leads to a gel–sol transition (lowest critical solution temperature is  $32^\circ\text{C}$ ).<sup>151</sup> In this case the exponent  $\rho$  behaves in a similar way and takes a zero value at about  $29^\circ\text{C}$ .

It should be noted that almost all transitions from the liquid to the solid state pass through critical regions where critical clusters are formed, *i.e.*, nuclei of the solid phase (here, the notion ‘phase’ has a kinetic and not necessarily thermodynamical meaning), which have a similar fractal structure.<sup>152</sup>

The numerical value of the exponent  $n$  varies depending on the system. For instance, for polymerisation of methacrylate oligomers  $n$  varies from  $0.4 \pm 0.2$  to  $0.6 \pm 0.1$  and increases as the degree of functionality of the initial oligomer increases.<sup>147</sup> In cross-linking of bifunctional oligo(dimethylsiloxane) having vinyl terminal groups, with a polyfunctional reagent (degrees of functionality were equal to 4 and 11) containing  $\equiv\text{SiH}$  reactive groups, the  $n$  value varies from  $0.69$  to  $0.76$  depending on the system. The cross-linking of poly(dimethylsiloxane) is characterised by  $n = 0.5$  (see Ref. 140) and curing of an epoxy resin by  $n = 0.7$  (see Ref. 153). The  $n$  values for an equilibrium gel formation are much lower, namely,  $0.225$  (see Ref. 150) and  $0.06$  (see Ref. 151).

Components of the complex modulus of branched polyethylene are related to frequency by a power law, *i.e.*, here we deal with a similar dependence and, therefore, the loss factor is frequency independent<sup>105,154,155</sup> if the number of branches is larger than one per  $10^5$  carbon atoms in the main chain.<sup>155</sup> The fractal characteristics of the topological structure of the critical cluster and the branched polymer chains are fundamentally different.

## 5. Structural parameters of polymer networks

The topological structure of a polymer network is usually treated as a set of cross-link points, chain fragments between cross-link points and ‘tails’ (pendant chains).<sup>3</sup> The classical theory of the rubbery state relates the equilibrium modulus to the concentration of chains and, in the framework of the simplest model of network structure, to the concentration of cross-link points.<sup>1,3</sup> However, only active chains contribute to the elasticity of a polymer. Therefore, typical of sparse polymer networks are such cross-link points whose effective functionalities are lower than it follows from chemical considerations.<sup>3,156–158</sup> (Here, the functionality of a cross-link point is the number of attached elastically active chains.) The concentration of such chains is lower than the concentration of chain fragments between cross-link points, as is determined by the topological structure. The concentration of active chains in highly cross-linked polymer networks is larger than it follows from the calculations involving the concentration of cross-link points in the network, because in this case entanglements also contribute to the relaxation modulus.<sup>3</sup> Nonuniform spatial distribution of cross-link points manifests itself in the properties of polymer networks;<sup>159,160</sup> however, even qualitative structure–property relations have not been established as yet. At the same time the relaxation behaviour of polymer networks is immediately related to parameters of the topological structure.

Indeed, it was shown<sup>161–163</sup> that the  $g(t)$ ,  $G'(\omega)$  and  $G''(\omega)$  relaxation curves are rather ‘sensitive’ to the content and molecular mass of ‘pendant’ chains [polymer networks were prepared by co-polycondensation of divinyl- and monovinylpoly(dimethylsiloxanes) with tris(dimethylsiloxy)phenylsilane]. The results obtained were analysed using the empirical equation<sup>164</sup>

$$g(t) = g_\infty \left[ 1 + \varphi \left( \frac{\tau_c}{t} \right)^m \right],$$

where  $g_\infty$  is the equilibrium modulus,  $\varphi$  is the concentration of ‘pendant’ chains and  $\tau_c$  and  $m$  are the empirical parameters dependent on the structure of the polymer network and on the molecular mass of the monofunctional modifier, respectively.

Since polymer networks are characterised by the equilibrium modulus, the thermomechanical curve will reach some limiting equilibrium compliance value with an increase in temperature. By studying the transition from the rubbery state to the equilibrium state it is possible to extract information on the topological structure of the polymer similarly to the case of non-cross-linked systems.

In this case the additivity principle is expressed as follows:<sup>48</sup>

$$J_T = J_0 \left[ 1 - \left( 1 - \frac{J_0}{J_{eq}} \right) \sum_m \varphi(m) \chi(T, m) \right]^{-1}, \quad (20)$$

where  $J_T$ ,  $J_0$  and  $J_{eq}$  are the compliance of the polymer network at temperature  $T$ , the compliance of a hypothetical polymer with an infinite molecular mass (base line) and the limiting (equilibrium) compliance, respectively.

Based on experimental facts, it was assumed<sup>48</sup> that, similarly to linear macromolecules, the gel fraction includes chain fragments between cross-link points, which are characterised by some molecular masses. However, the hypothesis was based on a model of a perfect network, *i.e.*, the authors assumed that (i) the bulk of the polymer consisted of chain fragments between cross-link points, (ii) there were no pendant ‘tails’ and (iii) all cross-link points were characterised by the same degree of functionality. A real polymer network has an incomparably more complex topological structure and contains not only chain fragments between cross-link points but also the sol fraction, pendant chains (‘tails’), loops and cross-link points of different functionality. All these structural elements are also characterised by certain melt flow transition temperatures. Apparently, at equal molecular masses the ‘tails’ will ‘flow’ at a lower temperature than chain fragments between cross-link points. In the polymer network the macro-



molecules not attached to the network are characterised by a lower mobility compared to the mobility in a block polymer.<sup>165</sup> Therefore, Eqn (20) characterises the mass distribution of elements of the topological structure of a polymer network over the relaxation times express through the corresponding flow temperatures. The relations between the flow temperature and the elements of the topological structure should be established independently in special-purpose experiments.

While on the subject of thermomechanical properties, we must consider the relation between the glass transition temperature of a polymer and the concentration,  $n_c$ , of cross-link points in the network.

The glass transition temperature,  $T_g$ , increases as  $n_c$  increases (see, e.g., Refs 156, 166). One can assume that this is a specific manifestation of the topological structure. However, a number of methods have been developed, which allow the glass transition temperature to be calculated from the chemical structure of the polymer.<sup>167–169</sup> In this case it is assumed that the variations of  $n_c$  affect only changes in the chemical structure of the polymer. For instance, the epoxy ring opening in the course of curing of epoxy oligomers with amines produces hydroxyl groups whose concentration increases with an increase in  $n_c$ . It is this parameter, which strongly affects the level of intermolecular interaction, that determines the glass transition temperature. At the same time the glass transition is immediately affected by such factors as the supramolecular structure, packing character and density fluctuations.<sup>14</sup> With inclusion of all these factors we find that the topological structure itself does not influence the glass transition but the changes in the topological structure cause changes in the character of packing and in the fraction of the free volume. For instance, it is this effect that is attained by varying the topological structure of epoxy amine polymers by (i) introducing monofunctional reagents and (ii) changing the ratio of functional groups.<sup>170</sup> Using dielectric spectroscopy and dynamical light scattering, it was established<sup>171</sup> that the parameters of the  $\alpha$ -transition, which vary in the course of curing of the diglycidyl ether of diphenylolpropane with diethylenetriamine, depend on the density fluctuations. Thus, the topological structure at the glass transition of polymers manifests itself indirectly.

Compared to non-cross-linked polymers, polymer networks in the region of the rubbery plateau exhibit a weaker dependence of the relaxation modulus on time

$$G(t) \propto t^{-m}, \quad (21)$$

i.e., the exponent  $m$  decreases with an increase in the degree of cross-linking of the polymer.<sup>146, 153, 172</sup> At the same time in the terminal zone (long relaxation times or low frequencies) the  $G^*(\omega)$  and  $G(t)$  curves for the relaxation modulus and the  $J^*(\omega)$  and  $J(t)$  curves for compliance reach the limiting values corresponding to the equilibrium strain.<sup>173, 174</sup>

The relaxation behaviour of polymers is described by the Kohlrausch–Williams–Watts (9)<sup>175</sup> and Havriliak–Negami (HN)<sup>176–179</sup> equations

$$G^*(\omega) = G_{\text{lim}} + \frac{G_0 - G_{\text{lim}}}{[1 + (i\omega\tau_0)^\alpha]^\beta},$$

where  $\alpha$  and  $\beta$  are empirical constants related to the character of the relaxation spectrum.<sup>177</sup> Here  $G_0$  and  $G_{\text{lim}}$  are the limiting values of the elastic modulus corresponding to the low and high frequencies, respectively, and  $\tau_0$  is an empirical parameter which can be associated with the relaxation time. The HN equation is more often used when analysing dielectric relaxation data.

Numerical values of the empirical parameters of the KWW and HN equations depend on the polymer structure including its topology. For instance, the parameter  $\beta$  (for the KWW equation containing only one term) decreases with an increase in the concentration of cross-link points (Table 3).<sup>179, 180</sup>

Similar results were also obtained in a broadband dielectric spectroscopy study of the curing of the diglycidyl ether of

**Table 3.** Effect of chain length between cross-link points ( $M_c$ ) on the parameter  $\beta$ .<sup>179, 180</sup>

| Polytetrahydrofuran |         | Polyvinylethylene |         |
|---------------------|---------|-------------------|---------|
| $M_c$               | $\beta$ | $M_c$             | $\beta$ |
| 650                 | 0.40    | 11100             | 0.34    |
| 1000                | 0.43    | 1500              | 0.35    |
| 2040                | 0.49    | 3800              | 0.37    |
| 2900                | 0.58    | non-cross-linked  | 0.41    |

diphenylolpropane with bis(4-aminophenyl)methane.<sup>181</sup> Although the KWW dependence was obeyed only approximately, the following  $\beta$  values were obtained for the 10%, 20%, 40% and 70% conversions: 0.53, 0.45–0.52, 0.3–0.4 and 0.17–0.2, respectively. Despite the fact that the network is formed at degrees of conversion exceeding 60%, it is reasonable to assume that the trend disclosed also holds in this range of conversions. At the same time the increase in the parameter  $\beta$  during the chemical reaction gives grounds to assume whether or not the network density is an indirectly affecting factor, whereas the chemical structure has a direct effect on the parameter  $\beta$ .

A decrease in  $\beta$  means that the higher the concentration of cross-link points, the smaller the decrease in the modulus with time. This is in qualitative agreement with the data described by relationship (21), namely, an increase in the degree of cross-linking of the polymer leads to a decrease in the exponent  $m$ .

The parameters of the HN equation also depend on the degree of cross-linking of the polymer network. For  $G_0$ , this dependence is obvious, viz., the value of this equilibrium elastic modulus is proportional to the concentration of chains. For instance, it was shown<sup>182</sup> that changes in the ratio of functional groups in the reaction of polyoxypropylenetriol (POPT) with bis(4-aminophenyl)methane cause appreciable changes in the compliance  $J_0$  and elastic modulus  $G_0$  (Table 4).

**Table 4.** Effect of stoichiometric ratio of OH and NCO functional groups on the  $J_0$  and  $G_0$  values in the terminal region.<sup>182</sup>

| $r = [\text{OH}]/[\text{NCO}]$     | $J_0 / \text{MPa}^{-1}$ | $\log G_0 (\text{Pa})$ |
|------------------------------------|-------------------------|------------------------|
| POPT with a molecular mass of 710  |                         |                        |
| 0.67                               | 6.27                    | 5.207                  |
| 0.8                                | 1.67                    | 5.777                  |
| 1.0                                | 0.40                    | 6.399                  |
| 1.3                                | 1.42                    | 5.848                  |
| 1.5                                | 7.45                    | 5.128                  |
| POPT with a molecular mass of 2670 |                         |                        |
| 0.67                               | 227.04                  | 3.652                  |
| 0.8                                | 6.59                    | 5.185                  |
| 1.0                                | 1.39                    | 5.857                  |
| 1.2                                | 5.25                    | 5.280                  |
| 1.35                               | 35.62                   | 4.449                  |

The effect of cross-linking on the parameters  $\alpha$  and  $\beta$  can be followed using the data for the curing of the diglycidyl ether of diphenylolpropane with bis(4-aminophenyl)sulfone at 140 °C (see Table 5).<sup>183</sup> As can be seen, the parameter  $\alpha$ , which characterises the width of the relaxation time distribution,<sup>181, 184, 185</sup> decreases with an increase in the concentration of cross-link points (the calculated degree of critical conversion for this system is 0.57), whereas the parameter  $\beta$ , which characterises the asymmetry of the distribution function, remains unchanged. Probably, changes in the chemical structure of the system in the course of the reaction and, as a consequence, the glass transition also play a significant role in this case.<sup>186</sup> Indeed, it was shown<sup>184</sup> that an epoxy system (the diglycidyl ether of diphenylolpropane + diethylenetriamine), which undergoes a glass transition in the course of curing, is

**Table 5.** Dependence of the HN equation parameters on the degree of cross-linking of a polymer network.<sup>183</sup>

| Conversion | $\alpha$ | Conversion | $\alpha$ |
|------------|----------|------------|----------|
| 0.79       | 0.665    | 0.83       | 0.581    |
| 0.80       | 0.651    | 0.84       | 0.554    |
| 0.81       | 0.615    | 0.85       | 0.532    |
| 0.82       | 0.607    |            |          |

**Note.** At all conversion values,  $\beta = 0.9$ .

characterised by a decrease in the parameter  $\alpha$  and an increase in the parameter  $\beta$ . At the same time a study of the formation of an elastic urethane network in the reaction of hexamethylenediisocyanate with a poly(oxypropylene)-based triol revealed an identical trend in changes in the parameters  $\alpha$  and  $\beta$  with time, but these changes were small. An attempt<sup>181</sup> to establish a correlation between the degree of cross-linking and the  $\alpha$  value for a related system failed. Thus, it is hard to draw an unambiguous conclusion about the relation between the parameters of the HN equation and the cross-link density of polymer networks based on the results presented above.

The topological structure of polymers is correctly reproduced in their relaxation properties, which can be studied by NMR spectroscopy.<sup>59, 187, 188</sup> Gotlib *et al.*<sup>189</sup> established that the temperature dependence of the spin–spin relaxation time  $T_2$  in polymer networks reaches a plateau with an increase in temperature, the  $T_{2\text{ lim}}$  being proportional to the average chain mass (length) between cross-link points,  $M_c$ .

Studies<sup>190, 191</sup> of polymer networks based on poly(tetrahydrofuran) and polyfurite [poly(oxytetramethylene glycol)] showed that the shape of the free induction decay curve depends on the MMD chains of the network

$$G(t) = \int_0^{\infty} P(N) G_0(t, N) dN, \quad (22)$$

where  $G_0(t, N)$  is the dependence of the free induction decay for a monodisperse polymer with chain length  $N$ .

The theory of NMR spectra<sup>190, 191</sup> allows this function to be described as a solution to the problem inverse to problem (22). Some examples illustrating a relation between the MMD of the chain fragments between the cross-link points of polymer networks and the NMR data were considered in a review.<sup>187</sup>

Apparently, estimates of the MMD function by this method are of limited use due to at least two reasons. First, one should take into account physical junction points (entanglements), which behave as cross-link points in long chains. This factor ‘cuts off’ the high-molecular-mass region of the MMD function (see, *e.g.*, Ref. 192). The second reason is the difference of the actual set of topologies from that given by an ideal model of a network. The cross-link points in real polymers are characterised by different degrees of functionality<sup>3, 156–158</sup> and, hence, by different mobilities.<sup>156</sup> The latter was directly shown in pulsed NMR studies.<sup>193–195</sup> Analysis of the free induction decay curves in epoxy amine polymers modified by adding the monoepoxy component or by varying the ratio of epoxy/amine functional groups revealed the presence of two (and more) kinetic phases with different mobilities. It was found that the proton concentration in these phases is proportional to the concentration of cross-links having different functionalities and that the mobilities of the cross-links correlate with the mobilities of the chains emerging from the cross-links. This was shown<sup>180, 196</sup> by, *e.g.*, <sup>31</sup>P NMR, taking the reaction of poly(tetrahydrofuran) polymer network with tris(4-isocyanatophenyl)thiophosphate as an example (the latter compound served as the component for cross-link point formation in the polymer network).

## 6. Equilibrium (physical) networks

The topological structures of the equilibrium networks have been the subject of theoretical and experimental research.<sup>197–203</sup> According to Flory,<sup>204</sup> physical gels can be classified as follows:

- well ordered lamellar structures;
- completely disordered covalent polymer networks;
- mainly disordered polymer networks formed by aggregation and containing ordered regions; and
- specific disordered structures.

As can be seen, polymeric systems with cross-links formed by clustering are also included. Conventional non-cross-linked polymers, which exhibit, in a particular relaxation time interval, the properties of three-dimensional polymers due to formation of physical junction points (*e.g.*, entanglements and/or orientation clusters)<sup>85, 87, 205</sup> as well as labile networks with equilibrium cross-links are left out of consideration. It is the last-mentioned type of network that is of particular interest, because they can be treated as models for covalent networks on the one hand and for non-cross-linked polymers on the other hand.

In contrast to cross-link points in a polymer network, which represent more or less complex fragments of the molecular structure,<sup>3, 169</sup> the junction points in a reversible network are ‘points’ in essence. Their concentration can be described by a simple equilibrium<sup>201, 206–209</sup>



where  $X$  is the content of the functional groups capable of forming chemical bonds, whose concentration equals  $X_2$ . Such bonds are labile cross-links.

In contrast to the cross-link points in a reversible network, the temporary junctions in a non-cross-linked polymer, which manifest themselves within a particular relaxation time interval (rubbery plateau zone), are not related to the chemical nature of the polymer. Indeed, entanglements, which are usually treated as temporary junction points,<sup>34</sup> are only due to impenetrability of chains. The formation of nematic clusters, which can also play the role of temporary junction points,<sup>85, 87, 205</sup> is due to natural properties of polymers (segment anisotropy and confined space available for arrangement of a polymer chain due to the excluded volume effect) rather than some specific intermolecular interaction.<sup>205</sup>

Thus, the junction points of reversible networks are similar to and at the same time different from cross-link points in non-cross-linked and three-dimensional polymers (Table 6). The relaxation properties of these three types of networks are qualitatively compared in Fig. 5 (see also Ref. 201). Curve 1 is the temporal

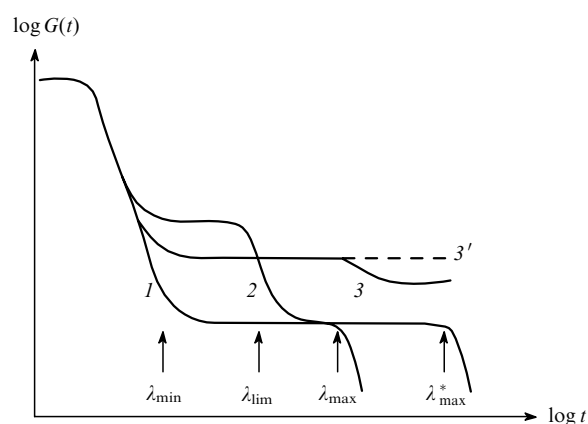


**Figure 5.** Relaxation elastic modulus plotted vs. time for a non-cross-linked polymer (1) and equilibrium (2) and non-equilibrium (3 and 3') networks.

**Table 6.** Characteristics of cross-links in different types of networks.

| Chain entanglements<br>(non-cross-linked polymers) <sup>a</sup>       | Physical network <sup>a</sup>                                                                   | Chemical network<br>(three-dimensional polymers)                                                        |
|-----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| Chemical structure of the polymer is immaterial                       | presence of polar H-bonding groups on the chains is essential                                   | presence of functional groups that can chemically react with one another                                |
| No energy is involved during cross-link creation – loss ( $\sim RT$ ) | energy of the order of units of kJ per mole ( $\leq 10 RT$ ) is involved during creation – loss | energy of the order of tens of kJ per mole ( $\geq 100 RT$ ) is involved during creation – loss         |
| Formation and loss are non-specific                                   | formation of cross-links requires specific site orientation and cooperative network mobility    | formation of cross-links obeys kinetic laws that are often complicated by diffusion and other processes |
| Non-cooperative                                                       | cooperativity effects are significant during zipping and unzipping of ladder-like structures    | usually, co-operative effects are ignored                                                               |
| Solvent does not affect physical networks                             | solvent effects can be crucial for the equilibrium constant                                     | conventional kinetic solvent effect                                                                     |

<sup>a</sup> According to Ref. 199.

dependence of the relaxation modulus of elasticity of a non-cross-linked polymer. In a particular relaxation time interval, from  $\lambda_{\min}$  to  $\lambda_{\max}$ , in the rubbery plateau zone, the polymer exhibits the properties of a network. Then, in the terminal zone, an abrupt decrease in the relaxation modulus characterises the transition to a viscous flow state. The relaxation modulus of a three-dimensional polymer (curve 3) in the vicinity of  $\lambda_{\max}$  either remains at the plateau level (highly cross-linked polymers for which chemical cross-link points and labile junction points are summed, curve 3'), or goes to the level of the equilibrium modulus (sparse networks for which only chemical cross-links are significant). Reversible networks (curve 2) are characterised by two plateau zones. The former corresponds to a physical network, in which an important role is played by both types of labile cross-link points. At relaxation times longer than  $\lambda_{\lim}$ , the relaxation modulus is determined by the concentration of the same cross-link points as in the non-cross-linked polymer. However, in the presence of functional groups interacting with one another to form cross-links with average lifetimes shorter than  $\lambda_{\lim}$ , the  $\lambda_{\max}$  value appreciably increases<sup>201</sup>

$$\lambda_{\max}^* = \lambda_{\max} \frac{2S^2 p^2}{12 - 9p + p^2},$$

where  $S$  is the average number of functional groups per chain and  $p$  is the probability of formation of a cross-link. The reason for the lowering of the relaxation rate is retardation of the diffusion motion of chains by the newly forming labile cross-links.

The relaxation behaviour of equilibrium polymer networks was studied<sup>206–211</sup> taking polybutadiene modified by 4-phenyl-1,2,4-triazolidine-3,5-dione as an example. On addition to polymers, the latter compound undergoes dimerisation and forms cross-links with a bond energy of  $57 \pm 15 \text{ kJ mol}^{-1}$  (see Ref. 206).

An increase in the concentration of modifier causes an increase in the relaxation modulus  $G_N^0$  in the rubbery plateau zone (Table 7).<sup>211</sup> Lowering the temperature leads to an increase in  $G_N^0$ , which is apparently due to the temperature dependence of the equilibrium constant (23). A significant effect of temperature on  $G_N^0$  is a distinctive feature of the equilibrium networks.<sup>208, 209</sup>

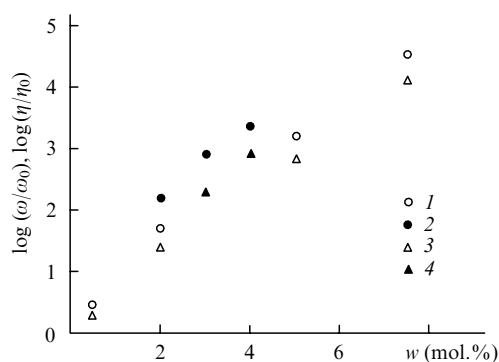
The extension of the rubbery plateau zone and the viscosity of polybutadiene ( $M_n = 2.6 \times 10^4$ ) are plotted vs. the concentration of modifier in Fig. 6 using the data taken from Refs 210 and 211. These results qualitatively substantiate theoretical conclusions, namely,<sup>201</sup> an increase in the concentration of active functional groups causes an appreciable increase in the viscosity and, as a consequence, an increase in  $\lambda_{\max}^*$ . The effect of temperature is also quite clear, that is, lowering the temperature leads to a corresponding increase in the viscosity. The extension of the rubbery plateau zone also increases.

**Table 7.** Effect of degree of cross-linking of an equilibrium network on the relaxation modulus in the region of the rubbery plateau at  $T = 273 \text{ K}$ .

| $10^{-3} M_n$   | Degree of modification<br>(mol.%) | $10^{-5} G_N^0$<br>/Pa |
|-----------------|-----------------------------------|------------------------|
| 26              | 0                                 | 6.0                    |
|                 | 0.5                               | 6.0                    |
|                 | 2                                 | 6.9                    |
|                 | 5                                 | 7.1                    |
|                 | 7.5                               | 9.1                    |
| 28 <sup>a</sup> | 2                                 | 8.7                    |
|                 | 3                                 | 9.6                    |
|                 | 4                                 | 13.6                   |
| 35              | 0                                 | 7.6                    |
|                 | 1                                 | 9.1                    |
| 48.5            | 0                                 | 7.5                    |
|                 | 1                                 | 8.6                    |
| 215             | 0                                 | 8.0                    |
|                 | 1                                 | 9.2                    |

<sup>a</sup> Data taken from Ref. 209 at  $T = 237 \text{ K}$ .

The concentration of functional groups also influences the parameters of the HN equation,<sup>208</sup> namely, with an increase in the concentration of functional groups the parameter  $\alpha$  slightly increases while the parameter  $\beta$  substantially decreases.

**Figure 6.** Rubbery plateau extension (1, 2) and viscosity (3, 4) of modified polybutadiene plotted vs. concentration of modifier at 273 (1, 3)<sup>210</sup> and 233 K (2, 4).<sup>211</sup>

#### IV. The relaxation time spectrum as a means of correct characterisation of topological structure

The possibility of obtaining a correct description of the relaxation behaviour of polymers using the relaxation time spectrum was initially considered as a hypothesis only.<sup>63, 64, 212</sup> Rouse<sup>213</sup> first showed that the dynamics of a polymer chain can be described using a discrete set of relaxation times that depend on the chain length (number of dynamical units). The totality of unambiguously determined pre-exponents can also be considered as a relaxation spectrum. Since then a number of models have been proposed, which describe the reptation motion of macromolecules with allowance for various relaxation mechanisms of the ‘tube’, *i.e.*, a region in which a restrained motion of a specified chain is realised.<sup>4, 11, 34, 52, 214, 215</sup> Each relaxation mechanism corresponded to a particular set of relaxation times and, hence, a relaxation spectrum. Comprehensive analysis of the dynamical models and consequences following from them was reported in a review.<sup>52</sup>

Some authors (see, *e.g.*, Refs 216–220) considered a theory which provides an alternative to the reptation theory. Basic to the new theory is the assumption that restrained chain motions are mainly due to close packing, which leads to intermolecular cooperativity on the length scale of a chain segment, rather than topological junctions. In this case the formation of nematic clusters also plays a significant role.<sup>89</sup>

Thus, in this case the relaxation spectrum, in contrast to local relaxation transitions, has a dynamical meaning. Namely, it is related to the polymer structure indirectly, through correlations between the dynamical properties and topology of macromolecules (of course, with allowance for the conditions under which the motion occurs).

## 1. Modified Rouse chain

The molecular structure can also to some extent affect parameters of the relaxation spectrum, but again this occurs due to specific features of dynamical processes. For instance, the relaxation properties of the modified Kargin–Slonimskii–Rouse model<sup>45, 213</sup> have been studied.<sup>214, 215, 221, 222</sup> The relaxation behaviour of these models was also analysed in other studies (see Refs 223 and 224), but this concerned the frequency or temporal dependences of the relaxation modulus while the effect of chain modification on the relaxation spectrum was not considered.

The modification consisted of the chain units being ascribed different friction coefficients. Stress relaxation of an unbalanced chain comprising  $n$  units is described by a system of  $n$  equations

$$\begin{aligned}\tau_1 \dot{x}_1 &= -x_1 + x_2 \\ \tau_2 \dot{x}_2 &= x_1 - 2x_2 + x_3 \\ &\dots\dots\dots \\ \tau_i \dot{x}_i &= x_{i-1} - 2x_i + x_{i+1} \\ &\dots\dots\dots \\ \tau_n \dot{x}_n &= x_{n-1} - x_n,\end{aligned}\tag{24}$$

where  $x_i$  is the coordinate of the  $i$ th unit; the relaxation characteristics of the units, which are due to different friction coefficients (*i.e.*, the interaction between the units and the environment), are described by the parameter  $\tau_i$ . Having solved the system (24), it is possible to derive the equations of motion for all units of the chain and to determine the change in the chain length,  $L = x_n - x_1$ , provided that the initial conditions are specified. An example of the initial conditions is given by  $L(0) = 1$ ,  $x_i(0) = (i - 1)/(n - 1)$ , which corresponds to a uniformly stretched equidistant chain.

The solution of system (24) in the form of a combination of exponents for relaxation of the chain length

$$L(t) = \sum_{i=1}^n h_i \exp(-p_i t),$$

where  $h_i$  is the relaxation time spectrum, is given by the roots  $z_i = \tau_i p_i$  of the polynomial  $D_n = 0$ , where  $D_n$  is the modified Rouse matrix

$$D_n = \begin{vmatrix} z_1 - 1 & 1 & 0 & 0 & \dots & 0 & 0 & 0 \\ 1 & z_2 - 2 & 1 & 0 & \dots & 0 & 0 & 0 \\ & & & & & & & \\ 0 & 0 & 0 & 0 & \dots & 1 & z_{n-1} - 2 & 1 \\ 0 & 0 & 0 & 0 & \dots & 0 & 1 & z_{n-1} \end{vmatrix} \quad (25)$$

Numerical solution of Eqn (25) makes it possible to obtain a total of  $(n - 1)$  roots  $p_1, p_2, \dots, p_i, \dots, p_{n-1}$ , which represent the reciprocal relaxation times ( $p_i = \lambda_i^{-1}$ ) characterising the relaxation behaviour of the entire chain. In the case of identical units the results obtained are exactly described by the Rouse relations

$$\lambda_i^{-1} = 4 \sin^2 \left( \frac{\pi}{2} \frac{i}{n+1} \right),$$

$$h_i = \frac{1}{2n} \left[ \tan\left(\frac{i\pi}{2n}\right) \right]^{-2},$$

where  $i$  is the mode number ( $i = 0$  corresponds to the maximum relaxation time);  $h_i = 0$  for the even  $i$  values.

Insertion of units with higher friction coefficients (type  $a$  units; type  $b$  was ascribed to unmodified units) into the chain causes significant changes in the set of relaxation modes. Figures 7 and 8 show that the total number of modes increases with an increase in the number of type  $a$  units, which divide the chain into blocks comprised of units with a low friction coefficient. However, higher-frequency modes are grouped into ‘packets’, *i.e.*, form groups characterised by similar relaxation times; a distinctive feature is that the higher the friction coefficient of the type  $a$  units, the smaller the separation between such modes (see Fig. 7). It is hard to assign the relaxation modes in the relaxation time spectrum characterising the Rouse chain to particular units. If the relaxation properties of the type  $a$  units inserted into the chain differ only slightly from those of the type  $b$  units ( $\tau_a/\tau_b = 2$ ), it is possible to select ‘packets’ of relaxation modes, which, although they have different parameters, are ‘clustered’ near the values characteristic of the type  $b$  blocks. The larger the  $\tau_a/\tau_b$  ratio, the smaller the separation between the modes in ‘packets’ (see Fig. 7). In the limiting case, chain elongation due to an increase in the number of blocks leads to a decrease in the number of modes.

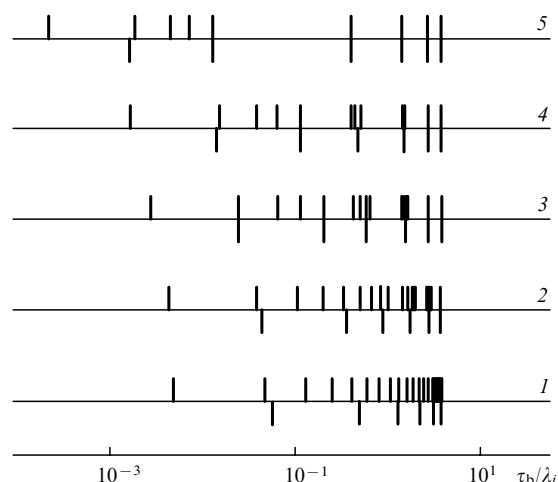


**Figure 7.** Relaxation modes for monoblock (below horizontal lines) and tetrablock chains (above horizontal lines) for the  $a-(b-b-b-b-b-a)_m$  structure.<sup>215</sup>  $\tau_a/\tau_b = 1$  (1), 2 (2), 5 (3), 10 (4) and 100 (5).

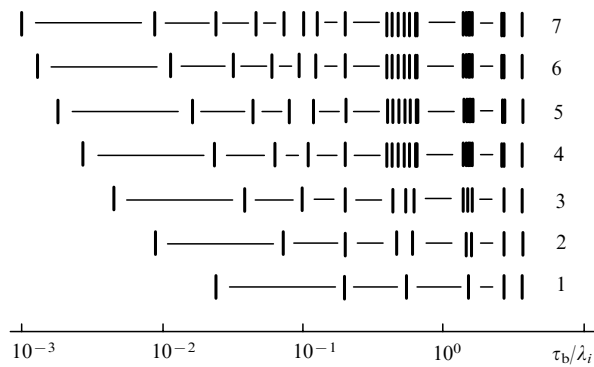


**Figure 8.** Relaxation modes for the  $a-(b-b-b-b-b-a)_m$  structure.<sup>215</sup>  
 $\tau_a/\tau_b = 2$ . Figures denote the  $m$  values.

which becomes smaller than the total number of units because high-frequency modes merge.

A comparison of polyblock chains with a ‘monoblock’ one (see Fig. 8) showed that high-frequency relaxation modes are grouped near the values characteristic of the corresponding block. The number of relaxation modes in a ‘packet’ becomes equal to the number of blocks. (In Fig. 8 we present the data for  $\tau_a/\tau_b = 2$  in order to distinguish between components of the ‘packet’.) Thus, the units with a high friction coefficient separate blocks from one another; because of this, the relaxation modes characterising the units possessing different relaxation properties can be separated in the relaxation spectrum of any chain.

The relaxation spectra of the chains having the structures described in Table 8 are shown in Fig. 9.

If the modified unit is present in the terminal zone of the chain, the  $\lambda_{\max}$  value somewhat increases, but the statistical weight of the corresponding mode decreases. Separation of the blocks comprised of units with higher mobility by the units of lower mobility

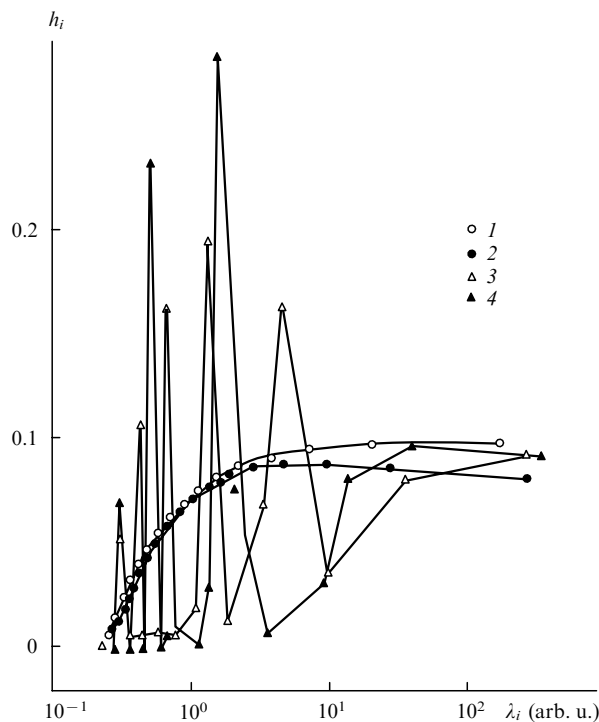


**Figure 9.** Relaxation modes for chains of different structure. For notations (1–4), see Table 8.

**Table 8.** Effect of the structure of the modified Rouse chain on the parameters of the relaxation spectrum (in arbitrary units).<sup>215</sup>

| No. | Chain structure <sup>a</sup>                      | $\lambda_{\max}$ | $\langle \lambda \rangle_w$ | $\langle \lambda \rangle_n$ |
|-----|---------------------------------------------------|------------------|-----------------------------|-----------------------------|
| 1   | $1-(1)_{18}-1 \rightarrow F$                      | 174              | 143                         | 20                          |
| 2   | $5-(1)_{18}-1 \rightarrow F$                      | 265              | 224                         | 25                          |
| 3   | $5-(1)_{12}-5-(1)_5-1 \rightarrow F$              | 261              | 232                         | 27                          |
| 4   | $5-(1)_3-5-(1)_6-5-(1)_4-5-(1)_2-1 \rightarrow F$ | 331              | 282                         | 36                          |

<sup>a</sup> Figures are the ratios of the friction coefficients of the units  $a$  and  $b$ ; subscripts denote the number of units in the block and  $F$  is the force exerted on the chain.

leads to the appearance of peaks in the relaxation spectra, the number of peaks being changed antiparallel to the number of blocks. This is due to a decrease in the block length.

Thus, this example allowed us to follow how the ‘molecular’ structure manifests itself in the relaxation time spectra through the mobilities of units.

Analysis<sup>214, 215</sup> showed that the strain and stress relaxation processes affect not only the relaxation spectrum (this was shown earlier for the uniform Rouse model, see, e.g., Ref. 34) but also the set of relaxation times. This is illustrated in Fig. 10. Apparently, this is a consequence of an indirect relation between the relaxation spectrum and the polymer structure through the macromolecular

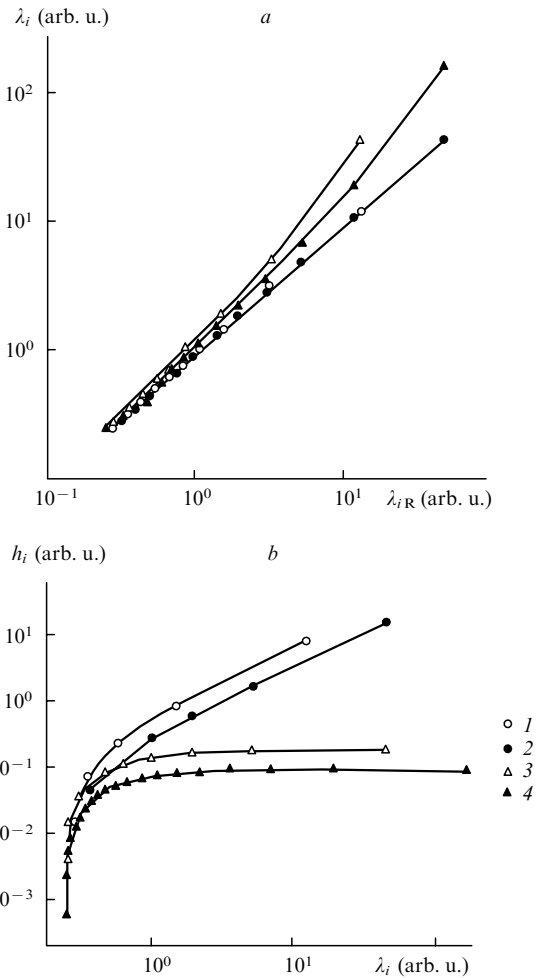


**Figure 10.** Correlation between the relaxation times  $\lambda_i$  and  $\lambda_{iR}$  (a) and the stress relaxation spectra (b, curves 1 and 2) and deformation relaxation spectra (b, curves 3 and 4) obtained for chains comprising ten (1, 3) and twenty (2, 4) units.

dynamics. This is also indicated by the fact that physically substantiated spectrum cannot be obtained under any initial relaxation conditions. For instance, if in the initial state the chain units are arranged nonuniformly, a number of pre-exponents can take negative values.<sup>225</sup>

## 2. Methods of calculation of the relaxation spectra from experimental data

The viscoelastic behaviour of polymers can be conveniently characterised by a spectrum of relaxation times. Usually, it is believed<sup>4,5</sup> that one can determine and predict the viscoelastic behaviour of polymers under any strain and loading conditions from the known relaxation spectrum. However, the relaxation spectrum was obtained in explicit form only for molecular models (see above). Comparison of the results of modelling with experimental data on certain relaxation properties gives no assurance of correctness of the former. In order to assess the ability of a theoretical model to describe experimental data, one should compare the model relaxation spectra with the experimental ones, which thus play the role of a generalised characteristic. Therefore, methods of calculation of relaxation spectra, which are based on analysis of experimental data (mainly temporal and frequency dependences of the elastic modulus) have been continuously developing.<sup>226</sup>

Calculations of the relaxation time spectrum from the known real and imaginary components of the elastic modulus belong to the class of ill-posed problems; therefore, the uniqueness problem of the results obtained poses.<sup>226–229</sup>

### a. Effective relaxation time as a characteristic of the relaxation spectrum

Is it always necessary to represent the relaxation time distribution function in explicit form? It was shown<sup>49,51,88</sup> that as a quantitative characteristic it is sufficient to use the effective relaxation time  $\lambda_{\text{ef}}$

$$\frac{1}{\lambda_{\text{ef}}} = -\frac{d \ln G(t)}{dt} = \frac{\sum_i h_i \lambda_i^{-1} \exp(-t/\lambda_i)}{\sum_i h_i \exp(-t/\lambda_i)} = \sum_i w_i(t) \lambda_i^{-1},$$

where  $h_i$  is the relaxation spectrum and  $w_i(t)$  is the relaxation time distribution function in the time domain, which is related to  $h_i$  at  $t = 0$  as follows

$$w_i = \frac{h_i}{\sum_i h_i}.$$

The use of the parameter  $\lambda_{\text{ef}}$  for comparison of experimental stress relaxation data with the dependences obtained using the polymer dynamics models led to good results.<sup>49,51</sup> For instance, the Rouse and Doi–Edwards models with the known (and different!) relaxation spectra give significantly different dependences  $\lambda_{\text{ef}}(t)$ . In the Rouse model the parameter  $\lambda_{\text{ef}}$  is proportional to  $t$  at  $\lambda_{\text{min}} \leq t \leq \lambda_{\text{max}}$ , i.e., in the region where the relaxation modulus of elasticity is proportional to  $t^{-1/2}$ . In the Doi–Edwards model the parameter  $\lambda_{\text{ef}}$  in the rubbery plateau zone is proportional to  $t^{1/2}$ .

The temporal dependences of the relaxation shear modulus and the effective relaxation time of narrow-MMD polystyrene ( $M_w/M_n = 1.03$ ) plotted using the data taken from Ref. 230 are shown in Fig. 11. In the transient region corresponding to transition from the glassy state to the rubbery plateau zone the parameter  $\lambda_{\text{ef}}$  is nearly proportional to the square root of time, the dependence in the rubbery plateau zone is nearly linear (the exponent is 1.2) and then it becomes weaker in the region where the effect of the molecular mass becomes pronounced. Eventually, the parameter  $\lambda_{\text{ef}}$  takes a constant value equal to the maximum relaxation time. It was shown<sup>49</sup> that the stress relaxation behaviour of other monodisperse polystyrenes (see Refs 74, 231, 232) also obeys these laws, with the maximum relaxation time being

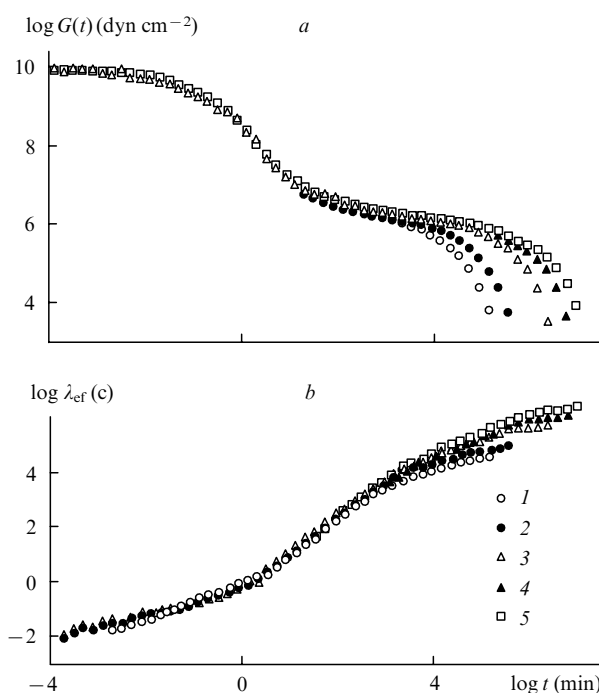


**Figure 11.** Shear modulus (a) and effective relaxation time (b) of polystyrene plotted vs. time.<sup>230</sup>  $M_w \times 10^{-3} = 80$  (1), 125 (2), 193 (3), 239 (4), 267 (5). The reduction temperature was 129 °C.

proportional to  $M^4$  (Fig. 12). This dependence cannot always be revealed. Indeed, if the molecular masses vary with a not too large interval, the dependence mentioned above can be distorted. Besides, if the molecular mass of a polymer varies over a broad range, the relaxation measurements are usually carried out at appreciably different temperatures and then their results are reduced to a certain specified temperature using the principle of temperature–time superposition. Small uncertainties introduced when using this procedure can lead (and do lead, see the data shown in Fig. 12) to errors. Analysis of the whole array of experimental data showed validity of the power law mentioned above. This dependence was also reported in other studies.<sup>104,233</sup>

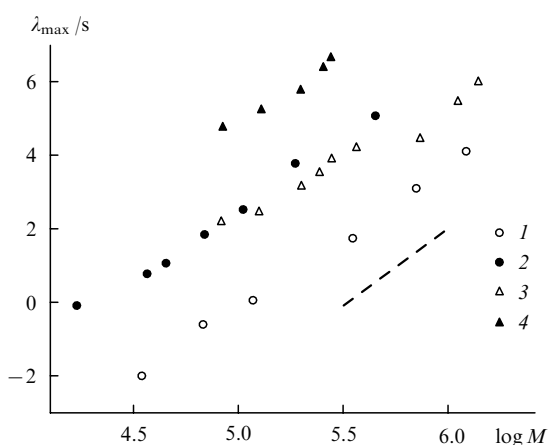


**Figure 12.** Maximum relaxation time plotted vs. molecular mass of polystyrene (1–4) using the data taken from Refs 231, 74, 230 and 232, respectively. Reduced temperature /°C: 160 (1), 139 (2, 3) and 127 (4). The dashed line describes the dependence  $\lambda_{\text{max}} \propto M^4$ .

The fact that for monodisperse polymers  $\lambda_{\text{ef}}$  in the rubbery plateau zone is proportional to  $t^{1.2}$  can indicate that the relaxation spectra of these compounds are more similar to the Rouse spectrum with respect to this characteristic.

Knowing the frequency dependence of the effective relaxation time, it is possible to determine<sup>51</sup> two parameters with different degrees of averaging over the relaxation times. In this case analysis is carried out using the real  $G'(\omega)$  and the imaginary  $G''(\omega)$  components of the relaxation modulus of elasticity separately.

Similarly to the case of the frequency dependence of the relaxation modulus, the frequency domain is divided into three zones with respect to the character of the frequency dependence of the effective relaxation time. These are the terminal zone (zone *I*, low frequencies), the rubbery plateau zone (zone *II*) and the high-frequency zone (zone *III*).

As mentioned above [see expression (12)] the effective relaxation time  $\lambda_{\text{efw}}(\omega)$  in the terminal zone *I* reaches a limiting value, which is frequency independent and equals the ratio of the second to the first moment of the relaxation time distribution, i.e., is the weight-average relaxation time [see relationship (13)].

In zone *III* at  $\omega \rightarrow \infty$  one has

$$\lambda_{\text{wIII}} = \frac{\sum_i h_i}{\sum_i (h_i/\lambda_i)}.$$

Since short relaxation times make a greater contribution to the last-mentioned expression, one gets  $\lambda_{\text{wIII}} < \lambda_{\text{wI}}$  and the  $\lambda_{\text{wII}}(\omega)$  dependence in zone *II* (rubbery plateau zone) is a decreasing function of frequency.

The effective relaxation time [see expression (14)] at  $\omega \rightarrow 0$  (region *I*) is the number-average relaxation time, which is also frequency independent

$$\langle \lambda \rangle_{\text{nI}} = \frac{\sum_i h_i(\lambda) \lambda_i}{\sum_i h_i(\lambda)}.$$

In region *III* one has

$$\lambda_{\text{efn}}(\omega) \rightarrow \frac{\sum_i h_i/\lambda_i}{\sum_i h_i/\lambda_i^2}.$$

This value can be either small or rather large depending on the character of the relaxation spectrum. Therefore, in region *II* the  $\lambda_{\text{efn}}(\omega)$  dependence can show rather complex behaviour.

Thus, analysis of the frequency dependence of the effective relaxation time makes it possible to estimate the relaxation time spectrum using a number of distribution moments. In particular, the ratio

$$\gamma_{\text{I}} = \frac{\langle \lambda \rangle_{\text{wI}}}{\langle \lambda \rangle_{\text{nI}}}$$

characterises the width of the relaxation time distribution in region *I*.

The relaxation spectrum of the Rouse model is given<sup>33</sup> by the relationship  $h_i = n^{-1}$ , where  $n$  is the chain length. Therefore, in the terminal zone one gets

$$\langle \lambda \rangle_{\text{wI}} = \lambda_{\text{max}} \frac{\sum_{i=1}^n i^{-4}}{\sum_{i=1}^n i^{-2}} \approx \lambda_{\text{max}}$$

and

$$\langle \lambda \rangle_{\text{nI}} = \frac{\lambda_{\text{max}}}{n} \sum_{i=1}^n i^{-2} \approx \frac{\lambda_{\text{max}}}{n}.$$

**Table 9.** Dependences of characteristics of the effective relaxation time on the chain length for various models.<sup>51</sup>

| Model                | $\langle \lambda \rangle_{\text{nI}}$ | $\langle \lambda \rangle_{\text{wI}}$ | $\lambda_{\text{max}}$ | $\gamma_{\text{max}}$ | $\omega_{\text{max}}$ | $\gamma_{\text{I}}$ |
|----------------------|---------------------------------------|---------------------------------------|------------------------|-----------------------|-----------------------|---------------------|
| Rouse model          | $n^1$                                 | $n^2$                                 | $n^2$                  | —                     | —                     | $n^1$               |
| Doi–Edwards model    | $n^3$                                 | $n^3$                                 | $n^3$                  | —                     | —                     | $n^0$               |
| Modified Rouse model | $n^1$                                 | $n^{1.66}$                            | $n^{1.7}$              | $n^{0.58}$            | $n^{-2.2}$            | $n^{0.66}$          |

Because, in accord with the Rouse model,  $\lambda_{\text{max}}$  is proportional to  $n^2$ , the parameter  $\langle \lambda \rangle_{\text{wI}}$  also increases in proportion to  $n^2$  and  $\langle \lambda \rangle_{\text{nI}}$  increases in proportion to  $n$ . The distribution width,  $\gamma_{\text{I}}$ , increases proportionally to the polymer chain length (Table 9).

The following relationships are valid in zone *III*:

$$\begin{aligned} \langle \lambda \rangle_{\text{wIII}} &= \lambda_{\text{max}} \frac{n}{\sum_{i=1}^n i^2} \approx \frac{\lambda_{\text{max}}}{n^2}, \\ \langle \lambda \rangle_{\text{nIII}} &= \lambda_{\text{max}} \frac{\sum_{i=1}^n i^2}{\sum_{i=1}^n i^4} \approx \frac{\lambda_{\text{max}}}{n^2}. \end{aligned}$$

Thus, the distribution width  $\gamma$  is independent of chain length in this frequency region.

In the Doi–Edwards reptation model the relaxation spectrum is given<sup>34</sup> by the expression  $h_i = i^{-2}$ ; therefore, in zone *I* one has

$$\begin{aligned} \langle \lambda \rangle_{\text{wI}} &= \lambda_{\text{max}} \frac{\sum_{i=1,3,\dots}^n i^{-6}}{\sum_{i=1,3,\dots}^n i^{-4}} \approx \lambda_{\text{max}}, \\ \langle \lambda \rangle_{\text{nI}} &= \frac{8}{\pi^2} \lambda_{\text{max}} \sum_{i=1,3,\dots}^n i^{-4} \approx \lambda_{\text{max}}. \end{aligned}$$

The distribution width  $\gamma_{\text{I}}$  is independent of chain length.

For zone *III* one has

$$\begin{aligned} \langle \lambda \rangle_{\text{nIII}} &= \lambda_{\text{max}} \frac{n}{\sum_{i=1}^n i^2} \approx \frac{\lambda_{\text{max}}}{n^2}, \\ \langle \lambda \rangle_{\text{wIII}} &= \lambda_{\text{max}} \frac{\sum_{i=1}^n i^{-2}}{n} \approx \frac{\lambda_{\text{max}}}{n}, \end{aligned}$$

and  $\gamma_{\text{III}}$  increases in proportion to  $n$ .

In the rubbery plateau zone (zone *II*) the parameter  $\lambda_{\text{wII}}$  is proportional to  $\omega^{-1}$  for the Rouse model and to  $\omega^{-1/2}$  for the Doi–Edwards model; respectively,  $\lambda_{\text{nII}} \propto \omega^{-1/2}$  and  $\lambda_{\text{nII}} \propto \omega^{-1}$ . From here the ratios of the average relaxation times for these models are also different, namely, the parameter  $\gamma_{\text{II}}$  decreases in the former and increases in the latter case nearly proportionally to the square root of the frequency.

Thus, different frequency dependences of the average relaxation times and their ratios reflect significant differences between the relaxation spectra of the models under consideration.

The average relaxation times and their ratios depend on the structures of the polymer chains. This dependence can be illustrated taking nonuniform Rouse chains (see above) as an example. We will consider chains whose structures can be expressed through the friction coefficients of units as follows:

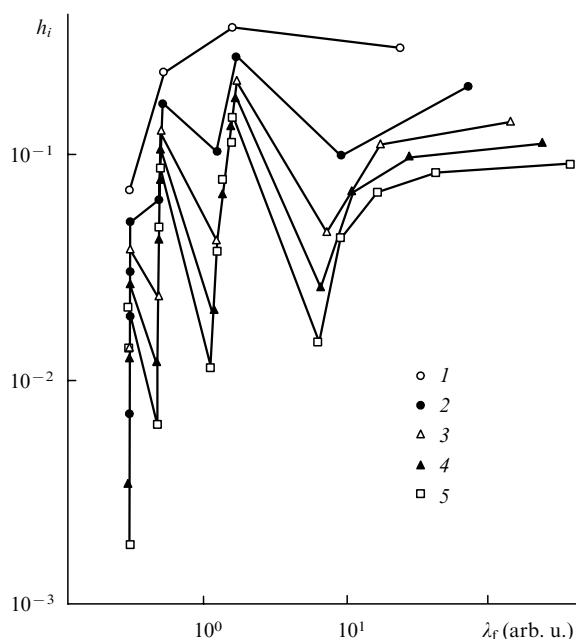


**Figure 13.** Relaxation spectra calculated for modified Rouse chains  $F \leftarrow (1-1-1-5)_m-1-1-1-5$  with  $m = 0$  (1), 1 (2), 2 (3), 3 (4) and 4 (5).<sup>51</sup>

$F \leftarrow (1-1-1-5)_m-1-1-1-5$ , where  $m = 0, 1, 2, 3, 4$ . The relaxation spectra calculated for these model chains are shown in Fig. 13. As can be seen, in contrast to the Rouse and the Doi–Edwards models, the nonuniform Rouse chain model leads to the formation of an essentially non-monotonic discrete relaxation spectrum. Qualitatively, the frequency dependences of the average relaxation times (Fig. 14) obey the same pattern as the analogous theoretical dependences shown above. However, the  $\gamma(\omega)$  dependence is basically different, namely, pronounced maxima appear in the curves. Quantitative relation of these parameters to the chain length also differs from the corresponding relations derived for the models considered above (see Table 9).

In the frequency regions *I* and *III* the parameters  $\langle \lambda \rangle_w$ ,  $\langle \lambda \rangle_n$  and  $\gamma$  take constant values, the average relaxation times in zone *I* being proportional to the chain length  $n = 4(m+1)$  raised to the power 1.66 and 1.00 for  $\langle \lambda \rangle_w$  and  $\langle \lambda \rangle_n$ , respectively; here for the average relaxation time ratio one has  $\gamma_I \propto n^{0.66}$  (see Table 9); in zone *III* the parameters  $\langle \lambda \rangle_{wIII}$  and  $\langle \lambda \rangle_{nIII}$  are independent of  $n$ . The frequency dependence of the ratio of the average relaxation times in the rubbery plateau zone can be quite accurately described by a power law with an exponent of about 0.5. The height of the maximum and its position on the frequency axis depend on the chain length, namely,  $\gamma_{\max} \propto n^{0.58}$  and  $\omega_{\max} \propto n^{-2.2}$ .

Thus, the nonuniform Rouse chain model is intermediate between the Rouse and the Doi–Edwards models with respect to the relaxation properties. This shows that the relaxation characteristics in question (effective relaxation times and their ratio) are rather sensitive to both the type of motion (the Rouse and Doi–Edwards models) and the chain structure (the classical and nonuniform Rouse models).

As an example Fig. 15 presents the frequency dependences of the effective relaxation times of polystyrene, obtained<sup>51</sup> using the tabulated data.<sup>50</sup> In the terminal zone the effective relaxation times are frequency independent and can be determined as the average values  $\langle \lambda \rangle_{wI}$  and  $\langle \lambda \rangle_{nI}$ .

The dependence of the average relaxation times on the molecular mass is described by a power law  $\langle \lambda \rangle \sim M^a$ . The exponents for  $\langle \lambda \rangle_{wI}$  and  $\langle \lambda \rangle_{nI}$  differ from each other (see Table 9), being in the former case larger than in the latter. For all polymers under study (data were taken from Refs 53, 57, 58)

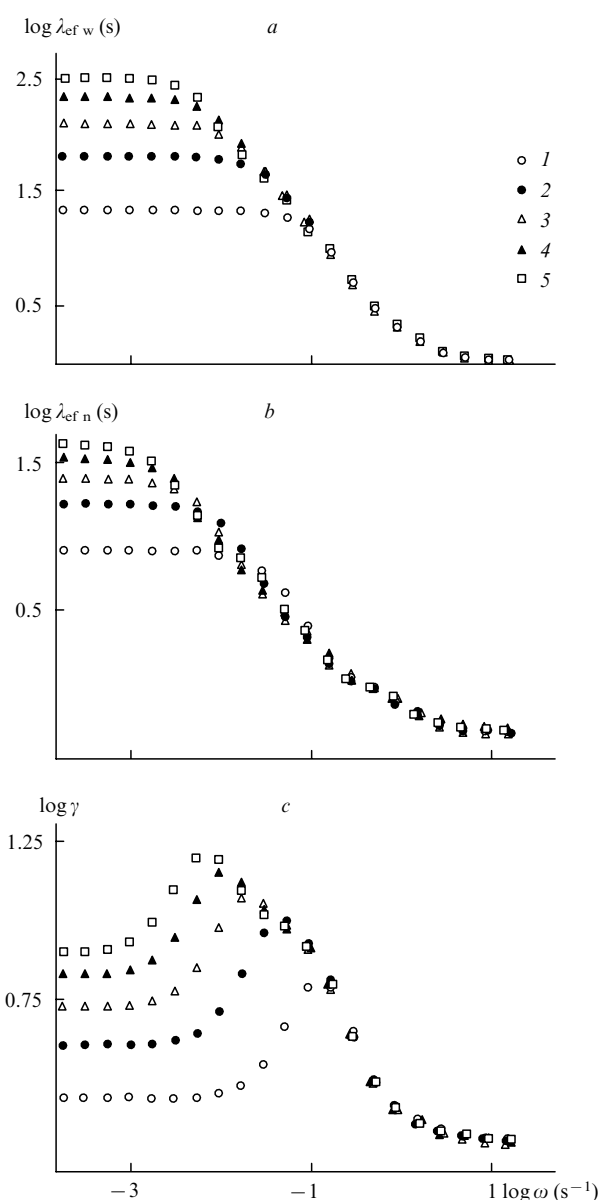


**Figure 14.** Frequency dependences of average relaxation times (*a*, *b*) and their ratios (*c*) obtained for the modified Rouse chains whose relaxation spectra are shown in Fig. 13.<sup>51</sup>

Notations (1–5) correspond to those used in Fig. 13.

the dependence of  $\langle \lambda \rangle_{nI}$  on the molecular mass is characterised by an  $a$  value of about 3.4. The same exponent value is also characteristic of the known dependence of viscosity on the molecular mass.<sup>4</sup>

The value of the exponent at  $M$  depends on the procedure of averaging over the relaxation times. This concerns both the limiting values and the rubbery plateau zone. Analysis of the dependences presented in Fig. 15 showed that at all molecular masses an increase in frequency causes a nearly linear (more exactly, the exponent approaches a value of 0.9) decrease in  $\langle \lambda \rangle_{nII}$  while  $\langle \lambda \rangle_{wII}$  is proportional to  $\omega^{-0.75}$ , so the corresponding ratio increases in proportion to  $\omega^{0.15}$ . With allowance for this dependence, which is common to all narrow-MMD polymers, one can assume that their relaxation spectra are intermediate between broad relaxation spectra characteristic of the Rouse model and narrow relaxation spectra characteristic of the Doi–Edwards model. The shape of the  $\gamma(\omega)$  plots points to a similarity between the relaxation spectra of real polymers and those of the polymers corresponding to the modified Rouse model.



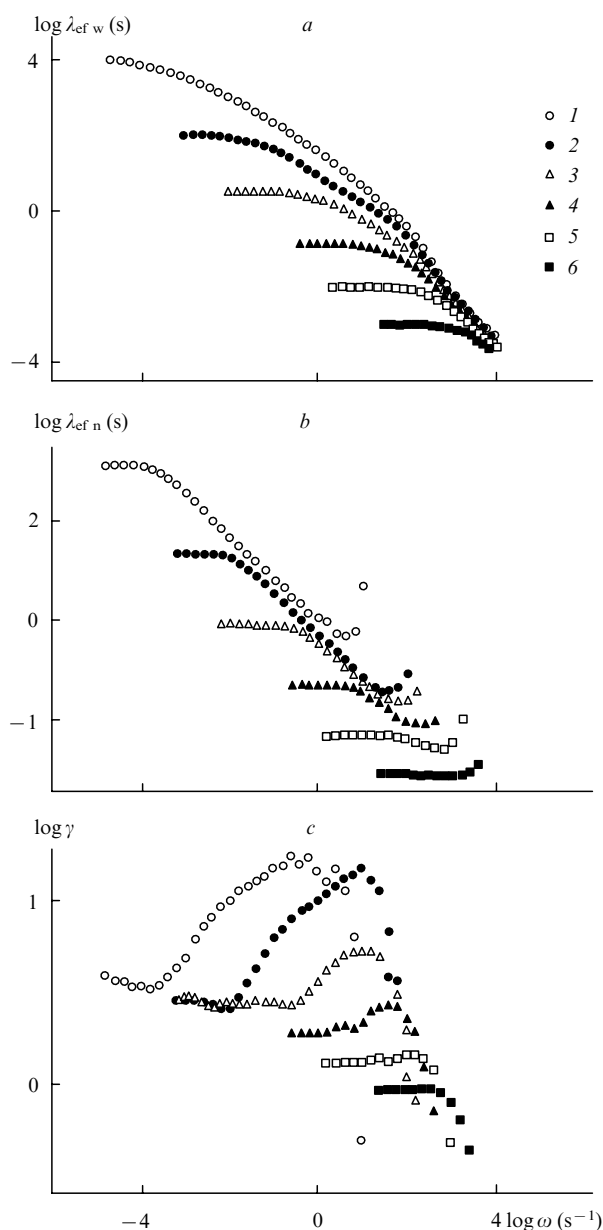


**Figure 15.** Frequency dependences of average relaxation times (a, b) and their ratio (c) at  $T = 180\text{ }^{\circ}\text{C}$  obtained for monodisperse polystyrene using the data taken from Ref. 50.

$M \times 10^{-3} = 3000$  (1), 770 (2), 275 (3), 128 (4), 70 (5) and 39 (6).

Comparison of the distribution parameters in zone III is complicated by the fact that real polymers undergo glass transitions in this frequency region. In contrast to a similar dependence obtained in model calculations, here a pronounced maximum in the frequency dependence of the parameter  $\gamma_{II}$  is not an artifact; rather, it has a particular physical meaning. Probably, the appearance of this maximum characterises the glass transition. Thus, the  $\gamma(\omega)$  dependence, as well as the loss factor  $\tan \delta$ , can be used for the description of this transition.

Depending on the molecular mass, the transition points are located at different positions on the frequency axis (see Fig. 15 c), namely, an increase in the molecular mass leads to a shift of the transition point towards lower frequencies. The position of the maximum on the frequency axis is nearly proportional to  $M^{-2}$ ; the exponent being almost equal to that for the nonuniform Rouse model ( $n^{-2.2}$ ).

## b. Continuous relaxation spectrum

In fact, the development of the Kargin – Slonimskii – Rouse model led to the idea that the relaxation spectrum characterising the viscoelastic properties of polymers is a continuous function,<sup>213</sup> because the number of modes in the Rouse spectrum equals the number of chain units and the difference between the relaxation times of the 'neighbouring' modes is much less than the relaxation times, *i.e.*,  $(\lambda_{i+1} - \lambda_i) \ll \lambda_i$ . This concept dominated in the polymer science in the 1950s–1960s.<sup>63, 212</sup> The relaxation behaviour of polymers was described using relaxation spectra, which were represented by a wedge, 'box' or their combination.<sup>212</sup> Even at present some authors often use a continuous function instead of the calculated discrete spectrum (see, *e.g.*, Ref. 234) assuming that only this representation is physically substantiated. Moreover, an opinion was offered<sup>228</sup> that discretisation is a necessary prerequisite for using numerical methods of solving the problem of determination of continuous relaxation spectrum from experimental data.

In mathematics, the determination of a spectrum is reduced to inversion of the Laplace transforms (1), (1a) or the Fourier transform (2), *i.e.*, this is a quite solvable problem

$$H(\lambda) = \hat{H}(s) = \frac{1}{2\pi i} \int_0^{\infty} g(t) e^{st} dt, \quad (26)$$

where  $s = 1/\lambda$ .

The difference is that (if we ignore the problems of accuracy and ambiguity of experimental data), first, the integration limits in expressions (1a) and (26) are limited by the experimental conditions; second, the  $g(t)$  and  $G^*(\omega)$  curves are non-analytical curves and therefore integral (26) can be calculated only using approximate numerical methods.

Probably, the most efficient<sup>235</sup> and, at the same time, the oldest<sup>236</sup> is the method based on the use of the expansion of the inverse Laplace transform (1a) into a series<sup>237</sup>

$$H_n(\lambda) = \frac{1}{(n-1)!} \sum_{i=1}^n (-1)^i a_m \frac{d^i g(t)}{d(\ln t)^i} \Big|_{t=\lambda}, \quad (27)$$

which is a particular case of a general relationship

$$h(\lambda) = \lim_{n \rightarrow \infty} \left[ (-1)^n \frac{nt^{n-1}}{(n-1)!} \frac{d^n h(t)}{dt^n} \Big|_{t=n\lambda} \right].$$

The  $a_{ni}$  coefficients are calculated using the recurrent relation

$$a_{ni} = (n-1)a_{n-1,i} + a_{n-1,i-1},$$

$i \leq n$ .

Usually, only two first terms of the series (27) are included in calculations of the relaxation spectra, therefore

$$H(\lambda) = - \frac{dg(t)}{d \ln t} \Big|_{t=\lambda} + \frac{d^2 g(t)}{d (\ln t)^2} \Big|_{t=2\lambda}. \quad (28)$$

Recently, this method was evaluated and then widely used for the characterisation of the structures and for the prediction of the properties of materials based on polyolefins in the studies by Kimel'blat *et al.*<sup>238–242</sup> The initial data represented the curves of the pressure drop in the cylinder of a capillary viscosimeter in the non-steady-state flow of a polymer melt through a capillary after stopping the plunger. The authors believed that the pressure drop and a parallel decrease in the shear rate were due to the mechanism proposed by Vinogradov<sup>43, 44</sup> with allowance for a broad relaxation time spectrum due to polydispersity of the polymer.<sup>68–71</sup>

Thus, the calculated characteristics of the relaxation spectrum, namely, the average relaxation times  $\langle \lambda \rangle_n$ ,  $\langle \lambda \rangle_w$  and  $\langle \lambda \rangle_z$  should correlate with characteristics of the MMD of the polymer. For instance, it was stated<sup>243</sup> that 'dispersion in the MMD and

dispersion in the relaxation spectrum go hand in hand'. Indeed, corresponding correlations were established for polyethylene and polyethylene copolymers.<sup>242</sup> For instance in the case of high-density polyethylene one has

$$\log M_n = 4.14 + 0.147 \log \langle \lambda \rangle_n$$

with the correlation coefficient  $r^2 = 0.89$ ,

$$\lg M_w = 4.64 + 0.839 \lg \langle \lambda \rangle_w$$

with the correlation coefficient  $r^2 = 0.96$  and

$$\lg M_z = 4.57 + 1.131 \lg \langle \lambda \rangle_z$$

with the correlation coefficient  $r^2 = 0.92$ .

Here

$$\langle \lambda \rangle_n = \frac{\int H(\lambda) d \ln \lambda}{\int [H(\lambda)/\lambda] d \ln \lambda}, \quad \langle \lambda \rangle_w = \frac{\int \lambda H(\lambda) d \ln \lambda}{\int H(\lambda) d \ln \lambda},$$

$$\langle \lambda \rangle_z = \frac{\int \lambda^2 H(\lambda) d \ln \lambda}{\int \lambda H(\lambda) d \ln \lambda}.$$

Correlations between characteristics of the relaxation spectrum and the topological structures of polymers are illustrated in Fig. 16 where the average relaxation times are plotted vs. the composition of polymer blends with different molecular masses (Fig. 16a) and vs. the degree of cross-linking (Fig. 16b).

Numerous examples of correlations between characteristic features of the relaxation spectrum and the technological and physicomechanical properties of materials based on polyolefins can be found in a monograph.<sup>242</sup> It is the shape analysis of the spectral curve that allowed the author of the monograph<sup>242</sup> to

optimise the procedure of welding of high-density polyethylene pipes and predict the lifetime of such pipes. The curves of the relaxation spectra of ethylene-propylene rubbers served as criteria in evaluating the stability of the synthesis of such materials. Optimisation of the composition of thermoplastic composites and weldment are also based on analysis of specific features of the shape of the relaxation spectra. It is important that it was the relaxation spectra rather than the experimental pressure drop curves that were used as sensitive tools in the above-mentioned and similar research and development studies.

### c. Discrete relaxation spectrum. Regularisation methods

Methods of determination of a discrete relaxation spectrum have been analysed in detail in a review by Malkin<sup>226</sup> who tried to show that the determination of a relaxation spectrum in order to interpret experimental data has no physical meaning in the general case because the final result is not unique. Therefore, in comparing the properties of materials with different topological structures it is more appropriate to lean upon characteristic data points obtained in direct relaxation experiments rather than the relaxation spectrum calculated using these data, because, according to Malkin,<sup>226</sup> the relaxation spectrum is 'nothing more than a method of possible approximation of experimental data within the limits of measurement error, which is convenient for various applications in the framework of the theory of viscoelasticity of continuous media'. Nevertheless, numerous calculations of the relaxation spectra have been and are being reported.

Physically, an approach<sup>244</sup> widely used in the analysis of the free induction decay curves (see, e.g., Ref. 193) seems to be the most evident. The method involves successive determination of the exponents and pre-exponents of the  $\ln[g(t)]$  function at  $t \rightarrow \infty$ . In this case the kinetics of the decay is governed by the exponent with the longest relaxation time. Of course, such a division of the relaxation curve is quite rough and exponents with similar decay constants are indistinguishable.<sup>212, 244</sup> However, calculations of model functions (in particular, the Rouse relaxation curve) showed that the first three terms of the relaxation spectrum (with the longest relaxation times) can be determined quite accurately. The advantage of this approach is the possibility of estimating the maximum relaxation time. In particular, the relation  $\lambda_{\max} \propto M^4$  was established<sup>230</sup> using this procedure.

Essentially the same strategy was used in another study.<sup>245</sup> The orientation relaxation curve of polystyrene samples, expressed by the Legendre polynomial  $P_2(t)$ , was approximated by three exponents, which provided the best agreement with the experimental data. The relaxation times thus obtained were significantly different, e.g.,  $\lambda_1 = 0.7$ ,  $\lambda_2 = 39$  and  $\lambda_3 = 1.65 \times 10^4$  s (obtained for a polymer with a molecular mass of  $2.34 \times 10^6$  at a temperature, which is  $20^\circ$  higher than the glass transition temperature). The relaxation time  $\lambda_1$  was independent of the molecular mass while the other two relaxation times were related to  $M$  as follows:  $\lambda_2 \propto M^{0.5}$  and  $\lambda_3 = 2 \lambda_1 M^{1.6}$ .

To determine a relaxation spectrum is to find the solution to a problem inverse to problem (1). To this end, the following relation is used:

$$g(t) = K[h(\lambda)](t) + \varepsilon(t),$$

where  $K$  is the operator relating the function  $h$  to the experimental data  $g$ , and  $\varepsilon(t)$  is the error. Often,  $K$  is a linear operator, which corresponds to the Fredholm integral equation. Examples of linear inverse problems are provided by the analysis of experimental data obtained by NMR spectroscopy, static light scattering and results of resistor conductivity measurements. The linear rubbery state theory also includes nonlinear problems. Besides, as mentioned above (see Introduction), inevitable experimental errors complicate calculations of the relaxation spectrum using expression (1). Finally, experimental data are always available within a limited range of argument values. Taken altogether, this makes the problem of calculating the relaxation spectrum an ill-posed problem.<sup>226, 246–248</sup>

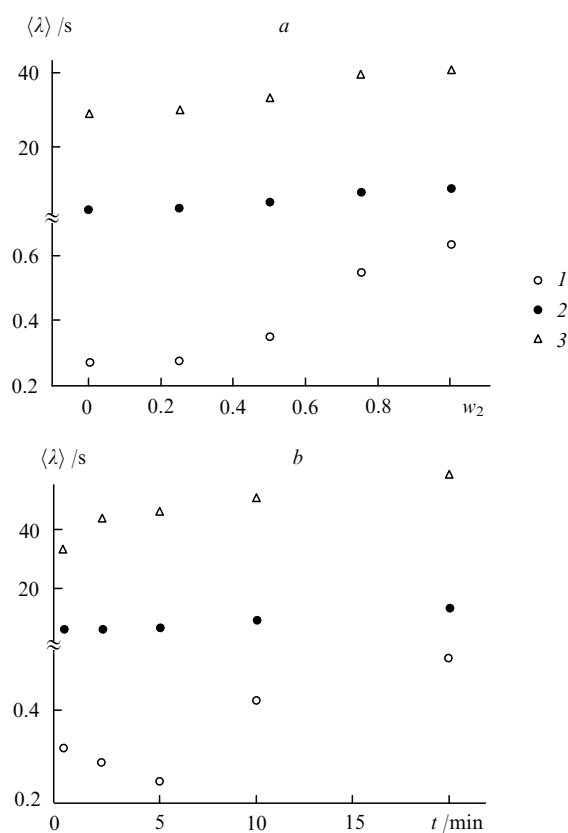


**Figure 16.** Average relaxation times  $\langle \lambda \rangle_n$  (1),  $\langle \lambda \rangle_w$  (2) and  $\langle \lambda \rangle_z$  (3) plotted vs. composition of a bidisperse blend of low-density polyethylenes (LDPE) (a) and vulcanisation time of butyl rubber (b).<sup>242</sup> Polymer blend: component 1 is LDPE-277 ( $M_w = 6 \times 10^4$ ,  $\bar{M}_w/\bar{M}_n \approx 5$ ), component 2 is LDPE-273 ( $M_w = 2 \times 10^5$ ,  $\bar{M}_w/\bar{M}_n \approx 15$ ).

The case for the problem inverse to the problem described by Eqn (3) is somewhat different. Indeed, Winter showed<sup>228</sup> that the frequency dependence of the relaxation modulus,  $G^*(\omega)$ , is the best source of initial experimental data for calculating the relaxation spectra. Also, mention was made<sup>228</sup> that the  $g(t)$  function can be determined more accurately from the same  $G^*(\omega)$  dependence rather than direct measurements. Systematic and statistical errors can be corrected using the Kramers–Kronig relation

$$\frac{G'(\omega)}{\omega^2} = \frac{2}{\pi} \int_0^\infty \frac{G''(x)}{\omega^2 - x^2} dx,$$

( $x$  is the integration variable), which leads to the following equality (at  $h > 0$ )

$$\frac{\lambda}{1 + (\omega\lambda)^2} = \frac{2}{\pi} \int_0^\infty \frac{x}{1 + (x\lambda)^2} \frac{dx}{\omega^2 - x^2}$$

for any  $\lambda$ .

Listed below are criteria which an algorithm for calculating a relaxation spectrum should satisfy. The choice of these criteria is an expression of personal preference rather than objective definition. The preferences of the author of Ref. 228 are as follows:

- good fit of experimental data;
- the algorithm should be able to find the optimum amount of detail which can be extracted from experimental data without producing artifacts;
- the format of the relaxation spectrum should not be predetermined; it has to be freely adjustable during the processing of the experimental data;
- the resulting parameters should have physical meaning;
- minimisation of the experimental data truncation errors;
- checking of experimental data quality is required (the data are always inconsistent to some extent, because the signal-to-noise ratios differ for  $G'$  and  $G''$ ; this may cause a large discrepancy between fit and experimental data);
- the relaxation spectrum  $H(\lambda)$  should be expressed by a function or a sum of functions, which can be integrated easily;
- the number of parameters of the model functions should not be large;
- the computation time should be short.

Calculations are based on the assumption that there exists a function  $H(\lambda)$ , which is sufficiently smooth that it can be taken as linear within small intervals  $[\lambda_i^-, \lambda_i^+]$  around  $\lambda_i$ .

To carry out calculations with a computer, the function  $g(t)$  should be discretised

$$g(t) = \int_0^\infty H(\lambda) d \ln \lambda = \sum_{i=1}^\infty \int_{\lambda_{i-1}}^{\lambda_{i+1}} H(\lambda_i) d \ln \lambda_i = \sum_{i=1}^\infty H(\lambda_i) \Delta_i,$$

where

$$\Delta_i = \frac{1}{2} \ln \frac{\lambda_{i+1}}{\lambda_{i-1}}.$$

The discretising frequency is given by  $\omega_i = 1/\Delta_i$ . The expression for  $g(t)$  takes the form

$$g(t) = g_0 + \sum_{i=1}^N h_i \exp\left(-\frac{t}{\lambda_i}\right), \quad (29)$$

where  $h_i = H(\lambda_i)\Delta_i$ .

The use of two data series ( $G'$  and  $G''$ ) eliminates the problem of ill-posedness. For the same reason simultaneous use of the  $g$  modulus and compliance data leads to the same result.<sup>249</sup> The uniqueness of the solution to the problem is due to the fact that the  $g$  modulus and compliance are interrelated.

The key point in calculations is minimisation of an error functional

$$\frac{1}{Z} \sum_{i=1}^Z \left[ \left( \frac{G'(\omega_i)}{\hat{G}'_i} - 1 \right)^2 + \left( \frac{G''(\omega_i)}{\hat{G}''_i} - 1 \right)^2 \right] = \min,$$

where

$$G' = \sum_{i=1}^N h_i \frac{(\omega\lambda_i)^2}{1 + (\omega\lambda_i)^2}, \quad G'' = \sum_{i=1}^N h_i \frac{\omega\lambda_i}{1 + (\omega\lambda_i)^2},$$

and  $\hat{G}'_i$  and  $\hat{G}''_i$  are the data measured at  $Z$  frequencies  $\omega_i$ .

The parameters  $\lambda_i$ ,  $h_i$ ,  $N$  are freely adjustable during the minimisation.

Analysis showed that the results of minimisation depend on the  $N$  value, but a stable solution is reached after a reasonably short time (in this case the error functional becomes independent of  $N$ ). Thus, the number of modes in the relaxation spectrum is limited by the minimum  $N$  value responsible for stability of the solution. Usually,  $N \leq 20$ .

A 'parsimonious' relaxation spectrum thus obtained is unique in the sense that different discrete sets of  $h_i$  and  $\lambda_i$  values lead to the same continuous function  $H(\lambda)$ .

Based on the results of experimental studies of polypropylene,<sup>250</sup> polybutadiene<sup>56, 141, 251</sup> and polystyrene,<sup>141, 234</sup> using the IRIS program (please visit a website at URL <http://128.119.197/Lab/IRIS.html>) it was concluded that the relaxation spectra of monodisperse polymers can be represented by two arms, a decreasing arm at  $\lambda \leq \lambda_1$  ( $\lambda_1$  corresponds to the inflection point) and an increasing arm at  $\lambda \geq \lambda_1$

$$H(\lambda) = \begin{cases} mG_N^0 \left[ \left( \frac{\lambda}{\lambda_c} \right)^{-n_g} + \left( \frac{\lambda}{\lambda_{\max}} \right)^{n_e} \right] & \text{at } \lambda \leq \lambda_{\max}, \\ 0 & \text{at } \lambda > \lambda_{\max}. \end{cases} \quad (30)$$

The  $\lambda_c$  value is determined from the equality  $H(\lambda_c) = H(\lambda_{\max}) = mG_N^0$  (the subscripts 'g' and 'e' at the exponents denote 'glass' and 'elastic', respectively).

Figure 17 presents some examples of this type of relaxation spectra, which are called the BSW spectra.<sup>†</sup>

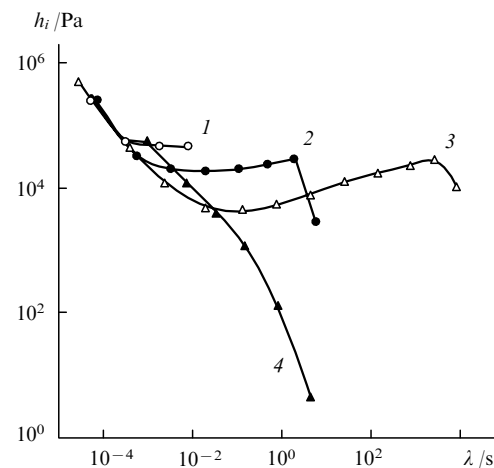


**Figure 17.** Continuous relaxation spectra of polystyrene<sup>50</sup> (1–3) and low-density polyethylene<sup>263</sup> (4).  $M \times 10^{-3} = 39$  (1), 275 (2) and 3000 (3).

Taking polybutadienes with different topological structures as examples, it was shown<sup>251</sup> that the BSW relaxation spectra consist of three regions, viz., a decreasing arm at  $\lambda \leq \lambda_1$ , an increasing arm at  $\lambda_1 \leq \lambda \leq \lambda_{\max}$  and an abrupt cut-off region at  $\lambda > \lambda_{\max}$

<sup>†</sup> BSW abbreviation is an using the first letters in the surnames of the authors of Ref. 234.

$$H(\lambda) = \left[ H_g \left( \frac{\lambda}{\lambda_c} \right)^{-n_g} + n_e G_N^0 \left( \frac{\lambda}{\lambda_{\max}} \right)^{n_e} \right] \exp \left[ - \left( \frac{\lambda}{\lambda_{\max}} \right)^\beta \right], \quad (31)$$

where

$$H_g = n_e G_N^0 \left( \frac{\lambda}{\lambda_{\max}} \right)^{n_e} \left( \frac{\lambda_1}{\lambda_c} \right)^{n_g},$$

and  $\lambda_1$  is the instant at which the first two branches merge (or intersect). Usually,  $n_g \approx 0.67$ ,  $n_e \approx 0.30$  and  $\beta = 2$ .

It should be noted that the relaxation spectrum described by Eqn (31) does not meet the smoothness condition. At the  $\lambda_{\max}$  point, the curve exhibits an abrupt kink. In particular, if in the double logarithmic coordinates the spectrum is sectionally linear but has abrupt wings, the method cannot be used. It was shown<sup>252</sup> that in this case one should use regularisation methods.

A regularisation method involves minimisation of the error function  $V_\xi(\ln h)$  (see Refs 252 and 253).

$$V_\xi(\ln h) = \sum_{i=1}^M \frac{1}{(\sigma'_1)^2} \left[ G'_\sigma(\omega_i) - \int_{-\infty}^{\infty} \frac{(\omega_i \lambda)^2}{1 + (\omega_i \lambda)^2} H(\lambda) d \ln \lambda \right]^2 + \sum_{i=1}^M \frac{1}{(\sigma''_1)^2} \left[ G''_\sigma(\omega_i) - \int_{-\infty}^{\infty} \frac{\omega_i \lambda}{1 + (\omega_i \lambda)^2} H(\lambda) d \ln \lambda \right]^2 + \xi R(\ln h),$$

where  $\sigma$  is the standard deviation of the Gaussian error function. The regularisation term,  $R(\ln h)$ , imposes constraints based on the *a priori* information on the shape of the relaxation spectrum. The regularisation parameter  $\xi$  'weights' the constraints with allowance for the *a priori* knowledge.

At present, a number of program packages<sup>‡</sup> (e.g., NLREG,<sup>254</sup> GENEREG,<sup>253</sup> CONTIN<sup>255</sup> and FTIKREG<sup>256</sup>) developed for solving ill-posed problems by the regularisation method are available.

The assumption of smoothness means that

$$R(\ln h) = \int_{-\infty}^{\infty} \left[ \frac{d^2 \ln h}{d(\ln \lambda)^2} \right]^2 d \ln \lambda.$$

Taking into account abrupt changes in the function in the wings leads to a more general expression for  $R$

$$R(\ln h) = \int_{-\infty}^{\infty} \frac{[d^2 \ln h / d(\ln \lambda)^2]^2}{\sqrt{1 + [\alpha d^2 \ln h / d(\ln \lambda)^2]^2}} d \ln \lambda, \quad \alpha \geq 0.$$

The problem thus formulated was solved<sup>252</sup> using the Edge Preserving Regularisation (EPR) and Edge Preserving Nonlinear Regularisation (EPNREG) programs. The approach considered here can be employed if there are reasons to assume that the relaxation spectrum is smooth except for the inflection points in the  $\lambda_1$  and  $\lambda_{\max}$  regions (at  $10^{-4}$  and  $10^0$  s, respectively). A decrease in the long-time region was reported<sup>154</sup> to be a linear function in the double logarithmic coordinates (slope is  $\sim -10$ ). It should be noted that both the EPR and IRIS calculations give nearly identical results in the region  $\lambda \leq \lambda_{\max}$ .

In essence, the criterion for uniqueness of solution formulated by Winter<sup>228</sup> means that the set of relaxation times is insignificant for the determination of a continuous relaxation spectrum. Therefore, a relaxation spectrum can be determined as a solution of the 'semi-inverse' problem (i.e., a problem with a prescribed set of relaxation times). It is this solution that was proposed in Refs 257 and 258.

Liu<sup>257</sup> reported a mathematical approach to the determination of a discrete relaxation spectrum from the temporal dependence of the relaxation modulus or creep compliance. The method is based on approximation theory.<sup>259</sup> According to Liu, 'discrete relaxation and retardation times do not necessarily have any physical meaning since the continuous relaxation modulus and creep compliance can be approximated arbitrarily closely by discrete variables with different sets of relaxation and retardation times'. Starting from this point, Liu experimented with the following sets of relaxation times:  $\lambda_k = \lambda/k$ ,  $\lambda_k = \lambda/k^2$ ,  $\lambda_k = \lambda/\rho^k$  ( $k$  is the mode number and  $\rho$  is an empirical constant). The function was minimised using the non-negative least squares method and the MATLAB software package,

$$F(g_0, g_1, \dots, g_n) = \sum_{i=1}^m w_i [G^*(t_i, n) - G(t_i)]^2,$$

where  $F(G_0, G_1, \dots, G_n) = \min F(g_0, g_1, \dots, g_n)$  at  $g_0, g_1, \dots, g_n \geq 0$ ,  $w_1, w_2, \dots, w_m$  are non-negative weights,

$$G^*(t, n) = g_0 + \sum_{j=1}^n g_j e^{-t/\lambda_j}.$$

Yet another set of relaxation times is given by:<sup>258</sup>

$$\lambda_i = \lambda_{\min} \left( \frac{\lambda_{\max}}{\lambda_{\min}} \right)^{(i-1)/(N-1)},$$

where  $i$  is the mode number and  $N$  is the limiting number of modes.

Then, the function  $\|\vec{K}\vec{h} - \vec{G}\|$  was minimised by the least squares method with a constraint  $\vec{h} \geq 0$ .

$$\vec{K}_{i,j} = \frac{(\omega_i \lambda_j)^2}{1 + (\omega_i \lambda_j)^2}, \quad i = 1, \dots, m; j = 1, \dots, N,$$

$$\vec{h} = \{h_i\},$$

$$G'_i = h'_i(\omega_i), \quad i = 1, \dots, m,$$

$$G''_i = h''_i(\omega_i), \quad i = m + 1, \dots, 2m,$$

$$m \geq N.$$

Experimental data on the frequency dependence of the relaxation modulus  $G^*(\omega)$  of poly(dimethylsiloxane) were used as the input data. The relaxation spectrum thus determined was used for calculating the viscosity  $\eta_0$  and compliance  $J_e^0$  as follows

$$\eta_0 = \sum_{i=1}^N h_i \lambda_i, \quad J_e^0 = \frac{1}{\eta_0^2} \sum_{i=1}^N h_i \lambda_i^2.$$

The results obtained were in good agreement with experimental data,

$$\eta_0 = \frac{G'(\omega)}{\omega}, \quad \omega \rightarrow 0; \quad J_e^0 = \frac{G''(\omega)}{[G'(\omega)]^2}, \quad \omega \rightarrow 0.$$

An interesting method of calculation of a relaxation spectrum was proposed by Davies and Anderssen.<sup>260, 261</sup> The relaxation spectrum  $h(\lambda)$  was related to

$$g_{ab} = \int_a^b h(\lambda) d\lambda = \int_{\ln a}^{\ln b} H(\lambda) d \ln \lambda.$$

A narrow frequency range  $[ab]$  was divided into a small odd ( $2L - 1$ ,  $L = 2, 3, 4$ ) number of intervals and centred on an experimental frequency range, which in turn was divided into  $k$  discrete frequencies  $\omega_k = \omega_0 \exp(kr)$ . Usually, one had  $\omega_0 = 10^{-3} - 10^{-2}$  and  $r = \pi/(2L - 1)$ . The expressions for the relaxation modulus components were as follows

<sup>‡</sup> These programs are available on the Internet at URLs  
<http://www.itp.ac.cn/english/itpnet/cpcindex/cpcindex.html> and  
<http://cpc.cs.qub.ac.uk/simmaries/ADOQ>.

$$g'_j = -\frac{1}{2} \int_{\ln \omega_{j-1} - \pi/2}^{\ln \omega_{j+1} + \pi/2} \left[ E'' \left( \ln \frac{\omega}{\omega_j} + r \right) - E'' \left( \ln \frac{\omega}{\omega_j} - r \right) \right] G'(\omega) d \ln \omega,$$

$$g''_j = -\frac{1}{2} \int_{\ln \omega_{j-1} - \pi/2}^{\ln \omega_{j+1} + \pi/2} \left[ E' \left( \ln \frac{\omega}{\omega_j} + r \right) - E' \left( \ln \frac{\omega}{\omega_j} - r \right) \right] G''(\omega) d \ln \omega,$$

$$E'(x) = E'_\varepsilon(x), \quad E''(x) = E''_\varepsilon(x), \quad \varepsilon \rightarrow 0,$$

$$E^*_\varepsilon(x) = E'_\varepsilon(x) + iE''_\varepsilon(x) = \frac{1}{\pi} \operatorname{erf} \left( \frac{x + \pi i/2}{\sqrt{2\varepsilon}} \right), \quad \varepsilon > 0.$$

As can be seen, this method also does not require a search for discrete relaxation times; it involves calculations of the function  $h(\lambda_i)$  for a set of relaxation times  $\lambda_i$ .

Among the key sources of ill-posedness of the problem of determination of a discrete relaxation spectrum is that the function being minimised is linear with respect to  $h(\lambda)$  and nonlinear with respect to  $\lambda$ . A method<sup>262</sup> of linearisation of functions involves transformation of the components of the complex modulus into new functions  $U_n$  and  $V_n$  using the polynomial  $P_n$

$$U_n(\omega)^2 = G'(\omega) \prod_{i=1}^n (1 + \lambda_i^2 \omega^2) = \sum_{i=1}^n u_i(\omega^2)^i,$$

$$V_n(\omega)^2 = \omega G''(\omega) \prod_{i=1}^n (1 + \lambda_i^2 \omega^2) = \sum_{i=1}^n v_i(\omega^2)^i,$$

$$P_n(\omega)^2 = \prod_{i=1}^n (1 + \lambda_i^2 \omega^2) = \sum_{i=1}^n p_i(\omega^2)^i.$$

Now we have a linear problem, *viz.*, search for the coefficients  $p_i$  and  $u_i$  or  $p_i$  and  $v_i$ , which can be solved using the least squares method. Each pair of these coefficients is in mutually unique correspondence with the pair  $\lambda_i$  and  $h(\lambda_i)$ , which is given by a system of simple algebraic equations.

Applicability of this linearisation technique was demonstrated by comparing an artificially constructed relaxation spectrum with a relaxation spectrum calculated from the corresponding relaxation function. Besides, calculations of the relaxation spectrum from  $G'$  and  $G''$  (polystyrene, 179 °C) gave almost coinciding results (Fig. 18).

Finally, Jensen<sup>263</sup> reported determination of a relaxation spectrum using a version of the Monte Carlo method called 'simulating annealing'.<sup>§</sup> The technique involves the generation of trial values of  $h_i$  and  $\lambda_i$  and the search for a global minimum of the error function. The method imposes no constraints on the relaxation spectrum and does not require smoothness or even continuity. A drawback of the technique is a rather long computation time (in some cases more than  $10^6$  functions should be calculated in order to reach a global minimum). Similarly to the study by Winter<sup>228</sup>, the number of modes was limited to avoid fitting of noise, so the so-called 'parsimonious' relaxation spectrum was determined. The number of modes was chosen to be equal to that at which the dependence of the minimum value on the number of modes reached a plateau.

The relaxation spectrum of low-density polyethylene calculated using this technique is presented in Table 10.

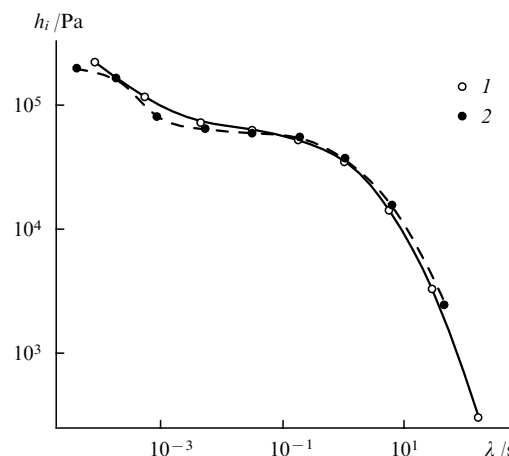


**Figure 18.** Relaxation spectra of polystyrene calculated from  $G'$  (1) and  $G''$  (2).<sup>262</sup>

**Table 10.** Relaxation spectrum of low-density polyethylene at 150 °C.<sup>263</sup>

| $k$ | $\lambda_k$ / s | $h_k$ / Pa | $k$ | $\lambda_k$ / s | $h_k$ / Pa  |
|-----|-----------------|------------|-----|-----------------|-------------|
| 1   | 4.22690885      | 8.6331     | 4   | 0.03429959      | 7770.0291   |
| 2   | 0.90131057      | 270.2802   | 5   | 0.00724564      | 23416.7956  |
| 3   | 0.15323119      | 2296.5292  | 6   | 0.00089831      | 111882.6500 |

The relaxation spectrum was also calculated<sup>103</sup> from dielectric relaxation data using the 'false position' algorithm. The method involves a comparison of experimental dependence (in this case the spectrum of dielectric loss  $\varepsilon''$ ) with a calculated dependence obtained using an arbitrary distribution function. The distribution function is refined by taking into account the error obtained and the iterative procedure is repeated until coincidence of the calculated and experimental data. Of course, the method requires *a priori* knowledge of the form of the distribution function; otherwise, a problem of uniqueness of the results obtained is posed.

Except for the authors of Refs 262 and 263, researchers are inclined to believe that only a continuous relaxation spectrum has physical meaning. In this case the relaxation spectrum can serve for characterisation of both the topological structure and the specific features of macromolecular dynamics. Discretisation can be arbitrary, being no more than a trick for computations. But here, first, it remains unclear how this inference can be related to the results of calculations of the models, which either directly or indirectly lead to the concept of a discrete relaxation spectrum. Second, a comparison of the continuous relaxation spectra shown in Figs 17 and 18 reveals ambiguity in the results of calculations. Therefore, one has to conclude that attempts at calculating a discrete relaxation spectrum (at least most of those considered above) failed.

Unfortunately, it is impossible to put forward a criterion for 'correctness' of a relaxation spectrum, because it can be determined if the condition for coincidence of the calculated and experimental data for  $g(t)$  or  $G^*(\omega)$  with certain accuracy is met. This inevitably means fulfillment of rheological characteristics, because the stress tensor components  $\sigma_{ij}$  are related to the relaxation function  $g(t)$  (see Ref. 4)

$$\sigma_{12} = \sigma_{21} = \dot{\gamma} \int_0^t g(t - t_1) dt_1,$$

$$\sigma_{11} - \sigma_{22} = 2\dot{\gamma}^2 \int_0^t (t - t_1) \cdot g(t - t_1) dt_1,$$

where  $\dot{\gamma}$  is the shear rate.

We believe that discussion of relaxation spectrum calculations concerns in fact two independent problems. One of them is concerned with the physical correctness of the mathematical models describing interrelations between viscoelastic characteristics and based on the concept of a relaxation spectrum. The other problem is to develop a corresponding mathematically correct formalism. Of course, it is irrational to criticise and reject a convenient fundamental concept of the relaxation spectrum on the basis of non-reliable results of spectrum reconstruction obtained in the framework of (mathematically) unstable models. Therefore, in the text below we will consider a stable method of calculation of a relaxation spectrum.

### 3. Stable method of calculation of a relaxation spectrum. The relaxation times distribution function

An approach<sup>264, 265</sup> to the representation of a relaxation spectrum using the distribution functions<sup>266</sup> and Stieltjes integral<sup>267</sup> provides an alternative to the methods considered above. Let  $P(\lambda)$  denote the integrated intensity of a relaxation spectrum. Then, the functions  $g(t)$  and  $G(\omega)$  can be expressed via the Stieltjes integral with respect to  $P(\lambda)$

$$g(t) = \int_0^\infty \exp\left(-\frac{t}{\lambda}\right) dP(\lambda), \quad (32)$$

$$G(\omega) = \int_0^\infty \frac{i\omega\lambda}{1 + i\omega\lambda} dP(\lambda). \quad (33)$$

A discrete relaxation spectrum corresponds to a step distribution function

$$P(\lambda) = \sum_{k=1}^N h_k \chi(\lambda - \lambda_k), \quad (34)$$

where  $\chi$  is the Heaviside step function. A continuous relaxation spectrum corresponds to the distribution function given by

$$P(\lambda) = \int_0^\lambda h(\xi) d\xi \quad (35)$$

( $\xi$  is the integration variable), i.e.,  $P(\lambda)$  is an antiderivative of the density  $h(\lambda)$ .

The problem of uniqueness of the function  $P(\lambda)$  and stability of  $P(\lambda)$  to perturbations in  $g(t)$  and  $G^*(\omega)$  has been studied.<sup>265</sup> In constructing  $P(\lambda)$  from the kinetic function  $g(t)$  (the procedure for relaxation spectrum reconstruction in the frequency domain differs insignificantly) it was shown that uniqueness of  $P(\lambda)$  follows from one-to-one reversibility of the Laplace transform. The notion of stability was formulated in terms of the weak convergence of monotonic functions in the positive semiaxis  $R_+$  as the following continuity principle.<sup>267, 268</sup>

Let  $g_n, P_n$  ( $n = 1, 2, \dots$ ),  $g, P$  be a sequence of kinetic curves and corresponding distribution functions. Then convergence  $g_n(t) \rightarrow g(t)$  at any  $0 \leq t < \infty$  is equivalent to weak convergence  $P_n \Rightarrow P$  in  $R_+$ .

This statement was proved<sup>265</sup> by combining the Helly selection principle for a converging subsequence of monotonic functions and the property of uniqueness.

The properties of uniqueness and continuity mean that a problem inverse to problem (35) with respect to  $P(\lambda)$  rather than  $h(\lambda)$  is well-posed and solution to this problem does not require application of a regularisation technique.

The development of a method of stable reconstruction of  $P(\lambda)$  from approximate values of the kinetic and frequency moduli required introduction of the notion of a generalised solution as a

solution to the problem of error functional minimisation. In the simplest case (quadratic functional) the procedure involves solution of the following problems

$$\int_T v(t) \left[ \int_0^\infty \exp\left(-\frac{t}{\lambda}\right) dP(\lambda) - g(t) \right]^2 dt \rightarrow \min, \quad (36)$$

$$\int_\Omega \mu(\omega) \left[ \int_0^\infty \frac{i\omega\lambda}{1 + i\omega\lambda} dP(\lambda) - G(\omega) \right]^2 d\omega \rightarrow \min, \quad (37)$$

where  $v(t)$  and  $\mu(\omega)$  are some non-negative weighting functions, which determine the error functional, and  $T$  and  $\Omega$  are respectively the domains in which the experimentally measured  $g(t)$  and  $G(\omega)$  functions are defined. The search for a minimum is carried out in the class of all distribution functions.

A solution  $P(\lambda)$  to problems (36) and (37) is called an optimum integral representation (OIR) of the corresponding functions of the kinetic or frequency moduli. In setting these problems it is possible to impose, without significant complication, various constraints that allow for the *a priori* information on the relaxation spectrum. The choice of the weighting functions is free, being governed by the *a priori* knowledge of the distribution of experimental errors. For instance, it is appropriate to use the coefficients  $v(t)$  and  $\mu(\omega)$  for relatively narrow (2–3 decades) ranges of changes in  $t$  and  $\omega$ , respectively. The choice of the  $v(t) = t^{-1}$  and  $\mu(\omega) = \omega^{-1}$  weighting functions provides a logarithmically uniform error functional, which can naturally be used in treatment of data characterised by a broad range of changes in  $t, \omega$  (more than four decades). The properties of existence, uniqueness and stability of OIR have been proved.<sup>264</sup> It was found that the over stability is unexpectedly high, namely, the OIR is stable to both integrally small errors of the functions  $g(t)$  and  $G(\omega)$  and to white noise of finite amplitude superimposed on these functions. All the results are also valid for a more general combined error functional, which permits reconstruction of  $P(\lambda)$  from the real and imaginary components of  $G(\omega)$  or from their combination.

Numerical implementation of this method requires a finite set of measuring times  $\{t_j\}, j = 1, \dots, n$ . When a continuous problem is discretised by introducing a grid with a fixed arrangement of nodes  $\{\lambda_i\}, i = 1, \dots, m$ , the desired distribution function is approximated by the step function

$$P(\lambda) = \sum_{i=1}^m h_i \chi(\lambda - \lambda_i), \quad (38)$$

where  $h = \{h_i\}, i = 1, \dots, m$  is the set of unknown non-negative coefficients. Application of some linear quadrature formulae to the outer integrals in expressions (36) and (37) gives the following discrete analogues, respectively

$$\sum_{j=1}^n v_j \left[ \sum_{k=1}^m \exp\left(-\frac{t_j}{\lambda_k}\right) h_k - g(t_j) \right]^2 \rightarrow \min, \quad h \geq 0, \quad (39)$$

$$\sum_{j=1}^n \mu_j \left[ \sum_{k=1}^m \frac{i\omega_j \lambda_k}{1 + i\omega_j \lambda_k} h_k - G(\omega_j) \right]^2 \rightarrow \min, \quad h \geq 0. \quad (40)$$

Here  $v_j, \mu_j$  is a set of positive weighting coefficients determined by the totalities of the nodes  $\{t_j\}$  and  $\{\omega_j\}$ . These coefficients are included in the quadrature scheme. For instance, constant weighting coefficients are obtained when the rectangle formula is applied to uniformly distributed nodes at  $v(t) = 1, \mu(\omega) = 1$  or to logarithmically uniformly distributed nodes at  $v(t) = t^{-1}, \mu(\omega) = \omega^{-1}$ .

Problems (39) and (40) are solved by the quadratic programming technique using some efficient finite-step algorithms incorporated into standard mathematical software (MAPLE, MATLAB) and FORTRAN libraries (IMSL, CXML), including the non-negative least squares method algorithm NNLS.<sup>269</sup> Some

difficulties in numerical solution can arise from the high dimensions of these problems ( $m$  and  $n$  can be of the order of several hundreds); good approximation of initial continuous problems (36) and (37) by discrete analogues requires about 10 to 30 nodes ( $t_j, \omega_j, \lambda_k$ ) per decade of corresponding range.

When a relaxation spectrum is reconstructed from model and experimental data, the experimental and calculated grid patterns have no effect on the quality of the solution, only the node density is significant. Different grid patterns require calculations of different sets of weights. The resulting antiderivative step distribution function  $P(\lambda)$  coincides with an accuracy determined by the grid densities and errors in  $g(t)$  and  $G(\omega)$ . Non-uniqueness of the solution (this is possible at  $m > n$ ) is of no concern because any set of the parameters  $h$ , at which minima of expressions (39) and (40) are reached, gives an equivalent approximation of the relaxation spectrum distribution.

Because the relaxation spectrum distribution functions reconstructed by this method are only stable in a specific 'weak' sense, it is appropriate to mention those characteristics of the relaxation spectrum that are related to this kind of stability. By definition of weak continuity, stable are linear integral average distribution functions of the type

$$\int_{R_+} f(\lambda) dP(\lambda),$$

where  $f(\lambda)$  is some continuous averaging function. A particular case of averaging is provided by the moments for which  $f(\lambda) = \lambda^n$ . The plot of the distribution function is stable in the sense mentioned above, namely, as 'entire geometric figure'. On the contrary, local numerical characteristics, in particular, the density  $h(\lambda) = dP(\lambda)/d\lambda$ , are unstable. Conversion of a discrete relaxation spectrum into the density function by direct interpolation of a comb-like plot of  $\delta$ -functions does not lead to 'weak stability', as was postulated by Winter.<sup>141</sup> A correct smoothing of arbitrary, in particular, discrete relaxation spectra requires an integral averaging over one or another kernel.

The working efficiency of this method was exemplified<sup>265</sup> by reconstructing the relaxation spectrum of an oligomeric nonuniform Rouse chain,<sup>214,215</sup> a continuous BSW-spectrum<sup>141</sup> and the frequency modulus of polystyrene from experimental data.<sup>234</sup>

A model example of relaxation spectrum reconstruction from the relaxation kinetics of the length of an equidistant chain containing  $n = 6$  nonuniform units involved calculations of the frequency dependence of the relaxation modulus  $G^*(\omega)$  using relationship (2). Noise produced by a software generator of evenly distributed random numbers was applied at the calculated  $(t, \omega)$

nodes, the noise intensity,  $\varepsilon$ , being equal to  $10^{-2}$  and  $10^{-3}$  of the corresponding amplitude. The calculated  $h_i$  and  $\lambda_i$  coefficients and the corresponding moments

$$\mu_k = \int \lambda^k dP(\lambda)$$

for  $k = 0, 1, 2$  are listed in Table 11. Simulation of experimental data was carried out using  $n = 300$  logarithmically uniform time values and frequencies in the ranges  $t \in [10^{-4} \text{ and } 10^3]$   $\omega \in [10^{-1}, 10^5]$ , respectively, and the spectrum reconstruction was performed following the scheme given by expressions (39) and (40) on a logarithmically uniform grid containing  $m = 400$  nodes in the range  $\lambda \in [10^{-2}, 10^2]$ .

Analysis of the data listed in Table 11 showed that the relaxation spectrum reconstructed from  $G$  is more similar to the exact spectrum than the relaxation spectrum reconstructed from the  $g$  data. As noise ( $\varepsilon$  value) decreases, the accuracy of the calculations increase. Although the calculated relaxation spectrum is somewhat different from the theoretical spectrum, in all cases the moments coincide excellently.

Yet another example involved the relaxation spectrum reconstruction from the frequency-dependent stress relaxation modulus determined in a series of experiments.<sup>234</sup> Data for monodisperse polystyrene with  $M = 3 \times 10^6$  were analysed using a complex data array ( $n = 44$ ). Calculations following scheme (40) involved a logarithmically uniform grid with  $m = 400$  in the range  $\lambda \in [10^{-5}, 10^4]$ .

A discrete relaxation spectrum reconstructed using the OIR technique is shown in Fig. 19. Experimental data were fitted to the theoretical curve  $G(\omega)$  calculated after reconstruction with a quadratic error of about 1% (see Fig. 19a). In Fig. 19 the OIR and IRIS reconstructed plots are superimposed. The errors in the approximation of the frequency-dependent relaxation moduli in both reconstructed relaxation spectra are similar (with respect to the order of magnitude), but the error of the OIR method is 'random' while the plot of the error of the IRIS procedure clearly exhibits systematic 'waves' (see Fig. 19b). The plots of the distribution functions in Fig. 19d are parallel in the range  $\lambda \in [10^{-4}, 10^1]$ . In this case a parallel shift of the distribution functions owing to initial jumps indicates a significant discrepancy between the reconstructions, which is due to insufficient width of the data window in the high-frequency region.

Thus, in the intermediate range the OIR and IRIS reconstructed relaxation spectra are similar in terms of the distribution functions, although the parameters of individual lines are appreciably different (see Fig. 19c).

**Table 11.** Parameters of the relaxation spectrum of a modified Rouse chain calculated using the OIR technique ( $\lambda$  in arbitrary units).

| Exact spectrum <sup>a</sup> |                         | $\varepsilon = 0.01$                   |                         |                                             |                         | $\varepsilon = 0.001$                  |                         |                                             |                         |
|-----------------------------|-------------------------|----------------------------------------|-------------------------|---------------------------------------------|-------------------------|----------------------------------------|-------------------------|---------------------------------------------|-------------------------|
|                             |                         | reconstructed from $g(t)$ <sup>b</sup> |                         | reconstructed from $G(\omega)$ <sup>c</sup> |                         | reconstructed from $g(t)$ <sup>d</sup> |                         | reconstructed from $G(\omega)$ <sup>e</sup> |                         |
| $\lambda$                   | $h(\lambda)$            | $\lambda$                              | $h(\lambda)$            | $\lambda$                                   | $h(\lambda)$            | $\lambda$                              | $h(\lambda)$            | $\lambda$                                   | $h(\lambda)$            |
| $0.5586 \times 10^0$        | $0.2287 \times 10^{-1}$ | $0.4281 \times 10^{-1}$                | $0.5865 \times 10^{-3}$ | $0.5813 \times 10^0$                        | $0.2637 \times 10^{-1}$ | $0.1000 \times 10^{-1}$                | $0.8093 \times 10^{-4}$ | $0.6088 \times 10^0$                        | $0.1699 \times 10^{-1}$ |
| $0.1068 \times 10^1$        | $0.1409 \times 10^{-1}$ | $0.9439 \times 10^0$                   | $0.1910 \times 10^{-1}$ | $0.5949 \times 10^0$                        | $0.1432 \times 10^{-2}$ | $0.5813 \times 10^0$                   | $0.7610 \times 10^{-2}$ | $0.6230 \times 10^0$                        | $0.1268 \times 10^{-1}$ |
| $0.1671 \times 10^1$        | $0.3533 \times 10^{-1}$ | $0.9660 \times 10^0$                   | $0.4656 \times 10^{-1}$ | $0.1643 \times 10^1$                        | $0.1376 \times 10^{-1}$ | $0.5949 \times 10^0$                   | $0.1872 \times 10^{-1}$ | $0.1568 \times 10^1$                        | $0.6310 \times 10^{-3}$ |
| $0.3165 \times 10^1$        | $0.9069 \times 10^{-2}$ | $0.1760 \times 10^1$                   | $0.1874 \times 10^{-2}$ | $0.1681 \times 10^1$                        | $0.3862 \times 10^{-1}$ | $0.1464 \times 10^1$                   | $0.8293 \times 10^{-2}$ | $0.1605 \times 10^1$                        | $0.3941 \times 10^{-1}$ |
| $0.1087 \times 10^2$        | $0.4186 \times 10^0$    | $0.1041 \times 10^2$                   | $0.4172 \times 10^0$    | $0.1065 \times 10^2$                        | $0.1047 \times 10^{-1}$ | $0.1498 \times 10^1$                   | $0.3593 \times 10^{-1}$ | $0.2547 \times 10^1$                        | $0.9668 \times 10^{-2}$ |
|                             |                         | $0.1066 \times 10^2$                   | $0.1067 \times 10^{-1}$ | $0.1090 \times 10^2$                        | $0.4086 \times 10^0$    | $0.3360 \times 10^1$                   | $0.1036 \times 10^{-1}$ | $0.2606 \times 10^1$                        | $0.9614 \times 10^{-3}$ |
|                             |                         | $0.1000 \times 10^3$                   | $0.3831 \times 10^{-2}$ | $0.1000 \times 10^3$                        | $0.1176 \times 10^{-2}$ | $0.3438 \times 10^1$                   | $0.7915 \times 10^{-3}$ | $0.1065 \times 10^2$                        | $0.8226 \times 10^{-1}$ |
|                             |                         |                                        |                         |                                             |                         | $0.1066 \times 10^2$                   | $0.5521 \times 10^{-1}$ | $0.1090 \times 10^2$                        | $0.3374 \times 10^0$    |
|                             |                         |                                        |                         |                                             |                         | $0.1090 \times 10^2$                   | $0.3630 \times 10^0$    | $0.8910 \times 10^2$                        | $0.7645 \times 10^{-6}$ |
|                             |                         |                                        |                         |                                             |                         |                                        |                         | $0.9118 \times 10^2$                        | $0.3044 \times 10^{-4}$ |

<sup>a</sup>  $\mu_0 = 0.5$ ,  $\mu_1 = 4.666$ ,  $\mu_2 = 49.67$ ; <sup>b</sup>  $\mu_0 = 0.4998$ ,  $\mu_1 = 4.907$ ,  $\mu_2 = 84.82$ ; <sup>c</sup>  $\mu_0 = 0.5004$ ,  $\mu_1 = 4.788$ ,  $\mu_2 = 61.69$ ; <sup>d</sup>  $\mu_0 = 0.5$ ,  $\mu_1 = 4.665$ ,  $\mu_2 = 49.66$ ;

<sup>e</sup>  $\mu_0 = 0.5$ ,  $\mu_1 = 4.668$ ,  $\mu_2 = 49.9$ .

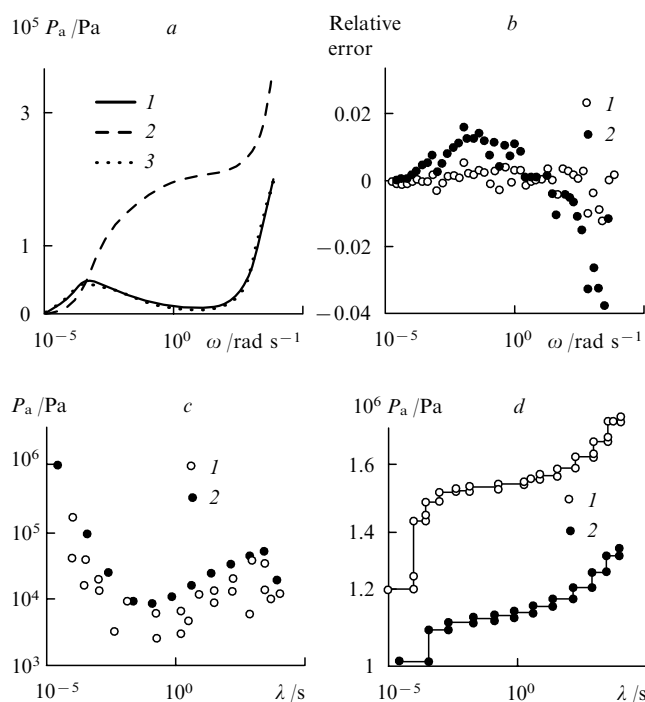


**Figure 19.** Relaxation spectrum of monodisperse polystyrene with  $M = 3 \times 10^6$  reconstructed from the complex frequency modulus  $G(\omega)$  using the data taken from Ref. 50.

(a) Experimental  $G'(\omega)$ ,  $G''(\omega)$  curves (1) and the corresponding calculated curves (2, 3); (b) relative errors in approximation  $G'(\omega)$ : error in OIR reconstruction (1), error in IRIS reconstruction (2); (c) reconstructed discrete relaxation spectrum: the OIR spectrum (1) and the IRIS spectrum (2); (d) distribution functions of reconstructed discrete relaxation spectra: the OIR spectrum (1) and the IRIS spectrum (2) (data were taken from Ref. 265).

The Stieltjes OIR theory provides an explanation for similarity of integral characteristics of seemingly distinct results obtained using different versions of relaxation spectrum reconstructions. Consistency occurs if these results are quite well approximated by experimental data and meet the condition of belonging to a 'convex local weakly compact set', which can be separated out by, e.g., a simple non-negativity condition. In accord with the OIR theory in this case the relaxation spectrum will be similar to the exact spectrum in terms of distribution functions, irrespective of the procedure employed to obtain the spectrum.

It should also be noted that representation of the relaxation spectrum in the form of integral distribution function  $P(\lambda)$  eliminates the problem of non-uniqueness of such a representation. Examples given in Ref. 265 show that seemingly different relaxation spectra give almost the same function  $P(\lambda)$ . Probably, this is the reason why experimental data are 'insensitive' to the local shape of the relaxation spectrum, as was shown in many studies and summarised in a review.<sup>226</sup>

The OIR technique makes it possible to determine stable values of the moments (as well as any integral characteristic) of a relaxation spectrum. Local characteristics of the relaxation spectrum, in particular, the limiting relaxation times, are unstable and of little informativity. Therefore, the dependence of the maximum relaxation time on the procedure for relaxation spectrum reconstruction<sup>226, 229</sup> is insignificant because the relaxation properties are determined by the distribution moments, which are highly stable characteristics.

At the same time this mathematical approach allows experimental methods of determination of relaxation spectra of polymers to be divided into methods producing artifacts and those providing rational results. Formally, the problem of minimisation of an error functional on the class of monotonic distribution

functions always has a unique solution, i.e., the OIR. By definition the resulting spectrum provides the best plausible explanation for experimental data when using a linear model with a non-negative relaxation spectrum, which has a physical meaning and is related to the polymer structure. But in linear theory one can face a problem of sign-alternating expansion of the viscoelastic functions in terms of exponential modes. This is indicated by the impossibility of correctly (with an accuracy to noise) reproducing the experimental dependences,  $g(t)$  and  $G(\omega)$ , using the OIR found. For instance, if in the chain retraction problem considered above the initial state of the chain is not equidistant, it is impossible to obtain a non-negative relaxation spectrum reproducing the model relaxation because some pre-exponents in expression (1) are negative. This shows that determination of a relaxation spectrum as a characteristic of the polymer structure requires a particular experimental design.<sup>225</sup> It is known that relaxation of a Rouse chain under stress and strain gives somewhat different relaxation spectra (see Ref. 33 and Fig. 10). Apparently, this is due to the fact that the polymer structure manifests itself indirectly if the entire chain moves (therefore the relaxation spectrum depends on the character of chain motion). This is clearly seen when comparing the Rouse and Doi–Edwards models.<sup>33</sup>

Thus, the problem of reconstruction of a monotonic relaxation time distribution function from the kinetic curve or frequency modulus is mathematically correct. But it should be interpreted in the framework of the OIR method rather than traditional methods for fitting a set of parameters of a point spectrum or as a solution of an integral equation of the first kind with respect to the density function of a continuous spectrum.

Summing up, the method<sup>264, 265</sup> of calculation of relaxation spectra is characterised by the following features.

The accuracies of reconstruction of the relaxation spectrum distribution function and any integral average characteristics of this distribution function are only limited by the systematic error and the 'density' of experimental data.

Theoretically, the OIR technique allows a relaxation spectrum to be reconstructed with arbitrary accuracy from a set of kinetic or frequency data obtained in any range. However, when narrowing such ranges, one should significantly improve the accuracy of data and the size of the data array.

Reliable reconstruction of the relaxation spectrum requires that the experimental data window be wider than the interval in which the relaxation spectrum is located (by 1–2 orders of magnitude for the 'kinetic' reconstruction and by 3–4 orders of magnitude for the 'frequency' reconstruction). Otherwise the distribution function can be determined with an accuracy of the initial jump, the local structure of which is not informative, and the accuracy of determination of moments decreases abruptly.

Statements that the relaxation spectrum is a fiction are senseless, because they are based on mathematically incorrect formalisms for both discrete and continuous descriptions. Of course, stable OIR mathematical formalism for reconstruction of relaxation spectra from the data of dynamical experiments does not mean that the relaxation spectrum is a physical reality. However, this approach makes revision of the results of relaxation experiments on the basis of stable interpretation of the relaxation spectrum in terms of distribution functions, aimed at establishing the applicability range of the notion of a relaxation spectrum as a fundamental characteristic and its relation to the polymer structure, promising and topical.

#### 4. Manifestation of topological structure in relaxation spectra

Interrelations between the relaxation behaviour and topological structure of polymers have been well documented (see Section III). However, information on immediate relations between the relaxation spectrum and parameters of topological structure is scarce. The reason is quite understandable, that is, ambiguity of calcu-



lations (see Section IV.2). Nevertheless, a little body of data are available.

First of all mention may be made of the studies of the BSW spectra and of the studies carried out by Winter *et al.*<sup>57, 83, 138–141, 152, 172, 228, 234, 250, 251, 270</sup>

The dependence of the characters of the BSW spectra on the molecular masses of the monodisperse polymers [see relationship (31) and Fig. 17] is determined by two parameters,  $\lambda_{\max}$  and  $\lambda_1$ . The former parameter is related to  $M$  by a conventional expression

$$\lambda_{\max} = KM^a,$$

or, according to Ref. 56,

$$\lambda_{\max} = \lambda_c \left( \frac{M}{M_c} \right)^a.$$

The  $\lambda_{\max}/\lambda_c$  ratio determines the extension of the rubbery plateau zone, the physical meaning of  $M_c$  is similar to that of  $M_e$ . Correspondingly,  $\lambda_1$  is defined by

$$\lambda_1 = \lambda_c \left( \frac{M}{M_c} \right)^{an_c/(n_c+n_g)}.$$

The numerical values of the parameters of the BSW spectra of polystyrene and polybutadiene listed in Table 12 were taken from Refs 57 and 83.

**Table 12.** Numerical values of parameters of the BSW spectra of polystyrene and polybutadiene.

| Parameter            | Polystyrene        | Polybutadiene         |
|----------------------|--------------------|-----------------------|
| $G_N^0/\text{Pa}$    | $2.28 \times 10^5$ | $1.65 \times 10^6$    |
| $n_c$                | 0.23               | 0.23                  |
| $n_g$                | 0.67               | 0.73                  |
| $\lambda_c/\text{s}$ | $2 \times 10^{-4}$ | $4.04 \times 10^{-7}$ |
| $M_c$                | $1.66 \times 10^4$ | $2.714 \times 10^3$   |
| $a$                  | 3.43               | 3.52                  |
| $T/^\circ\text{C}$   | 180                | 28                    |

Based on the results of studies of monodisperse polystyrene/monodisperse polybutadiene binary blends,<sup>83, 234</sup> it was concluded that the resulting relaxation spectrum can be expressed as follows

$$H(\lambda) = \sum_i B_i H_i \left( \frac{\lambda}{A_i} \right),$$

where

$$\sum_i B_i = 1, B_2 = w_2^2 + aw_1w_2, a \approx 0.1,$$

if the molecular masses of the components differ insignificantly and  $w_i$  is the mass proportion of the fraction. The  $A_i$  coefficients weakly depend on the blend composition. They are related to the molecular masses of the components, namely,  $A_i = \lambda_{\max, i, b}/\lambda_{\max, i}$  is the ratio of the maximum relaxation times of the blend component and of the homopolymer.

Clearly, this ratio is inconsistent with the postulated<sup>34, 271</sup> additivity with respect to relaxation times.

However, it should be noted that the relaxation spectrum of a blend, calculated by the EPR method,<sup>252</sup> has little in common with the BSW spectrum, although for monodisperse polymers both methods, EPR and IRIS, give identical relaxation spectra (see above).

When establishing relations between the relaxation properties and MMD of polymers, the dependences of relaxation times on the molecular mass are often considered. If the case in point is the dependence of  $\lambda_{\max}$  or any other average characteristic (*e.g.*,  $\langle \lambda \rangle_w$ ) on the molecular mass of the type  $\lambda_{\max} \sim M^a$ , this is quite understandable. But some authors (see, *e.g.*, Refs 104, 258, 271–273) assume this dependence for each relaxation time in the relaxation spectrum and simply use the function  $h(M^a)$  instead of  $h(\lambda)$ . It can be shown with ease, taking, *e.g.*, the Rouse relaxation spectrum as a simple example, that this replacement is incorrect because a change in the chain length first of all leads to a change in the number of modes.

Studies of star-branched polymers<sup>251</sup> revealed a much more complicated form of the BSW spectrum compared to the spectrum described by the equation of the type (31). Namely, it was found that expression (31) should be augmented with the following term

$$n_0 G_0 \left( \frac{\lambda}{\lambda_0} \right)^{n_0} \exp \left( \frac{\lambda}{\lambda_0} \right)^\beta.$$

The relaxation parameters of the (thus) modified BSW spectra of various star-branched polybutadienes of regular structure are listed in Table 13. Within the limits of experimental error, the parameters  $G_N^0$ ,  $H_g$  and  $\lambda_c$  can be considered independent of the molecular mass and the number of arms, whereas the parameters  $G_0$ ,  $\lambda_{\max}$  and  $\lambda_1$  seem to be stronger dependent on the molecular mass rather than the number of arms. The  $\lambda_0$  parameter is affected by both structural characteristics. The authors of Ref. 251 believed that these results are consistent with theoretical concepts.<sup>274, 275</sup> However, the available data are insufficient for making quantitative estimates.

Analysis of the relaxation spectra calculated by the OIR technique is also based on a very small amount of data<sup>276, 277</sup> because the problem, as applied to polymers, was formulated only recently.<sup>264, 265</sup>

Figure 20 presents the relaxation spectra of polymers in terms of the integral distribution functions, which were reconstructed using the OIR technique and the data taken from Ref. 50. In this connection a problem is posed by the methods for comparison and, hence, quantitative characterisation of distribution func-

**Table 13.** Numerical values of parameters of the relaxation spectra of star-branched polybutadienes (for all polymers,  $n_g = 0.67$ ,  $n_c = 0.30$  and  $\beta$  lies between 0.8 and 1).<sup>251</sup>

| Number of arms       | $10^{-3} M_a$ | $G_N^0/\text{MPa}$ | $\lambda_c/\text{s}$ | $10^{-4} \lambda_{\max}/\text{s}$ | $\lambda_1/\text{s}$ | $H_g/\text{MPa}$ | $10^3 G_0/\text{MPa}$ | $10^{-6} \lambda_0/\text{s}$ |
|----------------------|---------------|--------------------|----------------------|-----------------------------------|----------------------|------------------|-----------------------|------------------------------|
| Linear polybutadiene | 155           | 1.65               | 0.86                 | 90                                | 40.5                 | 0.49             | —                     | —                            |
| 4                    | 11.25         | 2.19               | 0.55                 | 0.4                               | 8.61                 | 0.66             | —                     | —                            |
| 62                   | 6.3           | 2.51               | 0.37                 | 0.015                             | 2.38                 | 0.75             | 6.08                  | 0.0065                       |
| 64                   | 23.9          | 2.00               | 0.53                 | 0.75                              | 10.2                 | 0.59             | 17.8                  | 0.55                         |
| 124                  | 6.8           | 2.51               | 0.37                 | 0.015                             | 2.38                 | 0.75             | 6.08                  | 0.0305                       |
| 125                  | 13            | 2.72               | 0.54                 | 0.3                               | 7.75                 | 0.82             | 1.48                  | 0.6                          |
| 114                  | 26.1          | 2.05               | 0.66                 | 2.5                               | 17.4                 | 0.62             | 0.89                  | 4.92                         |
| 127                  | 47            | 1.66               | 1.00                 | 5.4                               | 25.5                 | 0.49             | 11.2                  | 13.2                         |

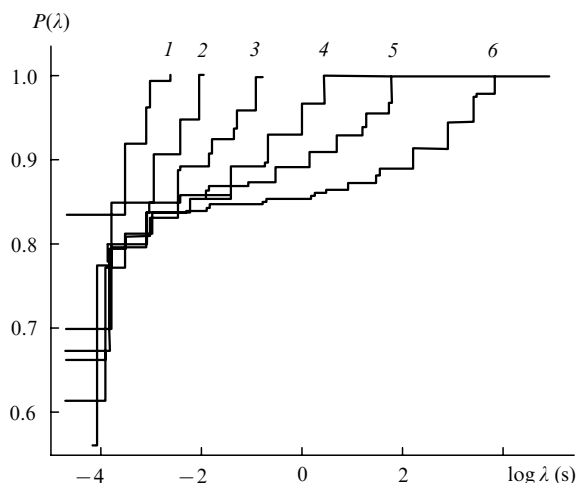


**Figure 20.** Relaxation spectra of monodisperse polystyrene-based polymers plotted in the form of distribution functions  $P(\lambda)$  using the data taken from Ref. 50.

$M \times 10^{-3} = 39$  (1), 70 (2), 128 (3), 275 (4), 770 (5) and 3000 (6).

tions. The most obvious is the method of central moments,<sup>278</sup> which in the case of the Stieltjes integral are defined by

$$\mu_k(\lambda) = \int (\lambda - \langle \lambda \rangle)^k dP(\lambda),$$

where  $\langle \lambda \rangle$  is the arithmetic mean of a random quantity  $\lambda$ . A set of appropriate characteristics includes the dispersion  $\sigma = (\mu_2)^{1/2}$ , asymmetry (skewness)  $\gamma_1 = \mu_3/\sigma^3$  and excess  $\gamma_2 = \mu_4/\sigma^4 - 3$ . Corresponding characteristics of the distribution functions shown in Fig. 20 are listed in Table 14. As can be seen, the average relaxation times and dispersions depend on the molecular mass (see also Table 1), whereas the asymmetry and excess show no dependence within the limits of data scatter. Therefore, one can state that the relaxation spectra of monodisperse polymers with different molecular masses, expressed in terms of the distribution function  $P(\lambda)$ , are similar.

The data listed in Table 15 show that the MMD of polymers affects their relaxation spectra. This manifests itself not only in the average and maximum relaxation times and dispersion but also in the  $\gamma_1$  and  $\gamma_2$  values (relaxation spectra were constructed using the OIR technique and the results reported by Watanabe and Kotaka<sup>67</sup>). A comparison with various polymer blends showed that the additivity principle is not valid for at least one binary blend (molecular masses were  $4.27 \times 10^5$  and  $3.89 \times 10^4$ ). Namely, the maximum relaxation time was composition independent; correspondingly, the dispersion was much larger than the value characteristic of the polymer blend.

**Table 14.** Characteristics of the distribution functions  $P(\lambda)$  for monodisperse polystyrene-based polymers having different molecular masses.

| $M$       | $\langle \lambda \rangle_n / s$ | $\langle \lambda \rangle_w / s$ | $\sigma$               | $\gamma_1$ | $\gamma_2$            |
|-----------|---------------------------------|---------------------------------|------------------------|------------|-----------------------|
| 3 000 000 | 2070                            | 20750                           | 31200                  | 1.34       | -0.181                |
| 770 000   | 19.93                           | 56.05                           | 32.01                  | 1.702      | 4.566                 |
| 275 000   | 0.916                           | 3.245                           | 4.326                  | 2.807      | 6.387                 |
| 128 000   | 0.0465                          | 0.09115                         | 0.0379                 | -0.984     | -0.707                |
| 70 000    | 0.0045                          | 0.00706                         | 0.0029                 | -0.965     | -0.776                |
| 39 000    | $9.456 \times 10^{-4}$          | $6.32 \times 10^{-4}$           | $1.423 \times 10^{-4}$ | 0.834      | $6.57 \times 10^{-4}$ |

This is qualitatively consistent with the conclusions drawn in another study.<sup>83</sup> Unfortunately, data for quantitative characterisation are insufficient. Nevertheless, it is clear that representation of a relaxation spectrum in the form of the distribution function  $P(\lambda)$  can serve as a reliable basis for establishment of interrelation between the relaxation spectrum and the topological structure of the polymer. This research avenue requires intensive development.

## V. Conclusion

Many researchers have put forward the idea of using the relaxation properties of a polymer for non-destructive quantitative characterisation of topological structure. This first of all concerns the MMD as the key structural parameter of high-molecular-mass compounds.<sup>31–33</sup> However, experience showed that the use of the relaxation curves leads to incorrect conclusions, because these methods are based on quite different and arbitrary mixing rules.<sup>83</sup> We believe that it would be more appropriate to use the relaxation spectrum, because it is obviously related to the polymer structure. Indeed, '...a normalised relaxation spectrum is a replica of the shape of the MMD curve'.<sup>243</sup> Here, two problems arise, namely, (i) calculations of relaxation spectra from relaxation data and (ii) establishment of a relation between the relaxation spectrum and the polymer structure.

In this review we tried to show some ways of attacking these problems. The OIR technique provides a means of stable calculations of relaxation spectra in the form of the distribution function  $P(\lambda)$ , which in turn serves as a reliable basis for the establishment of correlations between the relaxation spectrum and the polymer structure.

This approach seems to be not unique. For instance, the Havriliak–Negami equation (see above) is related<sup>177,243</sup> to the empirical relaxation spectrum, which is based on the Cole–Cole model.<sup>279</sup> The spectral parameters thus obtained correlate with the MMDs of some polyethylenes.<sup>243</sup> Probably, other characteristics of the topological structure can also be extracted from this type of relaxation spectra.

Nearly five decades ago G L Slonimskii put forward a basically different approach to analysis of the relaxation properties of polymers.<sup>280</sup> The method involves expression of the

**Table 15.** Characteristics of the distribution functions  $P(\lambda)$  for bidisperse polystyrene blends (processed data taken from Ref. 67).

| $w_2$   | $\lambda_{\max} / s$ | $\langle \lambda \rangle_n / s$ | $\langle \lambda \rangle_w / s$ | $\sigma$ | $\gamma_1$ | $\gamma_2$ |
|---------|----------------------|---------------------------------|---------------------------------|----------|------------|------------|
| 1.0     | > 10000              | 1.91                            | 8708                            | 129      | 77.5       | 6010       |
| 0.4     | 10000                | 9.54                            | 4455                            | 206      | 47.9       | 2322       |
| 0.2     | 21.5                 | 0.0408                          | 9.895                           | 0.634    | 33.7       | 791.15     |
| 0.1     | 13.6                 | 0.0113                          | 6.028                           | 0.261    | 157.9      | 2228       |
| 0.05    | 12.4                 | 0.0050                          | 2.263                           | 0.1065   | 1718       | 4951       |
| 0.01    | 11.3                 | 0.0025                          | 1.196                           | 0.0546   | 12450      | 36500      |
| 0       | 0.022                | 0.0020                          | 0.0112                          | 0.0043   | 3.34       | 11.9       |
| 0.4 add | 10000                | 3.95                            | 4609                            | 134.9    | 73.3       | 5429.5     |
| 0.2 add | 10000                | 1.97                            | 4620                            | 95.38    | 103.7      | 10861      |
| 0.1 add | 10000                | 1.15                            | 5262                            | 77.78    | 127.5      | 16381      |

relaxation relations between stress  $\sigma$  and strain  $\varepsilon$  using fractional derivatives

$$\sigma(t) = E\lambda^\alpha \frac{d^\alpha \varepsilon(t)}{dt^\alpha}, 0 \leq \alpha \leq 1.$$

At  $\alpha = 0$ , one gets an equation for the Hooke model (pure elasticity) while the equation derived at  $\alpha = 1$  describes a Newtonian flow.

However, attempts at using this approach in studies of particular systems (see, e.g., Ref. 281) have been undertaken only recently. Clearly, in this case we deal with quite a new view of the mathematical formalism and physical meaning of the relaxation spectrum. Here, one must keep in mind that ‘... if modelling is intended to understand or to discover new phenomena, the exact mathematical model should be sufficiently sophisticated, especially when several branches of solutions have different physical meanings. Hence, the study of a sophisticated exact inverse problem may be not only a pure mathematical research but also an applied one, where interactions between ways of modelling and inverse theory are essential’.<sup>282</sup>

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<sup>g</sup> — *Russ. J. Phys. Chem. (Engl. Transl.)*

# Microwave irradiation in organic synthesis

N N Romanova, A G Gravis, N V Zyk

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**Abstract.** Studies on applications of microwave irradiation to organic synthesis published over 2000–2002 are surveyed. The theoretical concepts concerning the influence exerted by microwave irradiation on the course of organic reactions are briefly discussed. The bibliography includes 354 references.

## I. Introduction

Nowadays, great investigation efforts in diverse fields of science and industry are put into the development of resource- and energy-conserving environmentally friendly technologies. In this regard, microwave irradiation (hereinafter, MWI) is becoming increasingly important, since it enables exceptional intensification of various processes, including those that cannot be optimised using traditional techniques.

The pioneering work on the utilisation of MWI as an efficient heating source dates back to the late 1940s, and over the 1970s and 1980s it came into common use in inorganic and analytical chemistry for analysis of various objects, drying and dehydration of samples, synthesis of inorganic materials, elucidation of polymorph transitions, *etc.*<sup>1</sup> An impetus to the use of MWI in organic synthesis was given by the studies of Gedye *et al.*<sup>2</sup> and Giguere *et al.*,<sup>3</sup> who observed a significant reduction in the time required for

the completion of several classical chemical reactions under MWI irradiation as compared to traditional heating conditions. Other advantages of MWI included the saving of electric power or other energy resources, the possibility of conducting a reaction at an elevated pressure at a temperature significantly exceeding the boiling point of the solvent used or under solvent-free conditions, the synthesis of compounds that are unattainable or difficult to prepare with other activation methods.

These factors favouring the use of MWI for the activation of organic reactions were rapidly appreciated by synthetic chemists. It is of note that the wide acceptance of the method was partly due to the simplicity of the experiments: they only required availability of an ordinary commercial MW-oven. Nevertheless, the use of such ovens for the realisation of microwave-assisted chemical reactions have several drawbacks:

- the ovens are not specifically suited for chemical experiments;
- the microwave field in a reaction vessel is inhomogeneous;
- changes in temperature and pressure of a reaction mixture during an experiment cannot be controlled;
- the MWI power varies over time.

All these factors result in poor reproducibility of results and sometimes give rise to explosion or ignition of solvents. Dedicated chemical microwave reactors are now available commercially, which provide homogeneous distribution of the electromagnetic field throughout the reaction volume and computer-controlled adjustment of the radiation power. Such reactors are normally equipped with magnetic stirrers and temperature and pressure gauges. Such special reactors are one order of magnitude more expensive than normal household MW-ovens and thus ~70% of experiments are still performed using the latter.

Several aspects of the application of MWI to organic synthesis have been surveyed in previous reviews, including the theoretical background and recent achievements of MW-assisted organic synthesis,<sup>4–8</sup> solvent-free synthesis,<sup>9</sup> reactions on solid sup-

N N Romanova, A G Gravis, N V Zyk Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax (7-495) 939 88 46, tel. (7-495) 939 35 18, e-mail: romanova@org.chem.msu.ru (N N Romanova), gravis@org.chem.msu.ru (A G Gravis), tel. (7-495) 939 46 52, e-mail: zyk@org.chem.msu.ru (N V Zyk)

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ports,<sup>10,11</sup> synthesis under the conditions of phase-transfer catalysis,<sup>12</sup> preparation of heterocyclic compounds<sup>13</sup> and cycloaddition reactions.<sup>14</sup>

Despite the great number of experimental works describing practical aspects of MWI utilisation, the theory of microwave-assisted organic synthesis has not been elaborated in sufficient detail. Potentially, MWI affects the course of a chemical process in several ways, including purely thermal effects (heating rate, overheating or 'hot spots'), the selective absorption of the radiation by polar compounds and the specific microwave effect (MWE) related to the nonthermal action of MWI.

The term MWE first introduced by Perreux and Loupy<sup>6</sup> is now frequently quoted in studies related to microwave-assisted organic synthesis. Based on the well-known Hammond postulate,<sup>15</sup> Perreux and Loupy suggested<sup>6</sup> that the transition state is close to the ground state for reactions characterised by low activation energies. In such cases, the difference in polarities of the transition and ground states is small and thus the microwave effect is insignificant. In contrast, for reactions characterised by high activation energies, the transition state is rather close to the reaction products. This means that the polarity change in the course of the reaction is prominent and thus the MWE is enhanced.

If polar aprotic solvents strongly absorbing MWI are used, it is the solvent molecules that predominantly feed the reagents with energy (*i.e.*, the energy transfer is indirect) and therefore the MWE is expected to be masked with MWI absorption by the solvent. As a result, the difference in the reaction rates under the conditions of microwave irradiation and convection heating is diminished.

On the other hand, if nonpolar solvents (*e.g.*, CCl<sub>4</sub>, alkanes, benzene, *etc.*) weakly interacting with microwaves are used, the

MWI directly interacts with the reagents, and the MWE in its pure form is manifested.<sup>6</sup>

The MWE is most prominent under solvent-free conditions, *i.e.*, when no external factors hinder the interaction of microwaves with reagents such that the overall MWI absorption is determined solely by their nature.

Unfortunately, in the vast majority of studies devoted to microwave organic synthesis, the influence of the MWI power, the stirring intensity and the reaction medium type on the reaction rates and yields of products were not considered systematically. Thus, the aim of the present review is to serve as a general source of reference data. It covers microwave-assisted syntheses of various classes of organic compounds published over the period from 2000 to 2002. Earlier studies have been reviewed by Lindstrom *et al.*<sup>7</sup> and are not cited here.

The literature data presented below are grouped according to the types of organic compounds concerned and reactions involving them.

## II. Formation of new C = C and C – C bonds under microwave irradiation

The most common reactions utilised for the formation of carbon – carbon bonds are the aldol-crotonic condensation or related reactions (examples Nos 1–7 in Table 1); the condensation of nitromethane or its derivatives with 5-nitro-6-chloromethylimidazothiazole (No. 8), benzaldehyde or its derivatives (No. 9); Wittig reaction (Nos 10–12) and elimination reactions (No. 13).

Unfortunately, comparative data on different activation methods were reported only in a few studies.<sup>22,25,26</sup> In particular, Gellis *et al.*<sup>22</sup> showed that the microwave-assisted condensation of

**Table 1.** Microwave-assisted formation of new C = C and C – C bonds.

| No.                          | Reaction                                         | Conditions                                      | Number of examples | Yield (%) | Ref. |
|------------------------------|--------------------------------------------------|-------------------------------------------------|--------------------|-----------|------|
| Formation of new C = C bonds |                                                  |                                                 |                    |           |      |
| 1                            | <br>$n = 1, 2.$                                  | KF/Al <sub>2</sub> O <sub>3</sub> , MW, 2–5 min | 9                  | 75–90     | 16   |
| 2                            |                                                  | NaOH–EtOH, MW, 2–4 min                          | 7                  | 66–85     | 17   |
| 3                            | <br>$R^1, R^2 = H, Cl, Me, OMe, Ph.$             | Lewis acids, MW, 8 min                          | 11                 | 0–84      | 18   |
| 4                            | <br>$R = Alk, Ph.$                               | MW, 1 h                                         | 3                  | 75–87     | 19   |
| 5                            | <br>$R^1 = Alk, Ph; R^2 = Me, CH_2CO_2Et.$       | MW, 1 h                                         | 6                  | 71–92     | 19   |
| 6                            | <br>$R^1, R^2 = H, Alk; X = NH, S; Y = H, NH_2.$ | AcONa, MW, 2–8 min                              | 7                  | 50–89     | 20   |



Table 1 (continued).

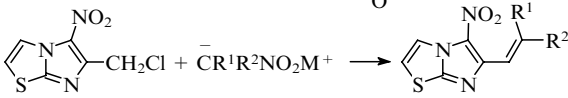
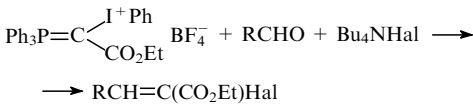
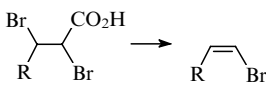
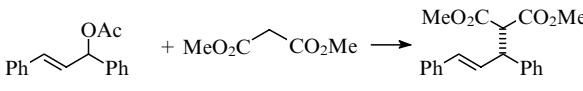
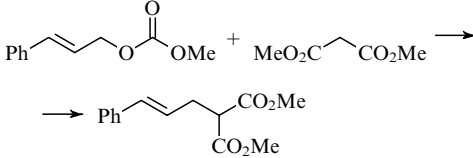
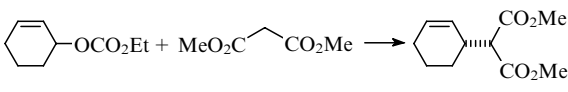
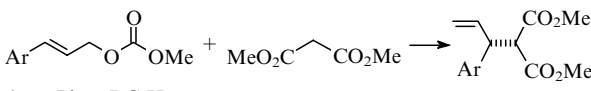
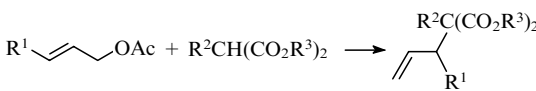
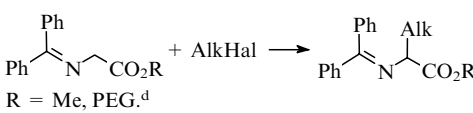
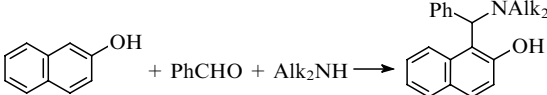
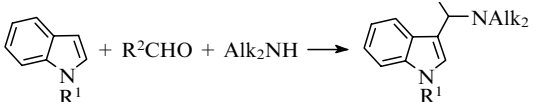
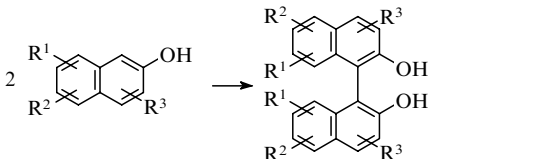
| No.                        | Reaction                                                                                                                                                                                             | Conditions                                                                                                                                                                                                                                                                             | Number of examples | Yield (%)       | Ref.     |
|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------|----------|
| Formation of new C=C bonds |                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                        |                    |                 |          |
| 7                          | $\text{ArCOMe} + \text{Me}_2\text{NCH(OMe)}_2 \longrightarrow \text{Ar}-\text{C}(=\text{O})-\text{CH}=\text{NMe}_2$                                                                                  | MW, 3–9 min                                                                                                                                                                                                                                                                            | 8                  | 83–95           | 21       |
| 8                          | <br>$\text{R}^1, \text{R}^2 = \text{H, Alk, Het}; \text{M} = \text{Li, NBu}_4$                                      | a) $\text{H}_2\text{O}, \text{Li}^+$ , MW, 6 min;<br>b) $\text{Bu}_4\text{N}^+$ , $\Delta$ , 24 h                                                                                                                                                                                      | 9<br>9             | 48–98<br>45–99  | 22<br>22 |
| 9                          | $\text{ArCHO} + \text{MeNO}_2 \longrightarrow \text{ArCH}=\text{CHNO}_2$                                                                                                                             | $\text{K}_2\text{CO}_3/\text{Al}_2\text{O}_3$ , MW, 4–6 min                                                                                                                                                                                                                            | 12                 | 71–95           | 23       |
| 10                         | $\text{R}^1\text{CH}_2\text{Br} + \text{R}^2\text{CHO} + \text{PPh}_3 \longrightarrow \text{R}^1\text{CH}=\text{CHR}^2$<br>$\text{R}^1 = \text{CN, CO}_2\text{Me, Ph}; \text{R}^2 = \text{Ar, Het}$  | $\text{K}_2\text{CO}_3$ , MeOH, MW, 5 min                                                                                                                                                                                                                                              | 15                 | 11–95           | 24       |
| 11                         | $\text{Ph}_3\text{P}=\text{CR}^1\text{R}^2 + \text{ArCHO} \longrightarrow \text{ArCH}=\text{CR}^1\text{R}^2$<br>$\text{R}^1 = \text{COMe, CO}_2\text{Et, CN, CON(Me)OMe}; \text{R}^2 = \text{H, Me}$ | a) DMSO, MW, 5 min<br>b) THF, $\Delta$ , 1 h                                                                                                                                                                                                                                           | 25<br>10           | 48–100<br>16–92 | 25<br>25 |
| 12                         | <br>$\text{R} = \text{Pr}^n, \text{Ar}$                                                                             | a) DMF ( $\text{CHCl}_3$ , MeCN, etc.), MW, 2–5 min<br>b) $\Delta$ , 8–32 min                                                                                                                                                                                                          | 13<br>13           | 68–97<br>61–97  | 26<br>26 |
| 13                         | <br>$\text{R} = \text{Alk, Ar}$                                                                                   | $\text{Et}_3\text{N}$ , DMF, MW, 0.2–1 min                                                                                                                                                                                                                                             | 15                 | 73–99           | 27       |
| Formation of new C–C bonds |                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                        |                    |                 |          |
| 14                         |                                                                                                                   | $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$ , AcOK, BSA, <sup>a</sup> L <sup>b</sup><br>a) MW, 0.25–15 min<br>b) $\Delta$ , 4.5–5760 min                                                                                                                                            | 17<br>6            | 85–99<br>56–99  | 28       |
| 15                         |                                                                                                                   | $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$ , BSA, <sup>a</sup> THF, MW, 5 min                                                                                                                                                                                                      | 1                  | 73              | 29       |
| 16                         |                                                                                                                   | $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$ , L, <sup>b</sup> MW, 1.5–6 min                                                                                                                                                                                                         | 5                  | 65–83           | 28       |
| 17                         | <br>$\text{Ar} = \text{Ph, } p\text{-RC}_6\text{H}_4$                                                             | a) $\text{Ar} = \text{Ph}$ : $\text{Mo(CO)}_6$ , L, <sup>b</sup> $\text{PPh}_3$ , BSA, <sup>a</sup> THF, MW, 4–9 min<br>b) $\text{Ar} = \text{Ph, } p\text{-RC}_6\text{H}_4$ : $\text{Mo(CO)}_6$ , L, <sup>b</sup> $\text{NaCH(CO}_2\text{Me)}_2$ , BSA, <sup>a</sup> THF, MW, 5–6 min | 10<br>8            | 59–84<br>50–89  | 29<br>30 |
| 18                         | <br>$\text{R}^1 = \text{H, Ph}; \text{R}^2 = \text{H, Me}; \text{R}^3 = \text{Me, Et}$                            | $\text{Pd}_2(\text{dba})_3$ (see <sup>c</sup> ), $\text{KF}/\text{Al}_2\text{O}_3$ , MW, 5–30 min                                                                                                                                                                                      | 4                  | 30–98           | 31       |
| 19                         | <br>$\text{R} = \text{Me, PEG}^{\text{d}}$                                                                        | $\text{PEG}^{\text{d}}$ , $\text{M}_2\text{CO}_3$ ( $\text{M} = \text{K, Cs}$ ), MW, 15–60 min                                                                                                                                                                                         | 8                  | 75–98           | 32       |

Table 1 (continued).

| No.                        | Reaction                                                                                                                                                                                                                                                                                                            | Conditions                                               | Number of examples | Yield (%) | Ref. |
|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|--------------------|-----------|------|
| Formation of new C—C bonds |                                                                                                                                                                                                                                                                                                                     |                                                          |                    |           |      |
| 20                         |  $\text{2-naphthol} + \text{PhCHO} + \text{Alk}_2\text{NH} \rightarrow \text{1-(2-hydroxy-1-phenylethyl)naphthalene}$                                                                                                              | $\text{Al}_2\text{O}_3$ , MW, 5 min                      | 3                  | 68–73     | 33   |
| 21                         |  $\text{Indole-1-}R^1 + R^2\text{CHO} + \text{Alk}_2\text{NH} \rightarrow \text{2-(1-(R}^2\text{)(NAlk}_2\text{)ethyl)indole-1-}R^1$ <p><math>R^1 = \text{H, Alk, } R^2 = \text{H, } p\text{-NO}_2\text{C}_6\text{H}_4</math>.</p> | $\text{Al}_2\text{O}_3$ , MW, 4–5 min                    | 4                  | 50–91     | 33   |
| 22                         |  $2 \text{ (substituted phenol)} \rightarrow \text{biaryl product}$ <p><math>R^1 = \text{H, Me, CO}_2\text{Me; } R^2 = \text{H, Br; } R^3 = \text{H, OH, OMe}</math>.</p>                                                          | $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ , MW, 4–20 min | 8                  | 80–97     | 34   |

<sup>a</sup> BSA is *N,O*-bis(trimethylsilyl)acetamide; <sup>b</sup> L means different diamide ligands; <sup>c</sup> dba is dibenzylideneacetone; <sup>d</sup> PEG is polyethylene glycol.

chloromethylimidazothiazole with 9 nitromethane derivatives proceeded 240 times faster than the respective reactions under thermal activation (see Table 1). Evidently the MWE can be observed here.

The microwave-assisted introduction of double bonds into organic molecules following the Wittig method (reactions Nos 10–12) is slightly accelerated as compared to the thermally activated reaction; the use of reagents grafted to a solid substrate does not result in a further reduction in the reaction time.

Table 1 also lists some examples of the formation of new single C—C bonds under MW conditions, including allyl substitution, C-alkylation, C-aminoalkylation and oxidative coupling reactions (Nos 14–22).<sup>†</sup> Unfortunately, no conclusions on the MWE involvement can be deduced in those cases owing to the absence of comparative data. Among them, the work by Kaiser *et al.*<sup>29</sup> is worth a special mention, where the allyl alkylation of methyl-(*E*)-3-phenylallylcarbonate (No. 17) was studied and the influence of several factors, such as the nature of catalyst (*cf.* with No. 15) and solvent, radiation power and grafting of the reagent on a solid substrate, on the yield of the target product was analysed.

### III. Reactions involving multiple carbon—carbon bonds

Table 2 lists examples of reactions involving C=C bonds, which are activated by microwave irradiation. The hydrogenation of double bonds is illustrated with three examples (Nos 1–3). These data show that the microwave-assisted hydrogenation proceeds nearly as fast as the thermally activated reaction but the use of a support in the former case results in a 360-fold acceleration.

The C-arylation of compounds containing a double bond in the presence of Pd-based catalysts is represented by reactions Nos 4–7. Olofsson *et al.*<sup>40</sup> found that the microwave-activated

C-arylation following the Heck method proceeds 200 times faster than the thermally activated one (reaction No. 6, Table 2).

In the case of the addition of aldehydes to alkenes with non-activated double bonds (reaction No. 8), the yields of target products are virtually the same for the microwave and thermal activations but the use of MWI gives rise to a 24-fold acceleration of the reaction.

The addition of compounds with reactive methylene or methine groups to alkenes with activated double bonds (*i.e.*, the Michael addition) is illustrated with reactions Nos 9–14 (see Table 2).

Michaud *et al.*<sup>47</sup> showed that the double Michael addition of benzylidenecyanoacetic esters to nitromethane (reaction No. 13) catalysed by piperidine followed by intermolecular cyclisation yields a mixture of functionalised cyclohexenes with either two (compound **A**) or one (compound **B**) methoxycarbonyl groups in a ratio dependent on the MWI parameters and amount of piperidine. For instance, with piperidine taken in equimolar proportion to nitromethane, the monomethoxycarbonyl product (**B**) is predominantly formed, and *vice versa*, the maximum yield (80%) of dimethoxycarbonylcyclohexene (**A**) is achieved with piperidine used in catalytic amounts.

The microwave-assisted Diels–Alder cycloaddition reactions that yield polycyclic systems with isolated double bonds are significantly accelerated both in the presence (reaction No. 16, see Table 2) and in the absence (reaction No. 15) of solvents as compared to the respective thermally activated reactions. It has to be noted that, although the yields of products under different conditions are comparable, some reactions (*e.g.*, see Ref. 50) can be realised only under microwave irradiation.

Table 3 gives some examples of catalytic reactions involving acetylene derivatives, such as Mannich aminomethylation (reactions Nos 1, 2), Sonogashira cross-coupling (No. 3–6), desilylation (No. 7), Glaser synthesis of conjugated diacetylene derivatives (No. 8), metathesis (No. 9) and C-acylation (No. 10).

The data presented indicate that the reaction times in the case of MWI activation are substantially reduced as compared to the

<sup>†</sup> For other examples of the formation of C—C bonds, see Table 2, which lists reactions involving C=C bonds.

**Table 2.** Reactions involving the C=C bond.

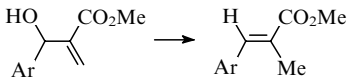
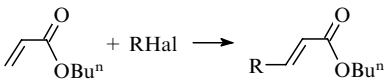
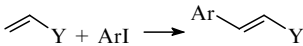
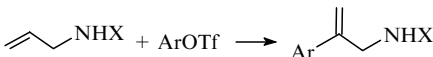
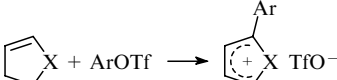
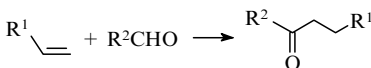
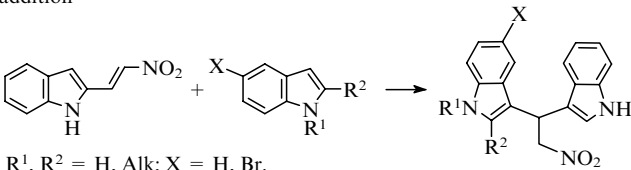
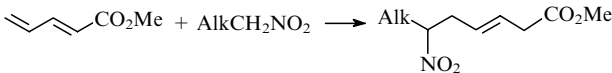
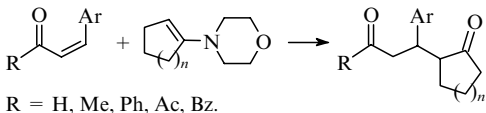
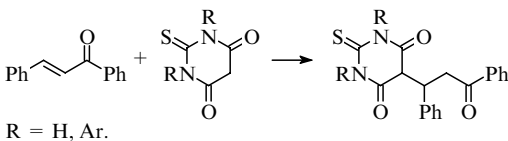
| No.                                            | Reaction                                                                                                                                                                                           | Conditions                                                                                                                                        | Number of examples | Yield (%)          | Ref.     |
|------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|----------|
| <b>Hydrogenation</b>                           |                                                                                                                                                                                                    |                                                                                                                                                   |                    |                    |          |
| 1                                              | $\text{R}^1\text{CH}=\text{CHR}^2 \longrightarrow \text{R}^1\text{CH}_2\text{CH}_2\text{R}^2$ $\text{R}^1 = \text{Et, Ph}; \text{R}^2 = \text{CO}_2\text{Alk, C(O)Me, C(O)NMe}_2, \text{CN, CHO.}$ | $a) \text{ } \text{---CH}_2\text{NMe}_3^+ \text{HCO}_2^-, \text{RhCl(PPh)}_3, \text{DMSO, MW, 30 s}$ $b) \Delta, 3 \text{ h}$                     | 8                  | 80–95              | 35       |
| 2                                              | $\text{PhCH}=\text{CHR} \longrightarrow \text{PhCH}_2\text{CH}_2\text{R}$ $\text{R} = \text{Ph, CO}_2\text{Me.}$                                                                                   | 10% Pd/C, HCO <sub>2</sub> NH <sub>4</sub> or HCO <sub>2</sub> NEt <sub>4</sub> , MW, 80 min                                                      | 4                  | 83–99              | 36       |
| 3                                              |                                                                                                                   | NaBH <sub>4</sub> /Al <sub>2</sub> O <sub>3</sub> , MW, 8–12 min                                                                                  | 6                  | 72–90              | 37       |
| <b>C-Arylation</b>                             |                                                                                                                                                                                                    |                                                                                                                                                   |                    |                    |          |
| 4                                              |  $\text{R} = \text{Ar, Het.}$                                                                                     | PdCl <sub>3</sub> , P(Tol- <i>o</i> ) <sub>3</sub> , (bmim)PF <sub>6</sub> (see <sup>a</sup> ), Et <sub>3</sub> N, MW, 5–45 min                   | 7                  | 39–95              | 38       |
| 5                                              |  $\text{Y} = \text{Ph, CO}_2\text{H, CO}_2\text{Me.}$                                                             | Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> , Bu <sub>4</sub> NBr, K <sub>2</sub> CO <sub>3</sub> , H <sub>2</sub> O, MW, 10 min           | 7                  | 86–93              | 39       |
| 6                                              |  $\text{X} = \text{Boc, Ph}; \text{Ar} = \text{Ph, 1-Naph, } p\text{-MeOC}_6\text{H}_4, \text{ etc.}$            | $\text{Pd(OAc)}_2, (\text{C}_5\text{H}_4\text{PPh}_2)_2\text{Fe, K}_2\text{CO}_3, \text{MeCN}$ $a) \text{ MW, 3–6 min}$ $b) \Delta, 20 \text{ h}$ | 14<br>14           | 6–68<br>7–74       | 40       |
| 7                                              |  $\text{X} = \text{CH}_2, \text{O.}$                                                                            | [Pd <sub>2</sub> (dba) <sub>3</sub> ]L, benzene, MW, 10–480 min                                                                                   | 11                 | 53–85 <sup>b</sup> | 41       |
| <b>Addition to a non-activated double bond</b> |                                                                                                                                                                                                    |                                                                                                                                                   |                    |                    |          |
| 8                                              |  $\text{R}^1, \text{R}^2 = \text{Alk, Ar.}$                                                                     | $a) 2\text{-NH}_2\text{-3-MeC}_5\text{H}_3\text{N, MW, 10 min}$ $b) \text{PhMe, } \Delta, 4 \text{ h}$                                            | 11<br>11           | 0–95<br>13–93      | 42<br>42 |
| <b>Michael addition</b>                        |                                                                                                                                                                                                    |                                                                                                                                                   |                    |                    |          |
| 9                                              |  $\text{R}^1, \text{R}^2 = \text{H, Alk}; \text{X} = \text{H, Br.}$                                             | $a) \text{SiO}_2, \text{MW, 7–10 min}$ $b) \text{room temperature, 8–14 h}$                                                                       | 6<br>6             | 70–86<br>69–84     | 43<br>43 |
| 10                                             |                                                                                                                 | Amberlyst A, MW, 7 min                                                                                                                            | 8                  | 55–75              | 44       |
| 11                                             |  $\text{R} = \text{H, Me, Ph, Ac, Bz.}$                                                                         | Al <sub>2</sub> O <sub>3</sub> , MW, 5–8 min                                                                                                      | 13                 | 80–89              | 45       |
| 12                                             |  $\text{R} = \text{H, Ar.}$                                                                                     | Al <sub>2</sub> O <sub>3</sub> , MW, 1.5–2.3 min                                                                                                  | 6                  | 83–88              | 46       |

Table 2 (continued).

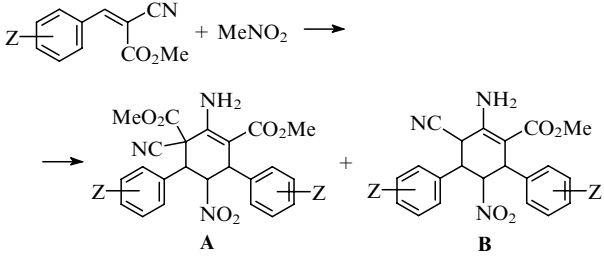
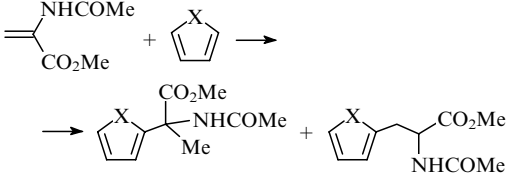
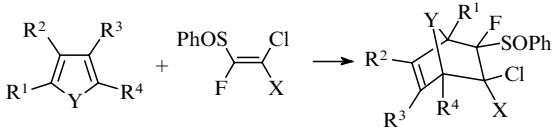
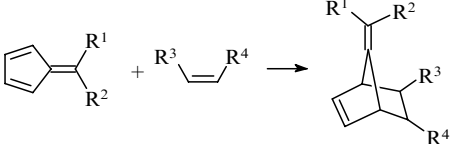
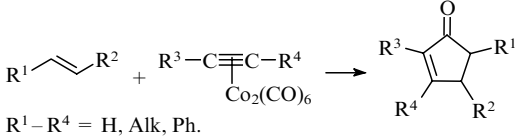
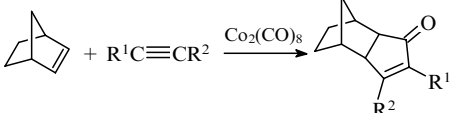
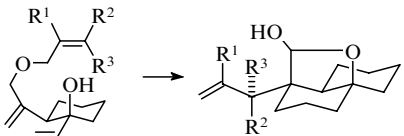
| No.                           | Reaction                                                                                                                                                                                                 | Conditions                                                                | Number of examples | Yield (%)              | Ref.           |
|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------|------------------------|----------------|
| Michael addition              |                                                                                                                                                                                                          |                                                                           |                    |                        |                |
| 13                            |  <p><math>Z = \text{H, Hal, OMe, NO}_2</math>.</p>                                                                      | piperidine, MW, 11–25 min                                                 | 7                  | 0–80 (A)<br>100–20 (B) | 47             |
| 14                            |  <p><math>X = \text{O, NH, NBn}</math>.</p>                                                                             | $\text{Si(M)}^c$ ( $M = \text{Zn, Al, Ti}$ ),<br>MW, 15–30 min            | 10                 | > 3–70 <sup>b</sup>    | 48             |
| Diels–Alder reactions         |                                                                                                                                                                                                          |                                                                           |                    |                        |                |
| 15                            |  <p><math>R^1, R^4 = \text{H, Ph}; R^2, R^3 = \text{H, Alk}; Y = \text{CH}_2, \text{O}; X = \text{F, Cl}</math>.</p>  | a) MW, 3–25 min<br>b) PhMe, $\Delta$ , 10–24 h                            | 7<br>5             | 71–90<br>70–90         | 49<br>49       |
| 16                            |  <p><math>R^1, R^2 = \text{H, Alk}; R^3, R^4 = \text{CO}_2\text{Me, C(O)OC(O), C(O)NHC(O), C(O)CH=CHC(O)}</math>.</p> | a) DMSO, MW, 2 h<br>b) DMSO, $\Delta$ , 5 h<br>c) benzene, $\Delta$ , 5 h | 9<br>6<br>9        | 30–78<br>0–75<br>0–89  | 50<br>50<br>50 |
| Pouson–Khand reactions        |                                                                                                                                                                                                          |                                                                           |                    |                        |                |
| 17                            |  <p><math>R^1-R^4 = \text{H, Alk, Ph}</math>.</p>                                                                     | $\text{C}_2\text{H}_4\text{Cl}_2$ , MW, 2–20 min                          | 9                  | 11–90                  | 51             |
| 18                            |  <p><math>R^1 = \text{Alk, Ph, CO}_2\text{Me}; R^2 = \text{H, CO}_2\text{Me}</math>.</p>                              | cyclo- $\text{C}_6\text{H}_{11}\text{NH}_2$ , MW, 5 min                   | 4                  | 48–81                  | 52             |
| Cascade cyclisation reactions |                                                                                                                                                                                                          |                                                                           |                    |                        |                |
| 19                            |                                                                                                                       | PhMe, DBO, <sup>d</sup> MW, 60 min                                        | 7                  | 60–98                  | 53             |

**Table 2** (continued).

| No.                    | Reaction                                                                                                                                                                                                                                                                        | Conditions                                | Number of examples | Yield (%) | Ref. |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|--------------------|-----------|------|
| Substitution reactions |                                                                                                                                                                                                                                                                                 |                                           |                    |           |      |
| 20                     | <p><math>\text{Ar}-\text{C}(\text{R}^1)=\text{C}(\text{R}^2)\text{CO}_2\text{H} + \text{Phthalimide-Hal} \longrightarrow \text{Ar}-\text{C}(\text{R}^1)=\text{C}(\text{R}^2)\text{Hal}</math></p> <p><math>\text{R}^1 = \text{H, Me, Ph}; \text{R}^2 = \text{H, Me.}</math></p> | LiOAc, MeCN–H <sub>2</sub> O, MW, 1–2 min | 15                 | 33–96     | 54   |

<sup>a</sup> bmim is 1-butyl-3-methylimidazole; <sup>b</sup> the total yield of isomers is given; <sup>c</sup> silicon-supported metals; <sup>d</sup> DBO is 1,4-diazabicyclo[2.2.2]nonane.

thermal activation. In particular, the aminomethylation is accelerated by a factor of 360 (reaction No. 2, see Table 3). Meanwhile, MWI gives no improvement in terms of yields of reaction products, and they even decrease in a few cases (*e.g.*, reaction No. 6).

#### IV. Synthesis of aromatic compounds and reactions with them

Table 4 lists selected examples of the use of MWI in the synthesis (reactions Nos 1–4) and modification of aromatics, *viz.*, Suzuki

**Table 3.** Microwave-assisted reactions involving the C≡C bond.

| No. | Reaction                                                                                                                                                                                                                                                        | Conditions                                                                                                                                                                                          | Number of examples | Yield (%)                        | Ref.     |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|----------------------------------|----------|
| 1   | $\text{R}^1\text{C}\equiv\text{CH} + (\text{CH}_2\text{O})_n + \text{R}^2\text{R}^3\text{NH} \longrightarrow \text{R}^1\text{C}\equiv\text{CCH}_2\text{NR}^2\text{R}^3$<br>$\text{R}^1 = \text{Alk, Ar}; \text{R}^2 = \text{Alk, Ph}; \text{R}^3 = \text{Alk.}$ | CuI/Al <sub>2</sub> O <sub>3</sub> , MW, 4 min                                                                                                                                                      | 8                  | 40–90                            | 55       |
| 2   | $\text{R}^1\text{C}\equiv\text{CH} + \text{HCHO} + \text{R}^2\text{R}^3\text{NH} \longrightarrow \text{R}^1\text{C}\equiv\text{CCH}_2\text{NR}^2\text{R}^3$<br>$\text{R}^1, \text{R}^2 = \text{Alk, Ph}; \text{R}^3 = \text{Alk.}$                              | a) CuCl/Al <sub>2</sub> O <sub>3</sub> , MW, 1 min<br>b) Δ, 6 h                                                                                                                                     | 13<br>13           | 70–94<br>73–95                   | 55<br>55 |
| 3   | $\text{R}^1\text{C}\equiv\text{CH} + \text{R}^2\text{I} \longrightarrow \text{R}^1\text{C}\equiv\text{CR}^2$<br>$\text{R}^1 = \text{CH}_2\text{OH, Ph, C}_6\text{H}_4\text{NO}_2\text{-}p; \text{R}^2 = \text{Alk, Ar.}$                                        | CuI–PPh <sub>3</sub> , K <sub>2</sub> CO <sub>3</sub> , DMF, argon<br>a) MW, 10 min<br>b) Δ, 10–24 h                                                                                                | 7<br>7             | 80–92<br>75–95                   | 56       |
| 4   | <p><math>\text{PEGO}_2\text{C}-\text{C}_6\text{H}_4-\text{I} + \text{RC}\equiv\text{CH} \longrightarrow \text{PEGO}_2\text{C}-\text{C}_6\text{H}_4-\text{C}\equiv\text{CR}</math></p> <p><math>\text{R} = \text{Alk, Ph.}</math></p>                            | Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> , CuI, K <sub>2</sub> CO <sub>3</sub> , MW, 1.5 min                                                                                              | 6                  | 68–91                            | 57       |
| 5   | $\text{R}^1\text{C}\equiv\text{CX} + \text{R}^2\text{I} \longrightarrow \text{R}^1\text{C}\equiv\text{CR}^2$<br>$\text{R}^1, \text{R}^2 = \text{Alk, Ar, Het}; \text{X} = \text{H, SiMe}_3.$                                                                    | Pd–CuI–PPh <sub>3</sub> , KF/Al <sub>2</sub> O <sub>3</sub> , MW, 2.5 min                                                                                                                           | 26                 | 31–98                            | 58       |
| 6   | $\text{HC}\equiv\text{CSiMe}_3 + \text{ArX} \longrightarrow \text{ArC}\equiv\text{CSiMe}_3$<br>$\text{X} = \text{Hal, OTf.}$                                                                                                                                    | Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> , CuI, Et <sub>2</sub> NH, DMF<br>a) MW, 5–25 min<br>b) Δ, 5–300 min                                                                             | 26<br>6            | 80–99<br>95–99                   | 59       |
| 7   | $\text{RC}\equiv\text{CSiMe}_3 \longrightarrow \text{RC}\equiv\text{CH}$                                                                                                                                                                                        | KF/Al <sub>2</sub> O <sub>3</sub> , MW, 1–3.5 min                                                                                                                                                   | 17                 | 0–98                             | 60       |
| 8   | $\text{RC}\equiv\text{CH} \longrightarrow \text{RC}\equiv\text{C}-\text{C}\equiv\text{CR}$<br>$\text{R} = \text{Alk, Ar.}$                                                                                                                                      | KF/Al <sub>2</sub> O <sub>3</sub> , CuCl <sub>2</sub> , MW, 8 min                                                                                                                                   | 7                  | 53–75                            | 61       |
| 9   | $\text{RC}\equiv\text{CR} + \text{PhC}\equiv\text{CPh} \longrightarrow \text{RC}\equiv\text{CPh}$<br>$\text{R} = \text{Alk, SiMe}_3.$                                                                                                                           | Mo(CO) <sub>6</sub> , n-C <sub>8</sub> H <sub>18</sub> , MW, 10–15 min                                                                                                                              | 7                  | ~50                              | 62       |
| 10  | $\text{PhC}\equiv\text{CH} + \text{RCOCl} \longrightarrow \text{PhC}\equiv\text{C}-\text{C}(=\text{O})-\text{R}$<br>$\text{R} = \text{Alk, Ar.}$                                                                                                                | CuI, Et <sub>3</sub> N<br>a) MW, 10 min<br>b) Δ, 30 h<br>Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> /CuI, Et <sub>3</sub> N, KF/Al <sub>2</sub> O <sub>3</sub><br>a) MW, 4 min<br>b) Δ, 8 h | 9<br>9<br>7<br>7   | 76–93<br>52–81<br>81–94<br>72–90 | 63<br>64 |

The microwave-assisted Suzuki cross-coupling reactions are complete in 1–15 min giving yields as high as 40%–98%. Unfortunately, no results for activation methods other than MWI have been reported in those cases, thus no conclusion on the extent of the MWE can be deduced.

The use of MWI for the activation of aromatic nucleophilic substitution reactions is not as efficient. In only a few cases, slight acceleration of the reactions (*e.g.*, Nos 8 and 10) and an increase in the yields of target products by 10%–20% were registered. An exception to this is the substitution of the hetarylthio group for the chlorine atom in the aromatic core (No. 21). In this specific case, the reaction rate increased ~140-fold in the presence of a solvent and 480-fold when the reaction was conducted in the absence of solvents on a solid support, which is plain evidence for the MWE.

**Table 4.** Synthesis of aromatic compounds and reactions with them.

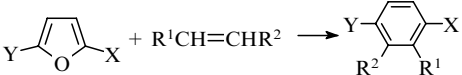
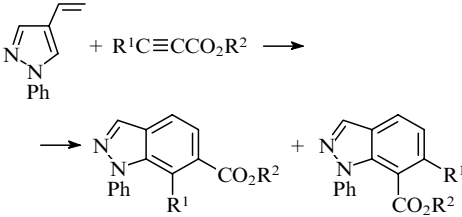
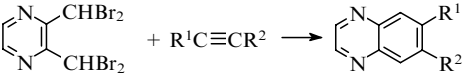
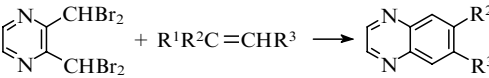
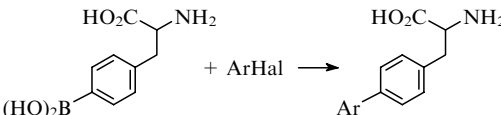
| No.                                            | Reaction                                                                                                                                                                                                                                                                                                                                                            | Conditions                                                                                                                                                                                                                                                      | Number of examples | Yield (%)                               | Ref.           |
|------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------------------------------|----------------|
| Synthesis of aromatics                         |                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                 |                    |                                         |                |
| 1                                              | <br>$\text{Y}-\text{furan}-\text{X} + \text{R}^1\text{CH}=\text{CHR}^2 \longrightarrow \text{Y}-\text{benzofuran}(\text{R}^2, \text{R}^1)-\text{X}$<br>$\text{X} = \text{Me, Et, OMe}; \text{Y} = \text{H, Me}; \text{R}^1 = \text{CN, CO}_2\text{Me}; \text{R}^2 = \text{H, CN}.$ | $a)$ Si(M) (M = Ti, Zn, Al), MW, 25–45 min<br>$b)$ $\Delta$ , 25–45 min                                                                                                                                                                                         | 25<br>8            | 0–100<br>3–31                           | 65<br>65       |
| 2                                              | <br>$\text{R}^1 = \text{H, CO}_2\text{R}^2, \text{Ph}; \text{R}^2 = \text{Me, Et}.$                                                                                                                                                                                               | $a)$ MW, 6–30 min<br>$b)$ $\text{CH}_2\text{Cl}_2$ , $\Delta$ , 3–7 days                                                                                                                                                                                        | 4<br>4             | 22–72 <sup>a</sup><br>7–53 <sup>a</sup> | 66<br>66       |
| 3                                              | <br>$\text{R}^1 = \text{H}; \text{R}^2 = \text{Ph, 1-Naph}; \text{R}^1 = \text{Me, R}^2 = \text{Ph}.$                                                                                                                                                                            | NaI, DMF, MW, 13–15 min                                                                                                                                                                                                                                         | 3                  | 38–43                                   | 67             |
| 4                                              | <br>$\text{R}^1 = \text{NO}_2, \text{R}^2 = \text{H, R}^3 = \text{Ph};$<br>$\text{R}^1 = \text{N}(\text{cyclopentyl}), \text{R}^2-\text{R}^3 = (\text{CH}_2)_n (n = 3, 4).$                                                                                                      | NaI, DMF, MW, 10–15 min                                                                                                                                                                                                                                         | 3                  | 33–69                                   | 67             |
| Cross-coupling reactions of aromatic compounds |                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                 |                    |                                         |                |
| 5                                              | $\text{HetHal} + \text{Ph}_2\text{BNa} \longrightarrow \text{HetPh}$                                                                                                                                                                                                                                                                                                | $\text{Pd}(\text{OAc})_2$ , $\text{Na}_2\text{CO}_3$ , $\text{H}_2\text{O}$ or $\text{MeNHCHO}$ , MW, 8–12 min                                                                                                                                                  | 7                  | 60–85                                   | 68             |
| 6                                              | $\text{Ar}^1\text{B}(\text{OH})_2 + \text{Ar}^2\text{Hal} \longrightarrow \text{Ar}^1-\text{Ar}^2$                                                                                                                                                                                                                                                                  | $a)$ $\text{PdCl}_2$ , KF, PEG-400, MW, 50 s<br>$b)$ $\text{Pd}(\text{OAc})_2$ , KF/ $\text{Al}_2\text{O}_3$ , MW 2–15 min<br>$c)$ $\text{Pd}(\text{OAc})_2$ , $\text{Na}_2\text{CO}_3$ , $\text{Bu}_4\text{N}^+\text{Br}^-$ , $\text{H}_2\text{O}$ , MW, 5 min | 16<br>6<br>25      | 66–92<br>40–98<br>45–96                 | 69<br>31<br>70 |
| 7                                              | <br>$(\text{HO})_2\text{B}-\text{C}_6\text{H}_4-\text{CH}_2-\text{CH}(\text{NH}_2)\text{CO}_2\text{H} + \text{ArHal} \longrightarrow \text{Ar}-\text{C}_6\text{H}_4-\text{CH}_2-\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$                                                       | $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ , $\text{Na}_2\text{CO}_3$ , $\text{MeCN}-\text{H}_2\text{O}$ , MW, 5–10 min                                                                                                                                             | 9                  | 68–86                                   | 71             |

Table 4 (continued).

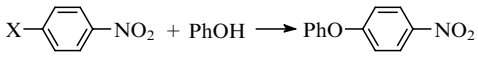
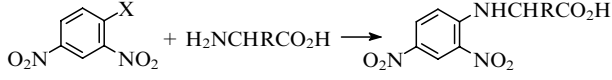
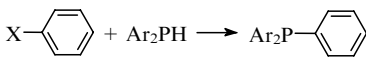
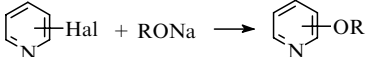
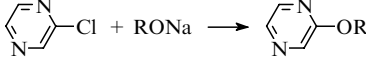
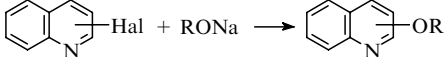
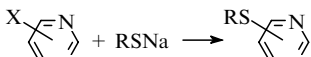
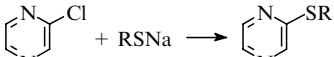
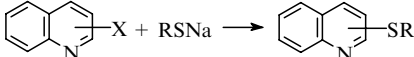
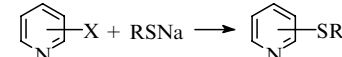
| No.                                          | Reaction                                                                                                            | Conditions                                                                                                                    | Number of examples | Yield (%)       | Ref.     |
|----------------------------------------------|---------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------|----------|
| Aromatic nucleophilic substitution reactions |                                                                                                                     |                                                                                                                               |                    |                 |          |
| 8                                            | <br>X = Cl, F.                     | a) KOH, R <sub>4</sub> N <sup>+</sup> Y <sup>-</sup> or 18-crown-6, MW, 0.5–10 min<br>b) Δ, 0.5–10 min                        | 15<br>14           | 38–98<br>24–86  | 72<br>72 |
| 9                                            | <br>R = H, Alk, Ph; X = F, Cl, Br. | NaHCO <sub>3</sub> , H <sub>2</sub> O, MW, 0.6–15 min (N-arylation)                                                           | 18                 | 48–93           | 73       |
| 10                                           | ArX + MeOK → ArOMe<br>X = F, Cl.                                                                                    | a) R <sub>4</sub> N <sup>+</sup> Y <sup>-</sup> or 18-crown-6, MW, 3.5–90 min<br>b) Δ, 3.5–1440 min                           | 15<br>9            | 38–100<br>24–93 | 72<br>72 |
| 11                                           | <br>X = I, Br, OTf.                | Al <sub>2</sub> O <sub>3</sub> , Pd(OAc) <sub>2</sub> or Pd/C or Pd(PPh <sub>3</sub> ) <sub>2</sub> , AcOK, DMF, MW, 2–20 min | 18                 | 26–98           | 74       |
| 12                                           | <br>R = Ph, Bn.                    | NMP <sup>b</sup> or HMPA, <sup>c</sup> or DMSO, MW, 45–900 s                                                                  | 28                 | 0–95            | 75       |
| 13                                           | <br>R = Ph, Et.                   | NMP or HMPA, or DMSO, MW, 35–600 s                                                                                            | 11                 | 20–88           | 76       |
| 14                                           | <br>R = Ph, Et.                  | NMP or HMPA, or DMSO, MW, 40–50 s                                                                                             | 4                  | 54–69           | 76       |
| 15                                           | <br>R = Me, Et; Hal = Cl, Br.    | NMP or HMPA, MW 30–360 s                                                                                                      | 12                 | 30–99           | 77       |
| 16                                           | <br>R = Me, Ph; X = Cl, Br.      | NMP or HMPA, or DMSO, MW, 30–60 s                                                                                             | 15                 | 7–97            | 76       |
| 17                                           | <br>R = Me, Ph.                  | NMP, MW, 35–50 s                                                                                                              | 2                  | 88–96           | 76       |
| 18                                           | <br>R = Me, Ph; X = Cl, Br.      | NMP or HMPA, MW, 30–240 s                                                                                                     | 17                 | 0–99            | 77       |
| 19                                           | <br>R = Me, Ph.                  | NMP or HMPA, MW, 1–10 min                                                                                                     | 5                  | 0–98            | 77       |
| 20                                           | <br>R = Me, Ph; X = Hal.         | NMP or HMPA, MW, 0.5–10 min                                                                                                   | 28                 | 0–99            | 78       |

**Table 4** (continued).

| No.                                          | Reaction                                                         | Conditions                                                                                                           | Number of exam-<br>ples | Yield (%)               | Ref.           |
|----------------------------------------------|------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|----------------|
| Aromatic nucleophilic substitution reactions |                                                                  |                                                                                                                      |                         |                         |                |
| 21                                           | <br>$\text{R} = \text{H, Cl, NO}_2, \text{CN; X} = \text{O, S.}$ | a) Al <sub>2</sub> O <sub>3</sub> , MW, 60–90 s<br>b) CH <sub>2</sub> Cl <sub>2</sub> , MW, 4–5 min<br>c) Δ, 10–12 h | 10<br>10<br>10          | 90–96<br>70–78<br>59–65 | 79<br>79<br>79 |
| Aromatic electrophilic substitution reaction |                                                                  |                                                                                                                      |                         |                         |                |
| 22                                           | <br>$\text{R} = \text{Alk, Ar; X} = \text{Cl, RC(O)O.}$          | EPZG <sup>®</sup> , <sup>d</sup> MW,<br>2–5 min (X = Cl),<br>4–8 min (X = RC(O)O)                                    | 12                      | 38–100 <sup>a</sup>     | 80             |

<sup>a</sup>The total yield of isomers is given. Hereinafter, <sup>b</sup>NMP is *N*-methylpyrrolidone-2; <sup>c</sup>HMPA is hexamethylphosphortriamide, <sup>d</sup>EPZG is a support material.

## V. Deuterated derivatives

Examples of the use of MWI for the introduction of deuterium labels through the substitution of a hydrogen (examples Nos 1 and 2) or halogen (No. 3) atom with deuterium or addition of deuterium to a double bond are given in Table 5. These data imply that neither microwave nor thermal activation is sufficient to complete the deuterioexchange, although the reaction proceeds somewhat faster in the former mode.

## VI. Synthesis of alcohols and phenols. Deprotection of the OH group

Studies reporting the application of MWI to the synthesis of alcohols and phenols are quite numerous. Most frequently, alcohols are produced by the reduction of aldehydes, ketones or esters with Pr<sup>i</sup>OH or NaBH<sub>4</sub> (reactions Nos 1–3, Table 6). In addition to reduction, the hydrolysis of esters (reaction No. 4) and opening of oxirane rings (reaction No. 5) are utilised. The

**Table 5.** Microwave-assisted introduction of deuterium labels.

| No. | Reaction                              | Conditions                                                | Number of exam-<br>ples | Yield (%)      | Ref.     |
|-----|---------------------------------------|-----------------------------------------------------------|-------------------------|----------------|----------|
| 1   |                                       | a) MW, 15–20 min<br>b) Δ, 8–24 h                          | 5<br>5                  | 75–96<br>68–90 | 81<br>81 |
| 2   |                                       | a) EtOH, MW, 10–600 s<br>b) Δ, 1–1200 min                 | 9<br>6                  | 0–95<br>2–92   | 82<br>82 |
| 3   |                                       | EtOH or DMSO, Pd/C or Pd(OAc) <sub>2</sub> , MW, 20 s     | 3                       | > 50           | 83       |
| 4   |                                       | RhCl <sub>3</sub> , Pd(OAc) <sub>2</sub> , DMSO, MW, 40 s | 3                       | > 95           | 84       |
|     | X = Cl, Br; R = H, CO <sub>2</sub> H. |                                                           |                         |                |          |



hydroxymethylation of uracils in basic media (reaction No. 6) and controlled Claisen rearrangement (No. 7) have also been reported.

The above reactions under MWI are complete in a few minutes affording the respective hydroxy-containing products in yields as high as 90%–99%. In particular, the reaction times of the Claisen rearrangement (No. 7) and benzaldehyde reduction (No. 1) were reduced by factors of 28 and 84, respectively, as compared to the thermally activated reactions, although the product yields remained essentially unchanged.

Several authors reported the microwave-assisted deprotection of OH groups (reactions Nos 8 and 9 in Table 6).

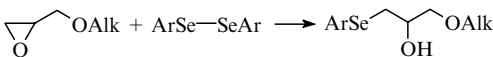
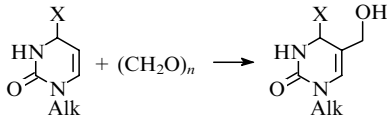
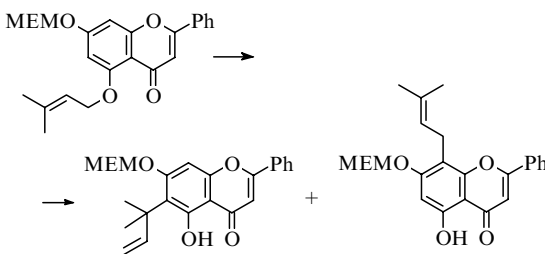
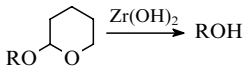
## VII. Reactions involving alcohols and phenols

Examples of chemical modifications of alcohols assisted by MWI given in Table 7 include substitution (No. 1), O-sulfonylation (No. 2), O-alkylation (Nos 3–11), O-glycosylation (Nos 12

and 13) and protection of the OH group (Nos 14–17). These data indicate that in some cases, the MWI reduces the reaction times and increases the yields of products as compared to the reactions under ordinary heating. For instance, the yields of 3,4-dialkoxybenzaldehydes (reaction No. 9) increased from 60% in the classical synthesis ( $K_2CO_3$ , boiling acetone) to 86% in the solvent-free MWI synthesis under conditions of phase-transfer catalysis with a simultaneous reduction of the reaction times from 1440 min to 10 min. The use of MWI proved promising in the opening of the aziridine ring with alcohols (reaction No. 11). The reaction time in this case was reduced by a factor of 480 as compared to the thermally activated reaction. Furthermore, the opening of the aziridine ring with phenol appeared possible only under the MWI conditions. This is a clear manifestation of the MWE.

Nevertheless, the use of MWI does not give positive results in all cases. For instance, the microwave-assisted O-alkylation (No. 3) proceeds 2 times slower than the thermally activated

**Table 6.** Synthesis of alcohols and phenols. Deprotection of the OH group.

| No.                   | Reaction                                                                                                                                        | Conditions                                                         | Number of examples | Yield (%)                             | Ref.     |
|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|--------------------|---------------------------------------|----------|
| Synthesis of alcohols |                                                                                                                                                 |                                                                    |                    |                                       |          |
| 1                     | $PhCHO + (CH_2O)_n \longrightarrow PhCH_2OH$                                                                                                    | a) $KF/Al_2O_3$ , MW, 5 min<br>b) $\Delta$ , 7 h                   | 1<br>1             | 92<br>85                              | 85<br>85 |
| 2                     | $R^1COR^2 \xrightarrow{Pr^iOH} R^1CH(OH)R^2$<br>$R^1 = Ph; R^2 = Me, Bu^t$ (conditions a);<br>$R^1 = Alk, Ar; R^2 = H, Alk, Ar$ (conditions b). | a) Ru catalyst, MW, 1.5–14 min<br>b) $Al_2O_3, KOH$ , MW, 9–16 min | 19<br>28           | 24–99<br>85–93                        | 86<br>87 |
| 3                     | $R^1CO_2R^2 \longrightarrow R^1CH_2OH + R^2OH$<br>$R^1 = Ar, Bn; R^2 = Me, Et$ .                                                                | $NaBH_4/LiCl$ , MW, 2–8 min                                        | 12                 | 55–97                                 | 88       |
| 4                     | $R^1CO_2R^2 + H_2O \longrightarrow R^1CO_2H + R^2OH$<br>$R^1 = Ph, Me; R^2 = Alk, Ph, Bn$ .                                                     | $KF/Al_2O_3$ , MW, 2 min                                           | 7                  | 92–97                                 | 89       |
| 5                     |                                                              | $NaBH_4, NaOH-EtOH$ , MW, 13 min                                   | 11                 | 84–92                                 | 90       |
| 6                     | <br>$X = O, NH_2$ .                                          | $KOH$ , MW, 3 min                                                  | 6                  | 93–99                                 | 91       |
| 7                     | <br>MEM = $MeOCH_2CH_2OCH_2$ .                               | a) $PhEt_2N$ , MW, 30–150 min<br>b) $Et_2Bu^iN, \Delta$ , 72 h     | 4<br>1             | 83–90 <sup>a</sup><br>86 <sup>a</sup> | 92<br>92 |
| Deprotection          |                                                                                                                                                 |                                                                    |                    |                                       |          |
| 8                     | $ROSiMe_3 + H_2O \longrightarrow ROH$<br>$R = Alk, Ar$ .                                                                                        | kaolinite, MW, 1–2.5 min                                           | 17                 | 58–87                                 | 93       |
| 9                     | <br>$R = Alk, Ar$ .                                          | a) MW, MeCN, 7–10 min<br>b) $\Delta$ , 65–95 min                   | 16<br>16           | 80–97<br>70–90                        | 94<br>94 |

<sup>a</sup> The total yield of products is given.

**Table 7.** Reactions involving alcohols and phenols.

| No.                           | Reaction                                                                                                                                   | Conditions                                                                                                                                                    | Number of exam-<br>ples | Yield (%)          | Ref.       |
|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|--------------------|------------|
| <b>Substitution reactions</b> |                                                                                                                                            |                                                                                                                                                               |                         |                    |            |
| 1                             | <br>$\text{R} = \text{H, Hal, NO}_2.$                                                                                                      | clay, MW, 2–8 min                                                                                                                                             | 15                      | 74–93 <sup>a</sup> | 95         |
| <b>O-Sulfonylation</b>        |                                                                                                                                            |                                                                                                                                                               |                         |                    |            |
| 2                             |                                                                                                                                            | K <sub>2</sub> CO <sub>3</sub> , THF, MW, 6 min                                                                                                               | 10                      | 69–91              | 96         |
| <b>O-Alkylation</b>           |                                                                                                                                            |                                                                                                                                                               |                         |                    |            |
| 3                             | <br>$\text{X} = \text{Cl, Br, OTs}; n = 4, 6, 8.$                                                                                          | KOH, Bu <sub>4</sub> <sup>n</sup> NBr, PhMe or xylene, or cyclohexane<br>a) MW, 5–30 min<br>b) Δ, 15 min (for X = OTs)                                        | 31<br>10                | 27–96<br>36–92     | 97         |
| 4                             | <br>$\text{X} = \text{Cl, Br, OTs, OMs, OSO}_2\text{R}.$                                                                                   | a) MOH (M = Li, Na, K, Cs), Bu <sub>4</sub> <sup>n</sup> NI, xylene, MW, 10 min<br>b) Δ, 10 min                                                               | 40<br>39                | 0–96<br>0–76       | 98<br>98   |
| 5                             | $\text{ArOH} + \text{RCl} \rightarrow \text{ArOR}$<br>$\text{R} = \text{Bn, Ar}.$                                                          | NaOH–H <sub>2</sub> O, MW, 1–2.5 min                                                                                                                          | 9                       | 52–88              | 99         |
| 6                             | <br>$n = 5–23.$                                                                                                                            | a) NaOH, MW, 2 min<br>b) Δ, 30 min                                                                                                                            | 9<br>5                  | 34–39<br>40–60     | 100<br>100 |
| 7                             | <br>$\text{X} = \text{CHO, CO}_2\text{Et}; \text{Y} = \text{H, OMe}.$                                                                      | MeONa, DMF–EtOH, MW, 7 min                                                                                                                                    | 3                       | 82–95              | 101        |
| 8                             |                                                                                                                                            | KOH, DMF–benzene<br>a) MW, 45–60 min<br>b) Δ, 6 h                                                                                                             | 2<br>2                  | 85–96<br>58–62     | 102        |
| 9                             | <br>$\text{Alk} = \text{C}_n\text{H}_{n+1} (n = 12, 14, 16, 18).$                                                                          | a) KOH + K <sub>2</sub> CO <sub>3</sub> , Bu <sub>4</sub> <sup>n</sup> NBr, MW, 10 min<br>b) K <sub>2</sub> CO <sub>3</sub> , Me <sub>2</sub> CO, Δ, 1440 min | 4<br>4                  | 80–86<br>49–66     | 103<br>103 |
| 10                            | <br>$\text{X} = \text{Hal, SAlk}.$                                                                                                         | anion-exchange resin, MW, 3–5 min                                                                                                                             | 10                      | 62–90              | 104        |
| 11                            | <br>$\text{R}^1, \text{R}^4 = \text{Alk, Ar}; \text{R}^2, \text{R}^3 = \text{H, Alk}; \text{R}^2-\text{R}^3 = (\text{CH}_2)_n (n = 3, 4).$ | Sn(OTf) <sub>2</sub> or BF <sub>3</sub> ·Et <sub>2</sub> O<br>a) MW, 15 min<br>b) Δ, 5–7200 min                                                               | 39<br>39                | 40–98<br>0–99      | 105        |

**Table 7** (continued).

| No.                                                                 | Reaction | Conditions                                                                                                                                                       | Number of exam-<br>ples | Yield (%)          | Ref.       |
|---------------------------------------------------------------------|----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|--------------------|------------|
| <b>O-Glycosylation</b>                                              |          |                                                                                                                                                                  |                         |                    |            |
| 12                                                                  |          | MW, 4–60 min                                                                                                                                                     | 20                      | 10–100             | 106        |
| 13                                                                  |          | a) K-10, <sup>b</sup> MW, 10–20 min<br>b) K-10, <sup>b</sup> PhCl, MW, 2–15 min                                                                                  | 6<br>20                 | 71–87<br>52–93     | 107<br>108 |
| R <sup>1</sup> = Alk, Ar; R <sup>2</sup> , R <sup>3</sup> = H, OAc. |          |                                                                                                                                                                  |                         |                    |            |
| <b>Protection of the OH group</b>                                   |          |                                                                                                                                                                  |                         |                    |            |
| 14                                                                  |          | a) Zr(OH) <sub>2</sub> , MW, 7–15 min<br>b) Δ, 50–110 min                                                                                                        | 20<br>21                | 81–97<br>70–91     | 94<br>94   |
| R = Alk, Ar.                                                        |          |                                                                                                                                                                  |                         |                    |            |
|                                                                     |          | c) Me–N <sup>+</sup> (Me) <sub>2</sub> –N <sup>–</sup> (Me) <sub>2</sub> –AlCl <sub>4</sub> <sup>–</sup> , MW, 15–30 min<br>d) FeSO <sub>4</sub> , MW, 0.5–4 min | 9<br>13                 | 74–98<br>78–97     | 109<br>110 |
| 15                                                                  |          | I <sub>2</sub> , THF, MW, 150–170 s                                                                                                                              | 5                       | 75–78 <sup>c</sup> | 78         |
| n = 2–6.                                                            |          |                                                                                                                                                                  |                         |                    |            |
| 16                                                                  |          | imidazole, MW, 30–120 s                                                                                                                                          | 14                      | 70–96              | 111        |
| R = Alk, Ar.                                                        |          |                                                                                                                                                                  |                         |                    |            |
| 17                                                                  |          | LiClO <sub>4</sub> , MW, 1–4 min                                                                                                                                 | 17                      | 58–83              | 93         |
| R = Alk, Ar.                                                        |          |                                                                                                                                                                  |                         |                    |            |

<sup>a</sup> The reaction is impossible with aliphatic alcohols and phenols; <sup>b</sup> Hereinafter, K-10 is a montmorillonite modification; <sup>c</sup> the yield of the disubstituted product is 15%–17%.

reaction. In a few cases, the yields of MWI reactions were lower than those of the thermal reactions, despite some acceleration (No. 6).

## VIII. Synthesis of aldehydes and ketones.

### Protection and deprotection of the carbonyl group

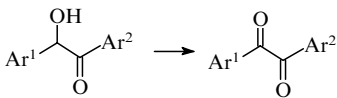
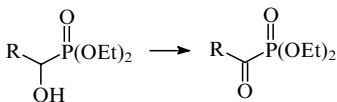
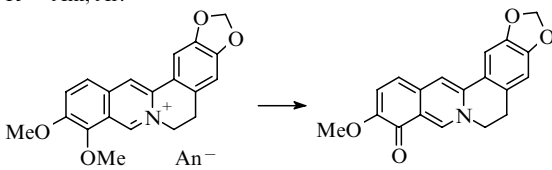
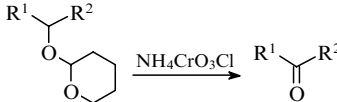
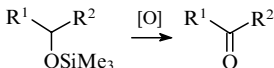
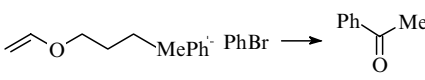
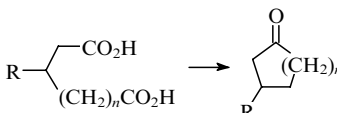
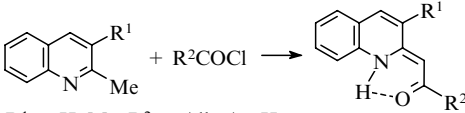
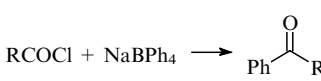
Among methods used for the microwave-assisted synthesis of carbonyl compounds, the most common are: oxidation of an activated methylene group (Table 8, reaction No. 1); selective oxidation of alcohols [in particular, oxidation of benzyl alcohols

with calcium hypochlorite (No. 2), mild oxidation of benzoin over alumina or zeolites without oxidants (No. 3) and oxidation of 1-hydroxyphosphonates on solid supports (No. 4)]; selective dealkylation (No. 5); oxidative deprotonation of tetrahydropyranyl (No. 6) or trimethylsilyl ethers (No. 7), the Heck reaction (No. 8), intramolecular condensation of dicarboxylic acids over graphite (No. 9), condensation of carboxylic acid chlorides with 2-methyl-quinolines (No. 10), cross-coupling of sodium organoborates with acyl and aroyl chlorides (No. 11), catalytic [2 + 2 + 1]-cycloaddition (the Pauson–Khand reaction, see Nos 17 and 18 in Table 2).

**Table 8.** Synthesis of aldehydes and ketones.

| No.                                        | Reaction | Conditions                                                     | Number of exam-<br>ples | Yield (%) | Ref. |
|--------------------------------------------|----------|----------------------------------------------------------------|-------------------------|-----------|------|
| 1                                          |          | HNIB, <sup>a</sup> MW, 90–150 s                                | 10                      | 45–90     | 112  |
| R <sup>1</sup> , R <sup>2</sup> = Alk, Ar. |          |                                                                |                         |           |      |
| 2                                          |          | H <sub>2</sub> O, Al <sub>2</sub> O <sub>3</sub> , MW, 6–120 s | 8                       | 57–98     | 113  |
| R = H, Alk.                                |          |                                                                |                         |           |      |

Table 8 (continued).

| No. | Reaction                                                                                                                                                                                                                                | Conditions                                                                                                                                                                                                                           | Number of examples  | Yield (%)               | Ref.              |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|-------------------------|-------------------|
| 3   |                                                                                                                                                        | a) Al <sub>2</sub> O <sub>3</sub> , MW, 1 min<br>b) zeolite A, MW, 6 min                                                                                                                                                             | 1 <sup>b</sup><br>6 | 65<br>69–91             | 113<br>114        |
| 4   | <br>R = Alk, Ar.                                                                                                                                       | Cr <sub>2</sub> O <sub>3</sub> /Al <sub>2</sub> O <sub>3</sub> , MW, 0.5–3 min                                                                                                                                                       | 17                  | 68–89                   | 115               |
| 5   |                                                                                                                                                        | Al <sub>2</sub> O <sub>3</sub> , MW, 5 min                                                                                                                                                                                           | 1                   | 98                      | 116               |
| 6   | <br>R <sup>1</sup> = Alk, Ar; R <sup>2</sup> = H, Alk.                                                                                                 | K-10, MW, 20–120 s                                                                                                                                                                                                                   | 10                  | 78–94                   | 117               |
| 7   | <br>R <sup>1</sup> = Alk, Ar; R <sup>2</sup> = H, Alk;<br>[O] — zeofen <sup>c</sup> (a), [PhCH <sub>2</sub> PPh <sub>3</sub> ][HSO <sub>5</sub> ] (b). | a) MW, 20–120 s<br>b) BiCl <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> , MW, 3–5 min                                                                                                                                              | 9<br>10             | 78–98<br>80–99          | 118<br>119        |
| 8   |                                                                                                                                                      | a) 1) DMF–H <sub>2</sub> O, MW, 1 h; 2) H <sup>+</sup><br>b) [Pd], Ph <sub>2</sub> P(CH <sub>2</sub> ) <sub>3</sub> PPh <sub>2</sub> (dppp), K <sub>2</sub> CO <sub>3</sub> , DMF–H <sub>2</sub> O (12.5:1), 80 °C, 16 h             | 1<br>1              | 62<br>82                | 120<br>120        |
| 9   | <br>R = H, Me; n = 2–4.                                                                                                                              | a) graphite, Fe, Al or Bi oxides, MW, 4 min<br>b) Δ, 30 min                                                                                                                                                                          | 11<br>6             | 10–90<br>7–90           | 121<br>121        |
| 10  | <br>R <sup>1</sup> = H, Me; R <sup>2</sup> = Alk, Ar, Het.                                                                                           | a) SiO <sub>2</sub> , MW, 4 min<br>b) 200 °C, 60 min                                                                                                                                                                                 | 13<br>13            | 53–91 <sup>d</sup><br>0 | 122<br>122        |
| 11  | <br>R = Alk, Ar.                                                                                                                                     | a) Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> , KF, Me <sub>2</sub> CO, MW, 9 min<br>b) Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> , KF/Al <sub>2</sub> O <sub>3</sub> , Me <sub>2</sub> CO, MW, 5 min<br>c) Δ, 20 h | 10<br>10<br>10      | 87–98<br>90–97<br>68–90 | 123<br>124<br>123 |

<sup>a</sup> HNIB is hydroxy(*p*-nitrobenzylsulfonyl)iodobenzene; <sup>b</sup> for Ar<sup>1</sup> = Ar<sup>2</sup> = Ph; <sup>c</sup> zeofen is Fe(NO<sub>3</sub>)<sub>3</sub>/HZSM-5 oxidant; <sup>d</sup> the reaction is impossible for carboxylic acid anhydrides with R<sup>2</sup> = Bu<sup>t</sup> and Pr<sup>i</sup>.

A comparison of the microwave and thermal methods for the activation of these reactions indicate that the yields of target products are virtually identical in both cases, but the use of MWI accelerates the reactions. Furthermore, the condensation of carboxylic acid chlorides with 2-methylquinolines (No. 10) is possible only under the MWI conditions.

Acid anhydrides (Table 9, No. 1), polyatomic alcohols (Nos 2 and 3) or hydroxylamine (No. 4) are commonly used to protect the carbonyl groups in various chemical transformations.

As deprotection methods, the oxidative deprotonation of acetals and ketals (Nos 5 and 6), mild oxidative conversion of

oximes (Nos 7 and 8), hydrazones (Nos 8 and 9) and semicarbazones (No. 10) over various supports (*e.g.*, K-10, SiO<sub>2</sub>, Al<sub>2</sub>O<sub>3</sub>, *etc.*) are utilised.

## IX. Synthesis of carboxylic acids, esters and lactones

Table 10 summarises examples of the utilisation of MWI in the synthesis of carboxylic acids. The hydrolysis of esters over solid supports (No. 1) and amides in the presence of sulfuric acid with variable concentrations (No. 2) and the so called Mathews dry

**Table 9.** Microwave-assisted protection and deprotection of the carbonyl group.

| No.                                | Reaction                                                                                                                                                                                                        | Conditions                                                                                     | Number of examples | Yield (%) | Ref. |
|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|--------------------|-----------|------|
| Protection of the carbonyl group   |                                                                                                                                                                                                                 |                                                                                                |                    |           |      |
| 1                                  | $\text{RCHO} + \text{Ac}_2\text{O} \longrightarrow \text{RCH}(\text{OAc})_2$                                                                                                                                    | a) envirocat EPZ10, <sup>a</sup> MW, 10–55 s                                                   | 13                 | 83–92     | 125  |
|                                    |                                                                                                                                                                                                                 | b) $\text{FeCl}_3/\text{SiO}_2$ , MW, 3–5 min                                                  | 12                 | 78–95     | 126  |
| 2                                  | $\text{R}^1-\text{C}(=\text{O})-\text{C}_6\text{H}_4\text{R}^{2-p} + (\text{CH}_2\text{OH})_2 \longrightarrow \text{R}^1-\text{C}(\text{OCH}_2\text{CH}_2\text{O})_2-\text{C}_6\text{H}_4\text{R}^{2-p}$        | a) $\text{H}^+$ , benzene, MW, 50–120 min                                                      | 4                  | 75–90     | 102  |
|                                    | $\text{R}^1 = \text{H, Me; R}^2 = \text{Alk.}$                                                                                                                                                                  | b) $\Delta$ , 4–5 h                                                                            | 4                  | 58–72     | 102  |
| 3                                  | $\text{R}^1-\text{C}(=\text{O})-\text{R}^2 + \text{HOCH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH} \longrightarrow \text{R}^1-\text{C}(\text{OCH}_2\text{CH}(\text{OCH}_2\text{CH}_2\text{OR}^2))_2-\text{R}^2$ | $\text{H}_3[\text{PW}_{12}\text{O}_{40}]$ , MeCN, MW, 2–12 min                                 | 10                 | 0–93      | 127  |
|                                    | $\text{R}^1 = \text{Alk, Ar; R}^2 = \text{H, Alk, Ar.}$                                                                                                                                                         |                                                                                                |                    |           |      |
| 4                                  | $\text{R}^1-\text{C}(=\text{O})-\text{R}^2 + \text{NH}_2\text{OH} \cdot \text{HCl} \longrightarrow \text{R}^1-\text{C}(\text{OH})=\text{N}-\text{R}^2$                                                          | a) $\text{Al}_2\text{O}_3$ , MW, 1–7 min                                                       | 18                 | 47–99     | 128  |
|                                    | $\text{R}^1 = \text{Alk, Ar; R}^2 = \text{H, Me.}$                                                                                                                                                              | b) molecular sieves, 20 °C, 30–95 min                                                          | 18                 | 0–88      | 128  |
| Deprotection of the carbonyl group |                                                                                                                                                                                                                 |                                                                                                |                    |           |      |
| 5                                  | $\text{Ar}-\text{C}(\text{OR})_2-\text{R} \xrightarrow{[\text{BnPPH}_3]^+[\text{HSO}_5]^-} \text{Ar}-\text{C}(=\text{O})-\text{R}$                                                                              | $\text{BiCl}_3$ , $\text{CH}_2\text{Cl}_2$ , MW, 4–6 min                                       | 6                  | 80–95     | 119  |
|                                    | $\text{R} = \text{H, Alk.}$                                                                                                                                                                                     |                                                                                                |                    |           |      |
| 6                                  | $\text{R}^1-\text{C}(\text{OR})_2-\text{R}^2 \xrightarrow{[\text{BnPPH}_3]^+[\text{HSO}_5]^-} \text{R}^1-\text{C}(=\text{O})-\text{R}^2$                                                                        | $\text{BiCl}_3$ , $\text{CH}_2\text{Cl}_2$ , MW, 3–5 min                                       | 10                 | 80–96     | 119  |
|                                    | $\text{R}^1 = \text{Alk, Ar; R}^2 = \text{H, Alk.}$                                                                                                                                                             |                                                                                                |                    |           |      |
| 7                                  | $\text{R}^1-\text{C}(\text{OR})=\text{N}-\text{OH} \longrightarrow \text{R}^1-\text{C}(=\text{O})-\text{R}^2$                                                                                                   | a) K-10, MW, 1–6 min                                                                           | 7                  | 80–94     | 129  |
|                                    | $\text{R}^1 = \text{Alk, Ar; R}^2 = \text{H, Alk, Ar.}$                                                                                                                                                         | b) BTSC <sup>b</sup> /K-10, MW, 60 min                                                         | 7                  | 88–93     | 130  |
|                                    |                                                                                                                                                                                                                 | c) BTSC <sup>b</sup> /K-10, $\text{CH}_2\text{Cl}_2$ , MW, 40 min                              | 7                  | 84–90     | 130  |
|                                    |                                                                                                                                                                                                                 | d) $\text{HCO}_2\text{H}/\text{SiO}_2$ , MW, 2–4 min                                           | 13                 | 86–94     | 131  |
| 8                                  | $\text{R}^1-\text{C}(\text{OR})=\text{N}-\text{X} \longrightarrow \text{R}^1-\text{C}(=\text{O})-\text{R}^2$                                                                                                    | zeolite-41/ $\text{SiO}_2$ , (see °), Cr-MSM-4/ $\text{SiO}_2$ (see °), MW, 5–10 min           | 30                 | 72–98     | 132  |
|                                    | $\text{R}^1 = \text{Alk, Ar; R}^2 = \text{H, Alk, Ar; X} = \text{OH, NHTs.}$                                                                                                                                    |                                                                                                |                    |           |      |
| 9                                  | $\text{R}^1-\text{C}(\text{OR})=\text{N}-\text{NMe}_2 \longrightarrow \text{R}^1-\text{C}(=\text{O})-\text{R}^2$                                                                                                | a) $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ , $\text{SiO}_2$ , MW, 5–10 min                   | 19                 | 83–91     | 133  |
|                                    | $\text{R}^1 = \text{Alk, Ar; R}^2 = \text{H, Alk, Ar.}$                                                                                                                                                         | b) $\text{PdCl}_2 \cdot \text{SnCl}_2 \cdot \text{H}_2\text{O}$ , MW, 90 s                     | 8                  | 78–98     | 134  |
| 10                                 | $\text{R}^1-\text{C}(\text{OR})=\text{N}-\text{NHCNHNH}_2 \longrightarrow \text{R}^1-\text{C}(=\text{O})-\text{R}^2$                                                                                            | a) $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O} + \text{K-10 (clayfen)}$ , MW, 20–240 s | 11                 | 82–95     | 135  |
|                                    | $\text{R}^1 = \text{Alk, Ar; R}^2 = \text{H, Alk, Ph.}$                                                                                                                                                         | b) $\text{CAN}^{\text{d}}/\text{Al}_2\text{O}_3$ , MW, 10–300 s                                | 11                 | 68–90     | 136  |

<sup>a</sup> Envirocat EPZ10 is a support material; <sup>b</sup> BTSC is bis(trimethylsilyl)chromate; <sup>c</sup> Cr-MSM-4 is an ion-exchange aluminosilicate; <sup>d</sup> CAN is cerium ammonium nitrate.

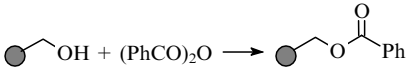
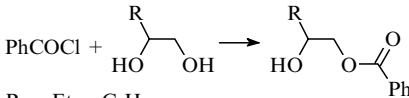
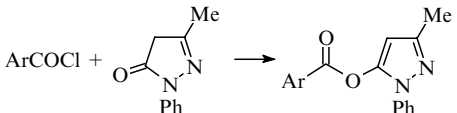
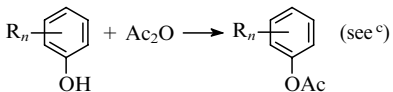
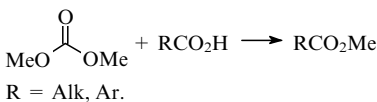
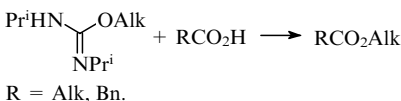
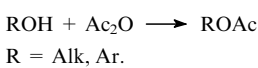
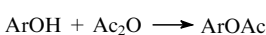
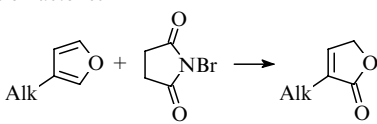
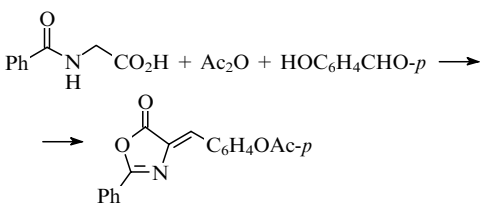
hydrolysis of amides and nitriles in the presence of phthalic acid under the solvent-free conditions (Nos 3 and 4) are the most common routes.  $\beta,\gamma$ -Unsaturated carboxylic acids can be prepared by Knoevenagel condensation of aldehydes with maleic acid followed by double bond isomerisation (No. 5). For the latter reaction, the use of solvent-free MWI conditions not only reduced the reaction time but also increased the yield of the product by 43%, which is evidence of the MWE.

Carboxylic acid esters can be prepared under MWI conditions by the interaction of acids with alcohols (Table 11, Nos 1–3). Polyesters are formed in the intermolecular polycondensation of L-2-hydroxy-3-phenylpropionic acid (No. 4) or catalytic polymerisation of lactones (No. 5).

Several examples of solid-state microwave synthesis of esters (Nos 6 and 7) by the interaction of aliphatic or aromatic acids with *para*-substituted benzyl chloride grafted to a solid support or



Table 11 (continued).

| No.                   | Reaction                                                                                                                                                                                                               | Conditions                                                                                                      | Number of exam-<br>ples | Yield (%)                   | Ref.              |
|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-------------------------|-----------------------------|-------------------|
| Synthesis of esters   |                                                                                                                                                                                                                        |                                                                                                                 |                         |                             |                   |
| 7                     |                                                                                                                                       | NMP, MW, 5–20 min                                                                                               | 10                      | 27–99                       | 146               |
| 8                     | <br>R = Et, n-C8H17.                                                                                                                  | a) Bu <sub>3</sub> SnO, Et <sub>3</sub> N, PhMe, MW, 9 min<br>b) Δ, 7–820 min                                   | 9<br>5                  | 29–99<br>61–95 <sup>b</sup> | 147<br>147        |
| 9                     |                                                                                                                                       | MW, 8 min                                                                                                       | 8                       | 37–87                       | 148               |
| 10                    | <br>R <sub>n</sub> = 2-Ac; 2,6-Bu <sub>2</sub> -4-X (X = OH, CO <sub>2</sub> H);<br>2-C(O)CH <sub>2</sub> OMe-3,5-(OH) <sub>2</sub> . | a) I <sub>2</sub> , MW, 2–4 min<br>b) Δ, 3–5 h                                                                  | 7<br>7                  | 94–98<br>50–70              | 149<br>149        |
| 11                    | <br>R = Alk, Ar.                                                                                                                      | a) DBU, <sup>d</sup> MW, 2–24 min<br>b) Δ, 4–24 h                                                               | 9<br>8                  | 95–99<br>90–99              | 150<br>150        |
| 12                    | <br>R = Alk, Bn.                                                                                                                    | THF, MW, 5 min                                                                                                  | 11                      | 75–94                       | 151               |
| 13                    | <br>R = Alk, Ar.                                                                                                                    | MW, 2–10 min                                                                                                    | 22                      | 80–95                       | 152               |
| 14                    |                                                                                                                                     | Al <sub>2</sub> O <sub>3</sub> , Py, MW, 1–6 min                                                                | 13                      | 54–100                      | 153               |
| Synthesis of lactones |                                                                                                                                                                                                                        |                                                                                                                 |                         |                             |                   |
| 15                    |                                                                                                                                     | a) MW, 15–60 min<br>b) ultrasound, 12–15 min<br>c) Δ, 32–48 h                                                   | 5<br>5<br>5             | 62–76<br>56–62<br>36–42     | 154<br>154<br>154 |
| 16                    |                                                                                                                                     | a) KF/AlPO <sub>4</sub> , <sup>e</sup> MW, 15 min<br>b) KF/Al <sub>2</sub> O <sub>3</sub> , <sup>e</sup> Δ, 4 h | 25<br>25                | 0–87<br>0–72                | 155<br>155        |

<sup>a</sup> Different durations of irradiation and radiation power were used; <sup>b</sup> products of the substitution of the second OH group were also obtained; <sup>c</sup> the acetylation of substituted 5-hydroxyflavones was also accomplished; <sup>d</sup> DBU is 1,2-diazabicyclo[5.4.9]undec-7-ene; <sup>e</sup> 25 support types were elucidated, the support indicated provided the maximum yield of products.

The esterification of carboxylic acids can also be realised with O-alkylated isoureas (No. 12).

The acetylation of alcohols and phenols with acetic anhydride affords the respective acetic acid alkyl and aryl esters (Nos 13 and 14).

Lactones can be prepared by the mild oxidation of furan with *N*-bromosuccinimide (Table 11, reaction No. 15). The reaction was applied to the synthesis of naturally occurring biologically active limonoids. Gopalakrishnan *et al.*<sup>154</sup> reported the prepara-

tion of lactones under the conditions of thermal, ultrasound and microwave activation. The maximum yield was obtained with microwave activation, whereas the reaction time was the minimum in the case of ultrasound activation: it was 4 and 190 times shorter than those under microwave and thermal activations, respectively.

The three-component condensation of acetic anhydride, *p*-hydroxybenzaldehyde and hippuric acid afforded azlactones (No. 16).

## X. Synthesis of amines, imines, oximes, substituted hydroxylamines, hydrazines and hydrazones and reactions with them

Table 12 lists examples of microwave-assisted syntheses of anilines (No. 1), imines (Nos 2 and 3), hydroxylamines (No. 4), hydrazines (Nos 5 and 6) and hydrazones (Nos 7 and 8). The yields of target products in these reactions were in the range of 81%–99% and the reaction times were from 0.5 to 30 min.

For several of the above reactions, comparative results on the microwave and thermal conditions were reported, which indicated that the MWI gave rise to their substantial acceleration.

Among the microwave reactions of amines, the following classes are of note: reductive elimination of styrenes (Table 13, No. 1) and alkynes (No. 2), numerous reactions of N-alkylation (Nos 3–11) and N-arylation (Nos 12–20) and hydrogenation (No. 21).

According to the studies reporting comparative data (which are, unfortunately, rather sparse, see Table 13), the use of MWI somewhat accelerates the reactions but the respective improvement in the yields of products is only insignificant.

**Table 12.** Synthesis of amines, imines, substituted hydroxylamines, hydrazines and hydrazones.

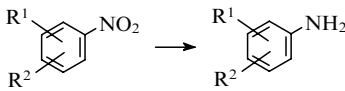
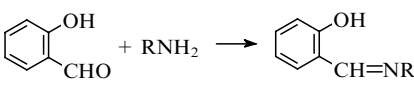
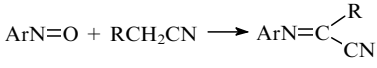
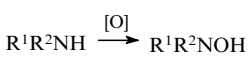
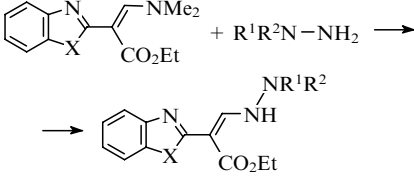
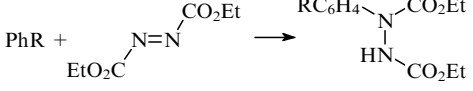
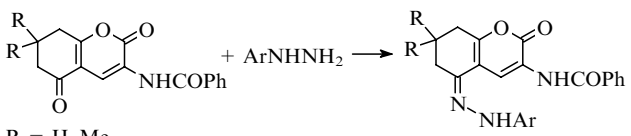
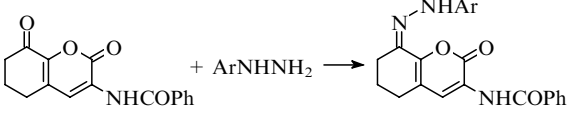
| No. | Reaction                                                                                                                                                                                                                                                                             | Conditions                                                                                                                                                                                                             | Number of examples | Yield (%)       | Ref.       |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------|------------|
| 1   |  <p>a) R<sup>1</sup>, R<sup>2</sup> = H, Me, Ph, OH, NH<sub>2</sub>, CONH<sub>2</sub>, CO<sub>2</sub>H, CN;<br/>b) R<sup>1</sup> = H, Hal, Me, OMe, OH, NH<sub>2</sub>; R<sup>2</sup> = H, Alk.</p> | <p>a) NaH<sub>2</sub>PO<sub>4</sub>, FeSO<sub>4</sub>·7 H<sub>2</sub>O, MW, 50–100 s<br/>b) N<sub>2</sub>H<sub>4</sub>·H<sub>2</sub>O/Al<sub>2</sub>O<sub>3</sub>, FeCl<sub>3</sub>·6 H<sub>2</sub>O, MW, 8–10 min</p> | 15<br>11           | 68–88<br>81–97  | 156<br>157 |
| 2   |  <p>R = Ar, Het.</p>                                                                                                                                                                                | MW, 0.5–4 min                                                                                                                                                                                                          | 16                 | 77–98           | 158        |
| 3   |  <p>R = Ar', CN, CO<sub>2</sub>H, CO<sub>2</sub>Alk, CPh, CONH<sub>2</sub>.</p>                                                                                                                   | LiBr, MW, 30–130 s                                                                                                                                                                                                     | 11                 | 60–90           | 159        |
| 4   |  <p>R<sup>1</sup> = Alk; R<sup>2</sup> = H, Alk.</p>                                                                                                                                              | OXONE, Al <sub>2</sub> O <sub>3</sub> or SiO <sub>2</sub><br>a) MW, 40–60 s<br>b) Δ, 0.5–24 h                                                                                                                          | 5<br>10            | 89–97<br>50–100 | 160        |
| 5   |  <p>R<sup>1</sup> = H, Me; R<sup>2</sup> = Me, Ph, CO<sub>2</sub>Me; X = O, S, NH.</p>                                                                                                            | <p>a) MW, 30 min<br/>b) Δ, 6–216 h</p>                                                                                                                                                                                 | 5<br>3             | 90–95<br>71–80  | 161<br>161 |
| 6   |  <p>R = Me, OMe.</p>                                                                                                                                                                              | <p>a) InCl<sub>3</sub>/SiO<sub>2</sub>, MW, 2–6 min<br/>b) Δ, 8–22 h</p>                                                                                                                                               | 13<br>13           | 68–92<br>60–80  | 162<br>162 |
| 7   |  <p>R = H, Me.</p>                                                                                                                                                                                | MW, 6–10 min                                                                                                                                                                                                           | 6                  | 61–85           | 163        |
| 8   |                                                                                                                                                                                                   | MW, 3–8 min                                                                                                                                                                                                            | 5                  | 65–98           | 164        |



**Table 13.** Reactions involving amines.

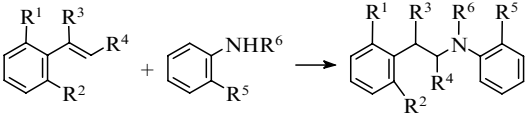
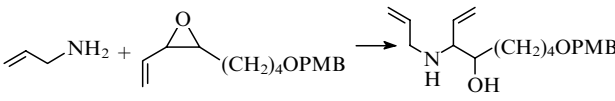
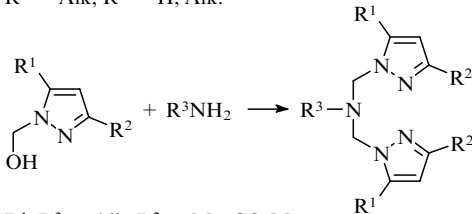
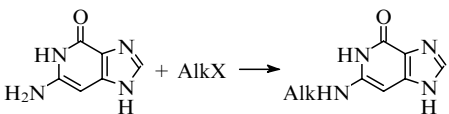
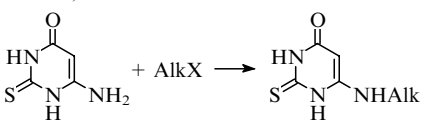
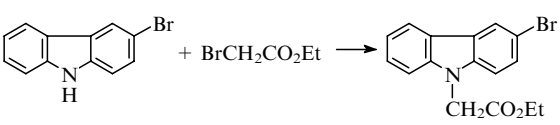
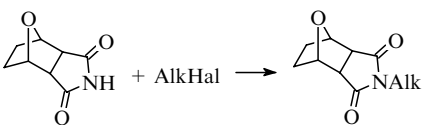
| No.                        | Reaction                                                                                                                                                | Conditions                                                                                                                | Number of examples | Yield (%)                                 | Ref.              |
|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|--------------------|-------------------------------------------|-------------------|
| Addition to multiple bonds |                                                                                                                                                         |                                                                                                                           |                    |                                           |                   |
| 1                          | <br>$R^1-R^6 = \text{H, Alk.}$                                         | Bu <sup>t</sup> OK, MW, 1.5–10 min                                                                                        | 7                  | 42–100                                    | 165               |
| 2                          | $R^1C\equiv CR^2 + R^3NH_2 \xrightarrow{1,2} R^1CH_2CH(R^2)NHR^3$<br>$R^1-R^3 = \text{Alk, Ar.}$                                                        | 1) Cp <sub>2</sub> TiMe <sub>2</sub> , PhMe, MW, 2–3 h;<br>2) H <sub>2</sub> , Pd/C                                       | 18                 | 34–93                                     | 166               |
| N-Alkylation               |                                                                                                                                                         |                                                                                                                           |                    |                                           |                   |
| 3                          | $RNH_2 + ArCHO + HO_2CCH_2CO_2Et \xrightarrow{AcOH} ArCH_2CH(NHR)CO_2Et$                                                                                | a) MW, 8–20 min<br>b) EtOH, Δ, 10–24 h                                                                                    | 11<br>2            | 0–27 <sup>a</sup><br>2–4                  | 167<br>167        |
| 4                          | <br>PMB = <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> . | LiOTf, MeCN, MW, 1 h                                                                                                      | 1                  | 92                                        | 168               |
| 5                          | $NH_4OH + R \text{ (epoxide)} \rightarrow R \text{ (polyol)}$<br>$R = \text{Me, Ph.}$                                                                   | a) AlkOH, MW, 35–180 min<br>b) Δ, 6 days                                                                                  | 8<br>2             | 43–100 <sup>b</sup><br>18–72 <sup>b</sup> | 169<br>169        |
| 6                          | $R^1R^2NH + HCHO \rightarrow R^1R^2NMe$<br>$R^1 = \text{Alk}; R^2 = \text{H, Alk.}$                                                                     | HCO <sub>2</sub> H, DMSO, MW, 1 min                                                                                       | 1                  | 93                                        | 170               |
| 7                          | <br>$R^1, R^3 = \text{Alk}; R^2 = \text{Me, CO}_2\text{Me.}$         | a) MW, 20 min<br>b) Δ, 4 h<br>c) MeCN, 25 °C, 4 days                                                                      | 5<br>5<br>5        | 75–90<br>80–87<br>80–85                   | 171<br>171<br>171 |
| 8                          | <br>X = Cl, Br.                                                      | DMF, MW, 6–9 min                                                                                                          | 3                  | 21–70                                     | 172               |
| 9                          | <br>X = Cl, Br.                                                      | a) DMF, MW, 9–11 min<br>b) Na <sub>2</sub> CO <sub>3</sub> , Bu <sub>4</sub> N <sup>+</sup> I <sup>−</sup> , MW, 6–10 min | 2<br>9             | 83–84<br>87–95                            | 172<br>172        |
| 10                         |                                                                      | KOH, DMF, MW, 2.4–6 min                                                                                                   | 8                  | 52–85                                     | 173               |
| 11                         |                                                                      | K <sub>2</sub> CO <sub>3</sub> , Bu <sub>4</sub> N <sup>+</sup> Br <sup>−</sup> , MW, 1–1.5 min                           | 7                  | 90–98                                     | 174               |

Table 13 (continued).

| No.                  | Reaction                                                                                                        | Conditions                                                                                       | Number of examples | Yield (%)      | Ref.       |
|----------------------|-----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|--------------------|----------------|------------|
| <b>N-Arylation</b>   |                                                                                                                 |                                                                                                  |                    |                |            |
| 12                   |                                                                                                                 | <br>a) NMP, MW, 5 h<br>b) Δ, 60 h                                                                | 3                  | 29–56          | 175        |
| 13                   | $R^1R^2NH + ArBr \longrightarrow R^1R^2NAr$<br>$R^1, R^2 = H, Alk.$                                             | Pd catalyst, Bu <sup>t</sup> ONa, PhMe, MW, 4–15 min                                             | 13                 | 0–86           | 176        |
| 14                   | $R^1C_6H_4Br-p + R^2R^3NH \longrightarrow R^1C_6H_4NR^2R^3-p$<br>$R^1 = H, Me, OMe, CN; R^2, R^3 = H, Alk, Ph.$ | Pd(OAc) <sub>2</sub> , Bu <sup>t</sup> OK, DMF, MW, 4 min                                        | 13                 | 48–85          | 177        |
| 15                   | <br>$R^1 = Alk; R^2 = H, Alk;$<br>$X^1 = Cl, Br; X^2 = H, Hal, OMe; X^3 = H, NH_2, OMe.$                        | Pr <sub>3</sub> EtN, Pr <sup>i</sup> OH, MW, 5–160 min                                           | 12                 | 29–97          | 178        |
| 16                   | <br>$R^1, R^3, R^4 = Alk; R^2 = H, OAlk, F; X = F, Cl.$                                                         | DMSO, MW, 8–35 min                                                                               | 9                  | 75–94          | 179        |
| 17                   | <br>$R^1 = H, OMe; R^2, R^3 = Alk, Ar.$                                                                         | CuI, K <sub>2</sub> CO <sub>3</sub> , NMP, MW, 20–40 min                                         | 6                  | 51–77          | 180        |
| 18                   | <br>$R^1 = R^2 = HO(CH_2)_2; R^1 = H, R^2 = HO(CH_2)_3.$                                                        | 1) NMP, MW, 30 min<br>2) CF <sub>3</sub> CO <sub>2</sub> H, H <sub>2</sub> O, 1 h                | 2                  | 77–89          | 181        |
| 19                   | <br>$R = CN, NO_2.$                                                                                             | a) DMSO, MW, 5 h<br>b) Δ, 60 h                                                                   | 2<br>2             | 65–76<br>16–37 | 175<br>175 |
| 20                   |                                                                                                                 | H <sub>2</sub> O, NH <sub>3</sub> , (NH <sub>4</sub> ) <sub>2</sub> SO <sub>3</sub> , MW, 30 min | 8                  | 70–90          | 182        |
| <b>Hydrogenation</b> |                                                                                                                 |                                                                                                  |                    |                |            |
| 21                   | $R^1R^2NX \longrightarrow R^1R^2NH$<br>$R^1 = Alk, Ar; R^2 = Alk; X = Bn, Cbz.$                                 | HCO <sub>2</sub> NH <sub>4</sub> , Pd/C, Pr <sup>i</sup> OH, MW, 3–8 min                         | 14                 | 70–95          | 183        |

<sup>a</sup> Ethyl esters of substituted cinnamic acids ArCH=CHCO<sub>2</sub>Et are also afforded in yields of 87%–34%; <sup>b</sup> the monosubstitution products are formed in low yields.

## XI. Synthesis of carboxylic acid amides and imides, their thio analogues, thioureas and thiosemicarbazides

Amides and imides can be synthesised by the microwave-assisted reactions of amines with carboxylic acids (or, alternatively, amine hydrochlorides with metal carboxylates) (Table 14, Nos 1–6) or

with their derivatives, such as esters (No. 7), chlorides (Nos 8 and 9) or anhydrides (Nos 9–14). Other methods for the formation of amides include the specific Wolff rearrangement of α-diazoketones (No. 15), Heck aminocarbonylation of aryl bromides catalysed by palladium with DMF as a source of carbon oxide (No. 16) and hydrolysis of aromatic nitriles using different catalysts (No. 17). The preparation of amides from ketones and

**Table 14.** Synthesis of carboxylic acid amides and imides, their thio analogues, thioureas and thiosemicarbazides.

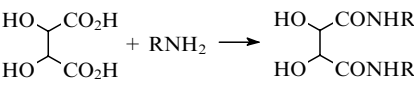
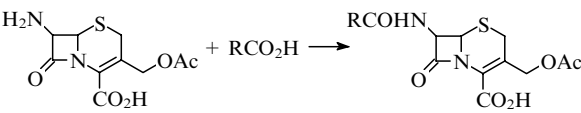
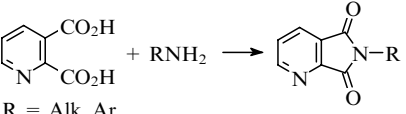
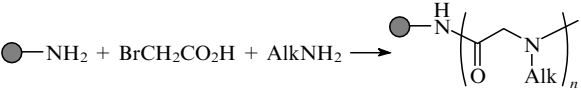
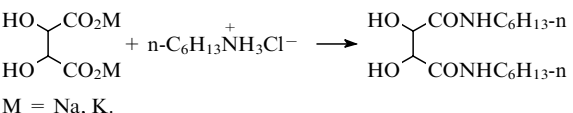
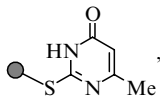
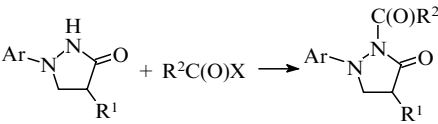
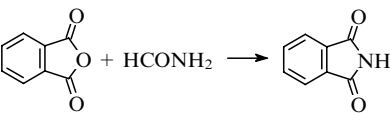
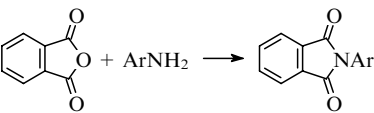
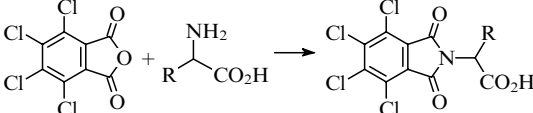
| No. | Reaction                                                                                                                                                                                                | Conditions                                                                                           | Number of exam-<br>ples | Yield (%)      | Ref.       |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-------------------------|----------------|------------|
| 1   | $R^1CO_2H + R^2NH_2 \longrightarrow R^1CONHR^2$<br>$R^1 = \text{Alk, Ph}; R^2 = \text{Alk, Ar.}$                                                                                                        | a) MW, 30–120 min<br>b) $\Delta$ , 30–120 min                                                        | 37<br>32                | 2–93<br>8–72   | 184<br>184 |
| 2   | <br>$R = \text{Alk, Ph.}$                                                                                              | MW, 12 min                                                                                           | 10                      | 30–83          | 185        |
| 3   | <br>$R = \text{Alk, Ar, Het.}$                                                                                         | a) $Al_2O_3$ , MW, 90–120 s<br>b) $\Delta$ , 2–6 h                                                   | 10<br>10                | 82–93<br>63–76 | 186<br>186 |
| 4   | <br>$R = \text{Alk, Ar.}$                                                                                              | a) $Et_3N$ , MW, 90–300 s<br>b) $\Delta$ , 0.5–2 h                                                   | 11<br>5                 | 51–95<br>0–20  | 187<br>187 |
| 5   |                                                                                                                        | a) DIC, <sup>a</sup> DMF, MW, 1 min<br>b) $\Delta$ , 105 min                                         | 6<br>5                  | 65–88<br>63–80 | 188<br>188 |
| 6   | <br>$M = \text{Na, K.}$                                                                                               | MW, 25 min                                                                                           | 2                       | 13–40          | 185        |
| 7   | $R^1CO_2R^2 + R^3R^4NH \longrightarrow R^1CONR^3R^4$<br>$R^1 = \text{Alk}; R^2 = \text{Me, Et}; R^3, R^4 = \text{H, Alk.}$                                                                              | a) $Bu^tOK$ , MW, 2–8 min<br>b) $\Delta$ , 3–48 h                                                    | 20<br>15                | 17–97<br>3–42  | 189<br>189 |
| 8   | $R^1COCl + R^2NH_2 \longrightarrow R^1CONHR^2$<br>$R^1 = \text{Me, Ph, } p\text{-XC}_6\text{H}_4 \text{ (X = Me, Cl, Br), Bn, PhCH=CH, } o\text{-BrC}_6\text{H}_4; R^2 = \text{Bn, (CH}_2)_4\text{OH.}$ |  , Py, MW, 3 min | 9                       | 42–100         | 190        |
| 9   | <br>$R^1 = \text{H, Me}; R^2 = \text{Alk, Ar}; X = \text{Cl, OC(O)R}^2.$                                             | MW, 1 h                                                                                              | 11                      | 19–63          | 191        |
| 10  | $R^1R^2NH + Ac_2O \longrightarrow AcNR^1R^2$<br>$R^1 = \text{Alk, Ar}; R^2 = \text{H, Alk.}$                                                                                                            | $Al_2O_3$ , MW, 0.25–16 min                                                                          | 36                      | 65–100         | 152        |
| 11  |                                                                                                                      | MW, 2 min                                                                                            | 1                       | 98             | 192        |
| 12  |                                                                                                                      | MW, 2–10 min                                                                                         | 8                       | 91–95          | 193        |
| 13  | <br>$R = \text{Alk, Ar.}$                                                                                            | a) MW, 4–8 min<br>b) $\Delta$ , 24.5 h                                                               | 30<br>6                 | 62–69<br>67–98 | 194<br>194 |

Table 14 (continued).

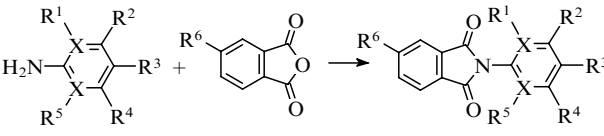
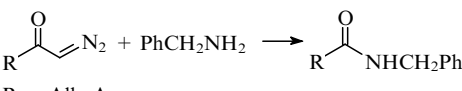
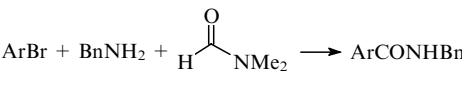
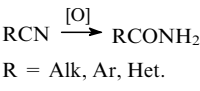
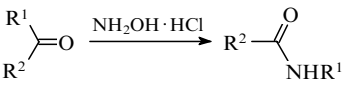
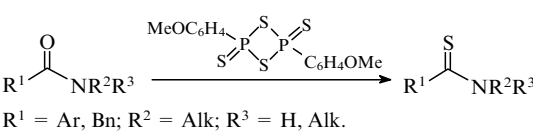
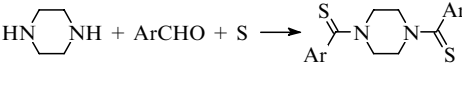
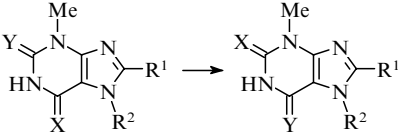
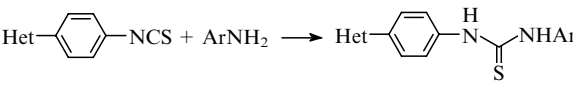
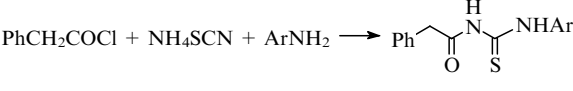
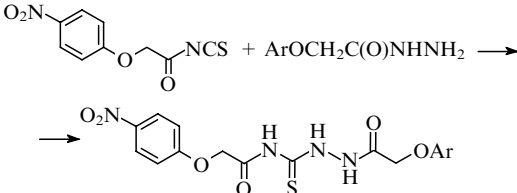
| No. | Reaction                                                                                                                                                                                                                                                                                               | Conditions                                                                                                                                          | Number of exam-<br>ples | Yield (%)      | Ref.       |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|----------------|------------|
| 14  |  <p>X = C: R<sup>1</sup>–R<sup>6</sup> = H, Alk, Hal, OMe, CO<sub>2</sub>Me;<br/>X = N: R<sup>1</sup> and R<sup>5</sup> are absent, R<sup>2</sup> = R<sup>4</sup> = H, R<sup>3</sup> = Br, R<sup>6</sup> = H, Me.</p> | MW, 8.5 min                                                                                                                                         | 28                      | 34–98          | 195        |
| 15  |  <p>R = Alk, Ar.</p>                                                                                                                                                                                                  | a) MW, 15–30 min<br>b) Δ, 10 min                                                                                                                    | 14<br>14                | 68–93<br>0–74  | 196<br>196 |
| 16  |                                                                                                                                                                                                                       | Pd(OAc) <sub>2</sub> L, Bu <sup>t</sup> OK, HN  ,<br>MW, 15–20 min | 9                       | 59–94          | 197        |
| 17  |  <p>R = Alk, Ar, Het.</p>                                                                                                                                                                                             | a) NaBO <sub>3</sub> ·4 H <sub>2</sub> O, H <sub>2</sub> O–EtOH,<br>MW, 2–4 min<br>b) MnO <sub>2</sub> /SiO <sub>2</sub> , MW, 14 min               | 8<br>9                  | 83–97<br>40–99 | 198<br>199 |
| 18  |  <p>R<sup>1</sup>, R<sup>2</sup> = Alk, Ar.</p>                                                                                                                                                                       | a) zeolite HY, MW, 2–3 min<br>b) zeolite HY, PhMe, N <sub>2</sub> ,<br>Δ, 9–11 h                                                                    | 8<br>8                  | 82–95<br>56–67 | 200<br>200 |
| 19  |  <p>R<sup>1</sup> = Ar, Bn; R<sup>2</sup> = Alk; R<sup>3</sup> = H, Alk.</p>                                                                                                                                        | MW, 8 min                                                                                                                                           | 20                      | 38–91          | 201        |
| 20  |                                                                                                                                                                                                                     | a) DMF, MW, 1.5–10 min<br>b) Δ, 5 min                                                                                                               | 10<br>1                 | 53–83<br>48    | 202<br>202 |
| 21  |  <p>R<sup>1</sup>, R<sup>2</sup> = H, Me; X = O, Y = S; X = S, Y = O.</p>                                                                                                                                           | MW, 5–10 min                                                                                                                                        | 8                       | 90–99          | 203        |
| 22  |                                                                                                                                                                                                                     | MW, 2–4.5 min                                                                                                                                       | 9                       | 83–95          | 204        |
| 23  |                                                                                                                                                                                                                     | PEG-400, CHCl <sub>3</sub> , MW, 14 min                                                                                                             | 10                      | 86–94          | 205        |
| 24  |                                                                                                                                                                                                                     | MW, 4 min                                                                                                                                           | 8                       | 82–95          | 206        |

Table 14 (continued).

| No. | Reaction | Conditions                                  | Number of examples | Yield (%) | Ref. |
|-----|----------|---------------------------------------------|--------------------|-----------|------|
| 25  |          | PEG-400, CHCl <sub>3</sub> –DMF, MW, 13 min | 12                 | 88–98     | 207  |
| 26  |          | PEG-400, CHCl <sub>3</sub> –DMF, MW, 13 min | 13                 | 82–95     | 208  |

<sup>a</sup> DIC is *N,N*-diisopropylcarbodiimide.

hydroxylamine (No. 18) was also reported. The MWI synthesis of thioanalogues of carboxylic acid amides is illustrated with reactions Nos 19 and 20, whereas the synthesis of thioureas is represented by reactions Nos 21–23. 1,4-Disubstituted thiosemicarbazides were obtained by nucleophilic substitution under solvent-free MWI conditions (Nos 24–26).

Some of the aforementioned reactions are impossible without microwave activation (Nos 4 and 15), which implies MWE manifestation. The involvement of MWE is also supported by increases in the yields of amines in the MWI-activated reactions as compared to the thermally activated ones (see reactions Nos 3, 4, 7, 18 and 20).

## XII. Preparation of nitriles

Aliphatic and aromatic nitriles can be prepared in high yields using the microwave-assisted reaction of aldehydes with hydroxylamine hydrochloride (Table 15, No. 1). The reaction is performed either in the presence of ammonium acetate (conditions *a*) or under solvent-free conditions over zeolites (conditions *b*) or in

*N*-methyl-2-pyrrolidone (conditions *d*). Aromatic nitriles can also be synthesised by the dehydration of the respective oximes (No. 2) with phthalic anhydride either in the presence of a solvent (*a*) or using molecular sieve A4 in the absence of solvents (*b*) or on the alumina surface in the presence of tetrachloropyridine (*c*). A catalytic conversion of aryl and vinyl halides into nitriles by the substitution of the cyano group for the bromine atom was realised (No. 3). In all those cases, the use of MW accelerated the reactions but did not noticeably increase the yields of products.

## XIII. Ionic liquids

Examples of the microwave-assisted preparation of ionic liquids composed of heterocyclic cations and inorganic anions are compiled in Table 16. For this purpose, the interaction of 1-methylimidazole (Nos 1 and 2) or pyridine (No. 3) with alkyl halides was exploited. The results presented indicate that the reaction times of the MW-activated reactions were substantially shorter than those of the thermal reactions at nearly the same yields of products.

Table 15. Synthesis of nitriles.

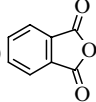
| No. | Reaction                                                                                              | Conditions                                                                                                                                                                                                                                             | Number of examples  | Yield (%)                        | Ref.                     |
|-----|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|----------------------------------|--------------------------|
| 1   | $\text{RCHO} \xrightarrow{\text{NH}_2\text{OH} \cdot \text{HCl}} \text{RCN}$ R = Alk, Ar.             | <i>a</i> ) AcONH <sub>4</sub> , MW, 1–3 min<br><i>b</i> ) zeolite HY, MW, 1–2 min<br><i>c</i> ) zeolite HY, PhMe, N <sub>2</sub> , Δ, 6–8 h<br><i>d</i> ) NMP, MW, 2–5 min                                                                             | 12<br>12<br>12<br>8 | 80–95<br>84–96<br>68–79<br>47–96 | 209<br>200<br>200<br>210 |
| 2   | $\text{ArHC=N-OH} \longrightarrow \text{ArCN}$                                                        | <i>a</i> )  , MeCN, MW, 3–15 min<br><i>b</i> ) molecular sieves A4, MW, 4–10 min<br><i>c</i> ) Al <sub>2</sub> O <sub>3</sub> , tetrachloropyridine, MW, 35–180 min | 10<br>14<br>15      | 78–94<br>30–95<br>60–85          | 211<br>212<br>213        |
| 3   | $\text{RBr} + \text{Zn(CN)}_2 \longrightarrow \text{RCN}$ R = Ar, R <sup>1</sup> R <sup>2</sup> C=CH. | Pd(PPh <sub>3</sub> ) <sub>4</sub> , DMF<br><i>a</i> ) MW, 2–2.5 min<br><i>b</i> ) Δ, 2–16 h                                                                                                                                                           | 8<br>7              | 78–95<br>71–97                   | 214                      |

**Table 16.** Synthesis of 1,3-dialkylimidazolium and 1-alkylpyridinium salts.

| No. | Reaction                                                                                                                                                                                                                                                   | Conditions                                                 | Number of examples | Yield (%)                | Ref.              |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|--------------------|--------------------------|-------------------|
| 1   | $\text{MeN} \begin{array}{c} \diagup \text{N} \\ \diagdown \end{array} + \text{AlkHal} \longrightarrow \text{MeN} \begin{array}{c} \diagup \text{N}^+ \text{Alk} \\ \diagdown \end{array} \text{Hal}^-$                                                    | a) MW, 75–240 s<br>b) MW, 1–2.5 min<br>c) $\Delta$ , 3–5 h | 7<br>10<br>10      | 82–100<br>71–94<br>50–95 | 215<br>216<br>216 |
| 2   | $\text{MeN} \begin{array}{c} \diagup \text{N} \\ \diagdown \end{array} + \text{Hal}-\text{R}-\text{Hal} \longrightarrow \text{MeN} \begin{array}{c} \diagup \text{N}^+ \text{R} \text{N}^+ \text{Me} \\ \diagdown \end{array} 2 \text{Hal}^-$              | a) MW, 50–90 s<br>b) $\Delta$ , 3–5 h                      | 8<br>8             | 78–94<br>56–97           | 216<br>216        |
| 3   | $\text{Pyridine} + \text{AlkHal} \longrightarrow \text{Pyridine}^+ \text{Alk} \text{Hal}^-$                                                                                                                                                                | MW, 400–600 s                                              | 2                  | 100                      | 215               |
| 4   | $\text{MeN} \begin{array}{c} \diagup \text{N}^+ \text{Alk} \\ \diagdown \end{array} \text{Cl}^- \xrightarrow{\text{AlCl}_3 \cdot 6 \text{H}_2\text{O}} \text{MeN} \begin{array}{c} \diagup \text{N}^+ \text{Alk} \\ \diagdown \end{array} \text{AlCl}_4^-$ | MW, 2–4 min                                                | 8                  | 100                      | 109               |
| 5   | $\text{MeN} \begin{array}{c} \diagup \text{N}^+ \text{Alk} \\ \diagdown \end{array} \text{Hal}^- \xrightarrow{\text{NH}_4\text{BF}_4} \text{MeN} \begin{array}{c} \diagup \text{N}^+ \text{Alk} \\ \diagdown \end{array} \text{BF}_4^-$                    | a) MW, 2.5–3.5 min<br>b) $\Delta$ , 3 h                    | 9<br>3             | 88–92<br>28–36           | 217<br>217        |

MWI also enabled anion exchange reactions (Nos 4, 5) significantly increasing their yields as compared to the thermal conditions. This means that the MWE is involved.

## XIV. Synthesis of heterocyclic compounds

### 1. Three-membered heterocycles

Chanda *et al.*<sup>218</sup> described a method for the catalytic microwave-assisted synthesis of diverse aziridines by the reaction of olefins with sodium haloamines (TsNXNa) (Table 17, No. 1). The oxidation of alkenes with hydrogen peroxides under MWI afforded epoxides (No. 2), whereas the reductive cyclisation of  $\alpha$ -haloketones and diethyl dithiophosphoric acid in the presence of alumina-supported sodium borohydride yielded thiiranes (No. 3). The yields of products depend on the structure of reagents and the reaction type. The MWE was manifested in all those cases both in the significant acceleration of the reactions and increases of yields of products.

### 2. Four-membered heterocycles

Table 18 lists some examples of the microwave-assisted preparation of four-membered heterocyclic compounds (*e.g.*,  $\beta$ -lactams, oxetanes and thietanes). The Staudinger reaction was utilised for the synthesis of  $\beta$ -lactams (Table 18, Nos 1–5). Oxetanes were prepared by the [2 + 2]-cycloaddition of alkynes to  $\beta$ -formylenamines. The reaction was accomplished over the alumina surface under solvent-free conditions (No. 6). Functionalised thietanes were prepared using the nucleophilic addition of HSP(S)(OEt)<sub>2</sub> to the double bond of  $\alpha,\beta$ -unsaturated ketones followed by the reductive cyclisation initiated by nucleophiles (No. 7).

### 3. Five-membered heterocycles

#### a. Five-membered heterocycles with one nitrogen atom

The microwave-assisted three-component condensation of amines, ketones (or aldehydes) and nitro compounds was utilised to synthesise substituted pyrroles (Table 19, Nos 1–3). Functionalised indoles were prepared by the Fischer reaction (No. 4) and by the condensation of *o*-iodoanilines with alkynes (Nos 5 and 6).

**Table 17.** Synthesis of three-membered heterocyclic compounds.

| No. | Reaction                                                                                                                                                                                                                                 | Conditions                                                                                  | Number of examples | Yield (%)        | Ref.       |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|--------------------|------------------|------------|
| 1   | $\text{R}^1 \text{C}=\text{C}(\text{R}^2)\text{R}^3 + \text{TsNXNa} \longrightarrow \text{Aziridine}$<br>$\text{R}^1 = \text{Alk, Ar}; \text{R}^2 = \text{H, Alk}; \text{R}^3 = \text{H, Alk, CO}_2\text{Me}; \text{X} = \text{Cl, Br}.$ | CuCl <sub>2</sub> , MW, 12 min                                                              | 5                  | 36–88            | 218        |
| 2   | $\text{R}^1 \text{C}=\text{C}(\text{R}^2)\text{R}^3 \xrightarrow{\text{H}_2\text{O}_2} \text{Epoxide}$<br>$\text{R}^1 = \text{Alk}; \text{R}^2, \text{R}^3 = \text{H, Alk}.$                                                             | a) hydrotalcite, MeCN, MW, 1–8 min<br>b) $\Delta$ , 4–24 h                                  | 13<br>13           | 62–100<br>25–100 | 219<br>219 |
| 3   | $\text{R}^1 \text{C}(=\text{O})\text{CH}(\text{R}^2)\text{Hal} \xrightarrow{\text{HSP}(\text{OEt})_2} \text{Thiirane}$<br>$\text{R}^1 = \text{Alk, Ar}; \text{R}^2 = \text{H, Alk, Ar}.$                                                 | a) NaBH <sub>4</sub> –Al <sub>2</sub> O <sub>3</sub> , MW, 2–4 min<br>b) $\Delta$ , 11–15 h | 11<br>11           | 81–94<br>39–49   | 220<br>220 |

**Table 18.** Microwave-assisted preparation of four-membered heterocyclic compounds with nitrogen, oxygen or sulfur atoms.

| No. | Reaction                                                                                                   | Conditions                                                                         | Number of examples | Yield (%)      | Ref.       |
|-----|------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|--------------------|----------------|------------|
| 1   |                                                                                                            | PhCl, Et <sub>3</sub> N, MW, 0.5–10 min                                            | 8                  | 70–75          | 221        |
| 2   |                                                                                                            | CH <sub>2</sub> Cl <sub>2</sub> , Et <sub>3</sub> N, MW, 3 min                     | 1                  | 90             | 222        |
| 3   | <p>R<sup>1</sup> = Cbz, Boc, Fmoc; R<sup>2</sup>–R<sup>4</sup> = Alk.</p>                                  | <i>o</i> -Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub> , MW, 5 min                | 7                  | 40–85          | 223        |
| 4   | <p>R<sup>1</sup>, R<sup>2</sup> = Alk, Ar; X = Cl, OH.</p>                                                 | a) PhOP(O)Cl <sub>2</sub> , Et <sub>3</sub> N, PhMe, MW, 4–6 min<br>b) Δ, 3.5–6 h  | 10<br>15           | 17–96<br>17–58 | 224<br>224 |
| 5   |                                                                                                            | a) Et <sub>3</sub> N, CH <sub>2</sub> Cl <sub>2</sub> , MW, 5–8 min<br>b) Δ, 5–8 h | 5<br>5             | 70–78<br>55–62 | 225<br>225 |
| 6   | <p>R<sup>1</sup>, R<sup>2</sup> = H, Alk; R<sup>3</sup>, R<sup>4</sup> = H, Alk, Ar, CO<sub>2</sub>Et.</p> | Al <sub>2</sub> O <sub>3</sub> , MW, 5–8 min                                       | 6                  | 72–80          | 226        |
| 7   | <p>X = CN, SAlk.</p>                                                                                       | Al <sub>2</sub> O <sub>3</sub> , MW, 2–4 min                                       | 9                  | 77–92          | 227        |

**Table 19.** Synthesis of pyrrole derivatives.

| No. | Reaction                                                                                                             | Conditions                                     | Number of examples | Yield (%) | Ref. |
|-----|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------|--------------------|-----------|------|
| 1   | <p>R<sup>1</sup> = H, Alk, Ar; R<sup>2</sup>, R<sup>5</sup> = H, Me, Ph; R<sup>3</sup>, R<sup>4</sup> = Alk, Ar.</p> | SiO <sub>2</sub> , MW, 5–10 min                | 19                 | 60–72     | 228  |
| 2   | <p>R<sup>1</sup>–R<sup>3</sup> = Alk.</p>                                                                            | Al <sub>2</sub> O <sub>3</sub> , MW, 13–15 min | 12                 | 71–81     | 228  |
| 3   | <p>R<sup>1</sup>, R<sup>2</sup> = Alk; n = 1–4.</p>                                                                  | Al <sub>2</sub> O <sub>3</sub> , MW, 13–15 min | 15                 | 74–86     | 228  |

Table 19 (continued).

| No. | Reaction                                                                                                                      | Conditions                                                                                                                                 | Number of examples | Yield (%)                       | Ref.       |
|-----|-------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|--------------------|---------------------------------|------------|
| 4   | <br>$\text{R} = \text{H, Et.}$                                                                                                | a) K-10, $\text{ZnCl}_2$ , MW, 35–180 min<br>b) $\Delta$ , 1-MeNaph, 3 h                                                                   | 2<br>2             | 50–65<br>25–35                  | 229<br>229 |
| 5   |                                                                                                                               | $\text{Pd}(\text{OAc})_2$ , AcONa, $\text{Ph}_3\text{P}$ , LiCl, DMA <sup>a</sup> or DMF–MeCN, MW, 8–17 min (DMF–MeCN) or 30–120 min (DMA) | 9 <sup>b</sup>     | 72–84 (DMF–MeCN)<br>34–63 (DMA) | 230        |
| 6   | <br>$\text{X} = \text{H, I.}$                                                                                                 | a) MW, 3–26 min<br>b) $\Delta$ , 4–48 h                                                                                                    | 6<br>6             | 8–100<br>56–100                 | 231<br>231 |
| 7   | <br>$\text{X} = \text{CN, CO}_2\text{Me.}$                                                                                    | MW, 15 min                                                                                                                                 | 6                  | 35–78                           | 232        |
| 8   | <br>$\text{R}^1, \text{R}^3, \text{R}^4 = \text{H, Alk}; \text{R}^2, \text{R}^5 = \text{Alk, Ar}; \text{X} = \text{OH, OMe.}$ | $\text{C}_2\text{H}_4\text{Cl}_2$ , MW, 5 min                                                                                              | 10                 | 0–89                            | 233        |
| 9   | <br>$\text{R}^1 = \text{H, CO}_2\text{Et}; \text{R}^2 = \text{Me, Et}; \text{X, Y} = \text{H, Hal, NO}_2, \text{OMe.}$        | a) $\text{KF}/\text{Al}_2\text{O}_3$ , MW, 7–10 min<br>b) $\Delta$ , 3–6 h                                                                 | 8<br>8             | 81–93<br>50–59                  | 234<br>234 |
| 10  | <br>$\text{R}^1 = \text{H, Me, F, Cl, NO}_2, \text{OMe, CN}; \text{R}^2 = \text{H, Me, Et, Bn.}$                              | $\text{Zn}^{2+}$ -montmorillonite, MW, 6–9 min                                                                                             | 10                 | 70–85                           | 235        |

<sup>a</sup> DMA is *N,N*-dimethylacetamide; <sup>b</sup> different temperature modes and solvents were tested.

The coupling of  $\alpha$ -amino acids with alkenes afforded pyrrolidine derivatives (Nos 7 and 8). The microwave 1,3-dipolar cycloaddition of alkynes to pyridinium salts was applied to the synthesis of 7,7'-bisindolizines (No. 9). Indolines were synthesised by the Cope rearrangement from *N*-allylamines (No. 10).

In the case of the Fischer synthesis of indoles (No. 4), the reaction proceeded at the same rates under microwave and thermal activations, but the yields of products were 2 times higher

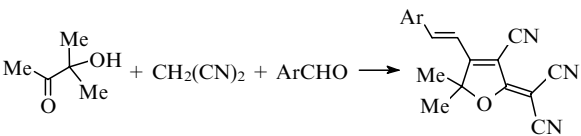
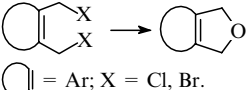
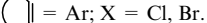
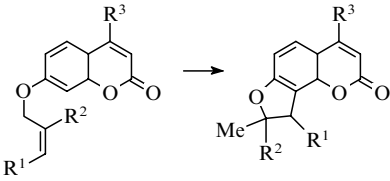
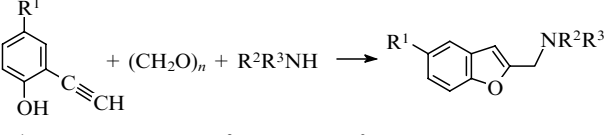
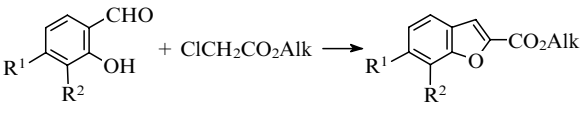
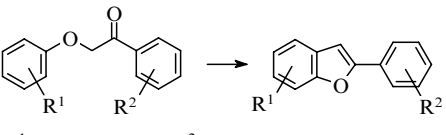
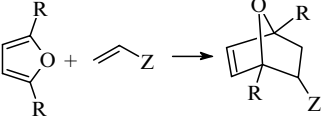
in the former mode. An increase in the yield of products under microwave irradiation (by 30%, on average) was also registered for the 1,3-dipolar cycloaddition (No. 9), which is indicative of the MWE.

#### b. Five-membered heterocycles with one oxygen atom

The three-component condensation of  $\alpha$ -hydroxy diketones with malonic dinitriles and aldehydes (Table 20, No. 1), intramolecu-



**Table 20.** Synthesis of furan derivatives.

| No. | Reaction                                                                                                                                                               | Conditions                                                                                                                            | Number of examples | Yield (%)      | Ref.       |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|--------------------|----------------|------------|
| 1   |                                                                                       | EtONa – EtOH, MW, 30 min                                                                                                              | 8                  | 65–84          | 236        |
| 2   | <br> | a) Al <sub>2</sub> O <sub>3</sub> , MW, 5–15 min<br>b) Al <sub>2</sub> O <sub>3</sub> , C <sub>6</sub> H <sub>14</sub> , Δ, 20–90 min | 5<br>5             | 59–82<br>49–98 | 237<br>237 |
| 3   | <br>R <sup>1</sup> = H, Me, Ph; R <sup>2</sup> , R <sup>3</sup> = H, Me.              | BF <sub>3</sub> · Et <sub>2</sub> O, NMF, <sup>a</sup> MW, 18–25 min                                                                  | 11                 | 54–74          | 238        |
| 4   | <br>R <sup>1</sup> = H, Me, C(O)Me; R <sup>2</sup> = Alk, Ph; R <sup>3</sup> = Alk.   | CuI – Al <sub>2</sub> O <sub>3</sub> , MW, 5 min                                                                                      | 12                 | 38–70          | 239        |
| 5   | <br>R <sup>1</sup> , R <sup>2</sup> = H, Alk, NEt <sub>2</sub> , OMe.               | K <sub>2</sub> CO <sub>3</sub> , Bu <sub>4</sub> NBr, MW, 8–10 min                                                                    | 12                 | 65–96          | 240        |
| 6   | <br>R <sup>1</sup> = H, Hal, Alk; R <sup>2</sup> = Me, Ph.                          | KSF, MW, 2–6 min                                                                                                                      | 14                 | 76–92          | 241        |
| 7   | <br>R = H, Me; Z = CN, CO <sub>2</sub> Me.                                          | a) SiO <sub>2</sub> or Si(M) (M = Ti, Al, Zn), MW, 7–45 min<br>b) 20 °C, 2–24 h                                                       | 11<br>14           | 0–80<br>0–79   | 242<br>242 |

<sup>a</sup> NMF is *N*-methylformamide.

lar cyclisation of dihalides (No. 2), rearrangement of phenol and allyl alcohol ethers (No. 3) were applied to the microwave synthesis of dihydrofurans. Benzofurans were prepared by the Mannich reaction (No. 4), condensation of chloroacetic acid esters with substituted salicylic aldehydes under phase-transfer catalysis conditions (No. 5) and intramolecular cyclisation of  $\alpha$ -phenoxyacetophenones (No. 6). The condensation of furans (or alkylfurans) with acrylic acid derivatives giving rise to tetrahydrofurans (No. 7) was performed under the conditions of both microwave and thermal activation. The microwave reaction was 32 times faster than the reaction activated by convection heating at nearly the same yields of products. The use of MWI also accelerated the synthesis of dihydrofurans (No. 2) but the yields of products were sometimes lower as compared to the thermally activated reactions.

### c. Five-membered heterocycles with two nitrogen atoms

The microwave-assisted synthesis of pyrazole derivatives from hydrazines and compounds with carbonyl groups was realised (Table 21, Nos 1–5). Non-substituted pyrazolylpyrazolino[60]-fullerenes were synthesised by the 1,3-dipolar cycloaddition of C<sub>60</sub> to arylhydrazones (No. 6), whereas the *trans*-amination of dimethylaminoacrylates followed by the cyclo-condensation of enehydrazines afforded 3-pyrazolones (No. 7). Non-substituted triarylimidazoles can be prepared by the condensation of  $\alpha$ -diketones, aldehydes and ammonium acetate; the condensation of the same reagents with amines afforded substituted derivatives (No. 8). Indolyl-substituted imidazoles were obtained by cyclisation of the respective ketoamides with ammonium acetate (No. 9). Benzimidazole derivatives were synthesised by the microwave cyclocondensation of *N*-trifluoromethylacetylphenylenediamine (No. 10) and condensation of *o*-phenylenediamines with carbonyl compounds (Nos 11–13). Imidazolones can be prepared by the

**Table 21.** Synthesis of pyrazole and imidazole derivatives.

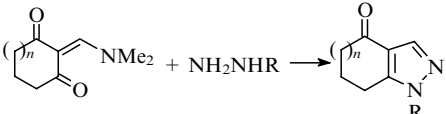
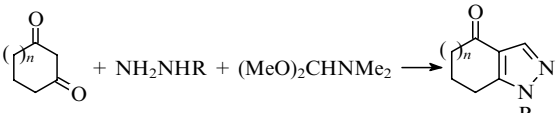
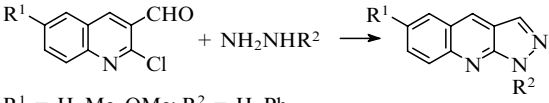
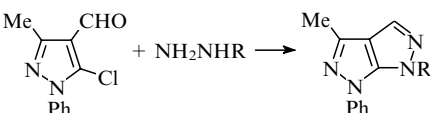
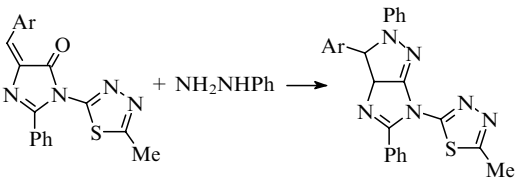
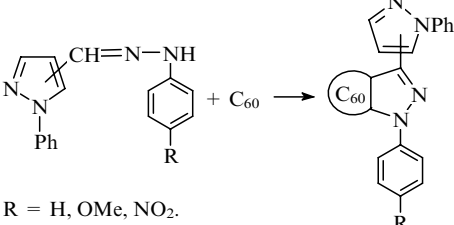
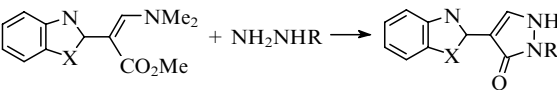
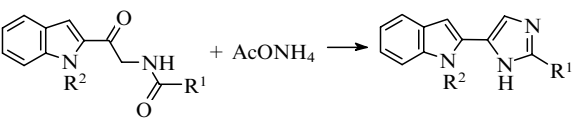
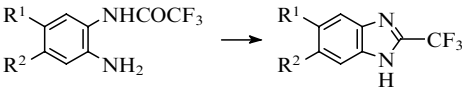
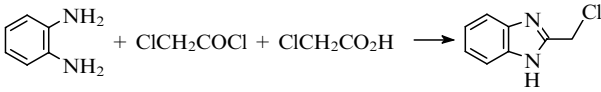
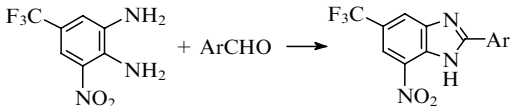
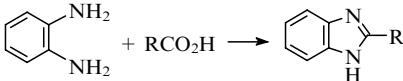
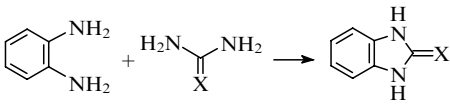
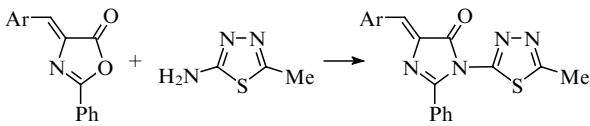
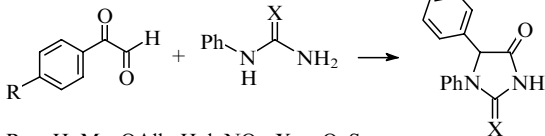
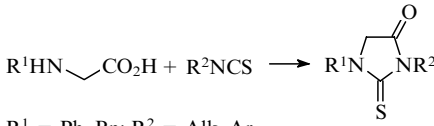
| No. | Reaction                                                                                                                                           | Conditions                                                                                                                                                               | Number of examples | Yield (%)                        | Ref.           |
|-----|----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|----------------------------------|----------------|
| 1   | <br>$n = 0-2$ ; R = H, Alk, Ar, Het.                              | AcOH, H <sub>2</sub> O, MW, 2 min                                                                                                                                        | 9                  | 65–99                            | 243            |
| 2   | <br>$n = 0-2$ ; R = H, Alk, Ar, Het.                              | AcOH, H <sub>2</sub> O, MW, 2 min                                                                                                                                        | 6                  | 66–87                            | 243            |
| 3   | <br>$R^1 = \text{H, Me, OMe}$ ; $R^2 = \text{H, Ph}$ .            | TsOH, MW, 1.5–2 min                                                                                                                                                      | 6                  | 78–97                            | 244            |
| 4   | <br>$R = \text{H, Ph}$ .                                          | TsOH, MW, 2–2.5 min                                                                                                                                                      | 2                  | 94–96                            | 244            |
| 5   |                                                                  | a) Al <sub>2</sub> O <sub>3</sub> , MW, 5–6 min<br>b) $\Delta$ , 7.5–8 h                                                                                                 | 3<br>3             | 89–92<br>70–74                   | 245<br>245     |
| 6   | <br>$R = \text{H, OMe, NO}_2$ .                                 | NBS, <sup>a</sup> Et <sub>3</sub> N, benzene, MW, 30 min                                                                                                                 | 6                  | 22–44                            | 246            |
| 7   | <br>$R = \text{Me, Ph}$ ; X = O, NH.                            | a) MW, 30 min<br>b) $\Delta$ , 2–264 h                                                                                                                                   | 1<br>2             | 96<br>74–92                      | 161<br>161     |
| 8   | <br>$R = \text{H, Alk, Ar}$ .                                   | $R = \text{H}$ :<br>a) zeolite HY, MW, 6 min<br>b) SiO <sub>2</sub> , MW, 6 min<br>$R = \text{Alk, Ar}$ :<br>a) zeolite HY, MW, 6 min<br>b) SiO <sub>2</sub> , MW, 6 min | 8<br>8<br>17<br>17 | 80–94<br>54–89<br>42–85<br>60–91 | 247<br><br>248 |
| 9   | <br>$R^1 = \text{Alk, Ar}$ ; $R^2 = \text{H, Bn}$ .             | a) DMF, MW, 10–30 min<br>b) DMF, 180 °C, 12–16 h                                                                                                                         | 10<br>9            | 50–75<br>25–75                   | 249<br>249     |
| 10  | <br>$R^1, R^2 = \text{H, Me, Cl, NO}_2, \text{CO}_2\text{Et}$ . | a) K-10, MW, 2 min<br>b) $\Delta$ , 20 h                                                                                                                                 | 7<br>6             | 84–95<br>18–31                   | 250<br>250     |

Table 21 (continued).

| No. | Reaction                                                                                                                                  | Conditions                                                                                                                 | Number of exam-<br>ples | Yield (%)      | Ref.       |
|-----|-------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-------------------------|----------------|------------|
| 11  |                                                          | a) SiO <sub>2</sub> , MW, 4 min<br>b) HCl, Δ, 8 h                                                                          | 1<br>1                  | 90<br>92       | 251<br>251 |
| 12  |                                                          | a) ZnCl <sub>2</sub> , Al <sub>2</sub> O <sub>3</sub> , MW, 4 min<br>b) Δ, 2 h                                             | 10<br>10                | 72–90<br>60–80 | 252<br>252 |
| 13  | <br>R = H, Alk, Ar.                                      | PPA, <sup>b</sup> MW, 6–8 min                                                                                              | 12                      | 39–88          | 253        |
| 14  | <br>X = O, S.                                            | PPA, <sup>b</sup> MW, 8 min                                                                                                | 2                       | 71–86          | 253        |
| 15  |                                                          | a) Al <sub>2</sub> O <sub>3</sub> , MW, 5–6 min<br>b) Δ, 7–8 h                                                             | 3<br>3                  | 90–94<br>70–72 | 245<br>245 |
| 16  | <br>R = H, Me, OAlk, Hal, NO <sub>2</sub> ; X = O, S.  | PPE, <sup>c</sup> MW, 2.5–3.5 min                                                                                          | 16                      | 80–95          | 254        |
| 17  | <br>R <sup>1</sup> = Ph, Bn; R <sup>2</sup> = Alk, Ar. | a) Et <sub>3</sub> N–C <sub>2</sub> H <sub>4</sub> Cl <sub>2</sub> , MW, 5 min<br>b) PS–DMAP, <sup>d</sup> MeCN, MW, 5 min | 5<br>4                  | 57–91<br>56–87 | 255<br>256 |
| 18  | <br>R = Alk, Ph.                                       | a) MW, 12 min<br>b) Δ, 12 h                                                                                                | 56<br>56                | 69–94<br>65–98 | 256<br>256 |

Hereinafter, <sup>a</sup>NBS is *N*-bromosuccinimide; <sup>b</sup>PPA is polyphosphoric acid; <sup>c</sup>PPE is polyphosphoric ester; <sup>d</sup>PS–DMAP is polystyrene-grafted dimethylaminopyridine.

reactions of *o*-phenylenediamine with urea or thiourea (No. 14) or of hetarylamine with oxazolones (No. 15). The condensation of  $\alpha$ -ketaldehydes with urea or thiourea can be applied to the preparation of hydantoins and thiohydantoins (No. 16); the latter compounds were also synthesised by the microwave cyclisation of glycine with isothiocyanates (Nos 17 and 18).

The yields of reaction products varied over a wide range, depending on the structure of reagents. In the majority of cases, the use of MWI accelerated the reactions.

#### d. Five-membered heterocycles with one nitrogen and one oxygen atom

Two methods, *viz.*, the 1,3-dipolar cycloaddition of aromatic aldehydes to imidates, *i.e.*, potential azomethine ylides, (Table 22, No. 1) and the intramolecular rearrangement of the

aziridine ring (No. 2) were used in the microwave synthesis of oxazolones.

Isoxazolines were synthesised by the 1,3-dipolar cycloaddition of oximes to allyl alcohols (Table 22, Nos 3–5) or of  $\alpha,\beta$ -unsaturated ketones to hydroxylamine (No. 6) under microwave activation. Isoxazolidines were prepared in a similar way using the 1,3-dipolar cycloaddition of alkenes to oximes (No. 7). The condensation of  $\alpha$ -amino acid derivatives with formaldehyde (No. 8) or other aldehydes (see Table 11, No. 15) and the intramolecular rearrangement of the aziridine ring (Table 22, No. 9) were utilised in the synthesis of oxazolones, whereas oxazolidines were prepared similarly from  $\alpha$ -aminoalcohols and aldehydes (No. 10). Although the use of MWI accelerated the reactions in some cases as compared to the thermal activation, the yields of products either remained unchanged or even decreased.

**Table 22.** Microwave-assisted synthesis of oxazole and isoxazole derivatives.

| No. | Reaction | Conditions                                                                                                                               | Number of examples | Yield (%)                                                      | Ref.              |
|-----|----------|------------------------------------------------------------------------------------------------------------------------------------------|--------------------|----------------------------------------------------------------|-------------------|
| 1   |          | a) MW, 1–4.5 h<br>b) $\Delta$ , 1–6 h                                                                                                    | 6<br>6             | 87–98<br>86–96                                                 | 257<br>257        |
| 2   |          | M(OTf) <sub>2</sub> (M = Zn, Cu) or BF <sub>3</sub> ·Et <sub>2</sub> O, or MgBr <sub>2</sub> ·Et <sub>2</sub> O; THF or PhMe, MW, 10 min | 7                  | 50–95 <sup>a</sup>                                             | 258               |
| 3   |          | a) Et <sub>3</sub> N, benzene, MW, 30–120 s<br>b) $\Delta$ , 50 h                                                                        | 22<br>11           | 15–90 <sup>a</sup><br>40–84 <sup>a</sup>                       | 259<br>259        |
| 4   |          | a) MeMgBr, PhCl or CCl <sub>4</sub> , MW, 1.5–90 min<br>b) CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 24–78 h<br>c) PhMe, 80 °C, 2–4 h     | 4<br>6<br>5        | 34–99<br>35–96<br>56–99                                        | 260<br>260<br>260 |
| 5   |          | NBS, Et <sub>3</sub> N, MW, 30 min                                                                                                       | 8                  | 16–36                                                          | 261               |
| 6   |          | a) PhMe–Py, MW, 6 min<br>b) HCl–MeOH, $\Delta$ , 16 h                                                                                    | 13<br>13           | 78–95<br>60–90                                                 | 262<br>262        |
| 7   |          | a) MW, 9–30 min<br>b) $\Delta$ , 12–120 h<br>c) <i>h</i> $\nu$ , 72–168 h                                                                | 6<br>6<br>5        | 73–93 <sup>a</sup><br>71–98 <sup>a</sup><br>66–81 <sup>a</sup> | 263<br>263<br>263 |
| 8   |          | TsOH, PhMe, MW, 3–6 min                                                                                                                  | 14                 | 81–98                                                          | 264               |
| 9   |          | M(OTf) <sub>2</sub> (M = Zn, Cu) or BF <sub>3</sub> ·Et <sub>2</sub> O, PhMe, MW, 10 min                                                 | 4                  | 65–99 <sup>a</sup>                                             | 265               |
| 10  |          | MW, 1–3 min                                                                                                                              | 14                 | 55–98                                                          | 266               |

<sup>a</sup> The total yield of isomers is given.

The synthesis of isoxazolidines (No. 7) is worth a special discussion. Kusurkar and Kannadkar<sup>263</sup> compared three types of activation, *viz.*, UV, thermal and microwave. The reaction time

under the microwave conditions was shorter than 0.5 h, whereas it was in the range of 12–120 h and 72–168 h for the thermal and

Substituted pyridines can be synthesised using the Bohlmann–Rahtz (Table 24, No. 1) or Diels–Alder (Nos 2 and 3) reactions or by the aromatisation of 1,4-dihydropyridine with various oxidants (No. 4) (urea nitrate was found to be the best one). Symmetrical dipyrazolopyridine was afforded by the condensation of 5-amino-1,3-dimethylpyrazole with *p*-methylbenzaldehyde (No. 5). The three-component condensation of aldehydes, secondary amines and 2-azidobenzophenones gave rise to quinoline derivatives (No. 6) and the condensation of 2-amino substituted benzaldehyde or benzimides with different heterocyclic compounds yielded polycondensed quinolines (No. 7). The condensation of diarylamine with carboxylic acids (the Berthsen reaction) was applied to the synthesis of acridine (Nos 8–10). The Hantzsch method was used to synthesise 1,4-dihydropyridine derivatives (Nos 11–15), and 1,2-dihydroquinolines were prepared by the Skraup reaction (No. 16). Dihydroisoquinolines

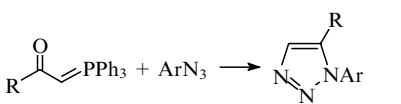
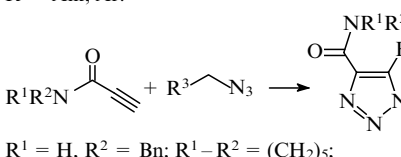
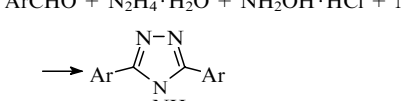
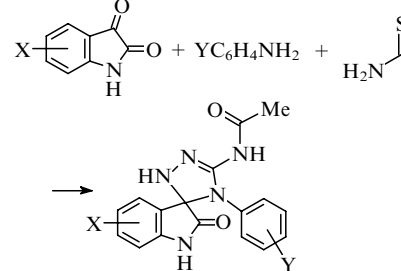
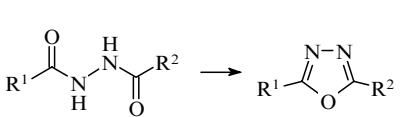
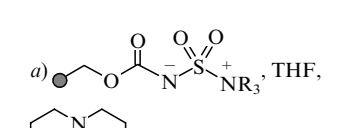
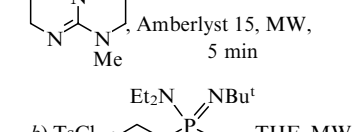
| No. | Reaction                                                                                                                                                                                                                                               | Conditions                                                                                                                                                                                      | Number of examples | Yield (%) | Ref. |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------|------|
| 1   | <br>$\text{R} = \text{Alk, Ar.}$                                                                                                                                      | SiO <sub>2</sub> , MW, 4–10 min                                                                                                                                                                 | 6                  | 67–82     | 267  |
| 2   | <br>$\text{R}^1 = \text{H, R}^2 = \text{Bn; R}^1 - \text{R}^2 = (\text{CH}_2)_5;$<br>$\text{R}^3 = \text{Ph, PhCH}_2\text{CH}_2, \text{MeCCH}_2\text{OCH}_2.$        | MW, 30 min                                                                                                                                                                                      | 6                  | 62–84     | 268  |
| 3   | $\text{ArCHO} + \text{N}_2\text{H}_4 \cdot \text{H}_2\text{O} + \text{NH}_2\text{OH} \cdot \text{HCl} + \text{N}_2\text{H}_4 \cdot 2\text{HCl} \longrightarrow$<br> | NMP, (CH <sub>2</sub> OH) <sub>2</sub> , MW, 5–12 min                                                                                                                                           | 8                  | 42–67     | 210  |
| 4   | <br>$\text{X} = \text{H, Hal, NO}_2; \text{Y} = \text{CF}_3.$                                                                                                       | AcOH, MW, 4–9 min                                                                                                                                                                               | 5                  | 80–86     | 269  |
| 5   | <br>$\text{R}^1 = \text{H, Alk, NHX (X = Alk', Bn), Ar; R}^2 = \text{Me, Ph.}$                                                                                      | a) <br>b) <br>c) Δ, 4 h | 16                 | 0–100     | 270  |
|     |                                                                                                                                                                                                                                                        |                                                                                                                                                                                                 | 16                 | 49–100    | 270  |
|     |                                                                                                                                                                                                                                                        |                                                                                                                                                                                                 | 16                 | 38–100    | 270  |

Table 23 (continued).

| No. | Reaction                                                                                                                                                                                                                                                             | Conditions                                                                                                                        | Number of examples  | Yield (%)                        | Ref.                     |
|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|---------------------|----------------------------------|--------------------------|
| 6   | <br>$R = \text{Ar, Bn.}$                                                                                                                                                                                                                                             | DMF or DMSO, or Py,<br>MW, 0.5–2 min                                                                                              | 27                  | 69–84                            | 271                      |
| 7   | <br>$\xrightarrow{\text{Hg}(\text{OAc})_2}$                                                                                                                                                                                                                          | a) $R = p\text{-ClC}_6\text{H}_4$ : AcOH,<br>MW, 4.5 min<br>b) $R = p\text{-MeOC}_6\text{H}_4\text{OCH}_2$ :<br>AcOH, MW, 4.5 min | 10<br>8             | 86–94<br>86–91                   | 272<br>273               |
| 8   | <br>$\xrightarrow{\text{MeOC}_6\text{H}_4\text{P}(\text{S})_2\text{P}(\text{S})_2\text{C}_6\text{H}_4\text{OMe}}$<br>$\longrightarrow R^2\text{-1,2,4-oxadiazole-3-C}_6\text{H}_4\text{R}^1\text{-}p$<br>$R^1 = \text{H, Br, OMe}; R^2 = \text{Alk, Ar, OAlk, OAr.}$ | MW, 3–13 min                                                                                                                      | 15                  | 0–95                             | 274                      |
| 9   | <br>$\xrightarrow{\text{AcOH}}$<br>$R = \text{furan-2-yl (a, b), } o\text{-ClC}_6\text{H}_4\text{-furan-2-yl (c), } o\text{-MeC}_6\text{H}_4\text{OCH}_2\text{-furan-2-yl (d).}$                                                                                     | a) MW, 5 min<br>b) $\Delta$ , 6 h<br>c) MW, 5 min<br>d) MW, 5 min                                                                 | 10<br>3<br>10<br>10 | 94–98<br>78–85<br>86–98<br>91–97 | 275<br>275<br>276<br>277 |
| 10  | <br>$\longrightarrow \text{Ar-1,2,4-oxadiazole-3-SH}$                                                                                                                                                                                                                | $\text{NH}_4\text{Cl, DMF}$<br>a) MW, 10–25 min<br>b) $\Delta$ , 3–96 h                                                           | 8<br>6              | 36–98<br>35–97                   | 214<br>214               |

Table 24. Synthesis of pyridine derivatives.

| No. | Reaction                                                             | Conditions                                                                                                                                                                                                                      | Number of examples | Yield (%)               | Ref.              |
|-----|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-------------------------|-------------------|
| 1   | <br>$R^1 = \text{H, Me, Ph, SiMe}_3; R^2 = \text{Me, Ar.}$           | a) DMSO, MW, 10–20 min<br>b) DMSO, $\Delta$ , 10 min                                                                                                                                                                            | 5<br>1             | 24–94<br>27             | 278<br>278        |
| 2   | <br>$\xrightarrow{\text{MeO}_2\text{CC}\equiv\text{CCO}_2\text{Me}}$ | $\text{C}_2\text{H}_4\text{Cl}_2$ , (bmim)PF <sub>6</sub> , MW, 5 min                                                                                                                                                           | 1                  | 82                      | 279               |
| 3   | <br>$R^1, R^2 = \text{Alk.}$                                         | MW, 3–20 min                                                                                                                                                                                                                    | 11                 | 18–71                   | 280               |
| 4   | <br>$R = \text{H, Alk, Ar.}$                                         | a) $\text{H}_2\text{N-C(=O)-NHONO}_2$ , MeCN,<br>MW, 0.5–2 min<br>b) $\text{K}_2\text{S}_2\text{O}_8/\text{Co(II)}$ , MeCN, MW,<br>10–15 min<br>c) $\text{K}_2\text{S}_2\text{O}_8/\text{Co(II)}$ , MeCN,<br>$\Delta$ , 1.5–3 h | 14<br>14<br>14     | 89–98<br>80–94<br>18–96 | 281<br>281<br>281 |

Table 24 (continued).

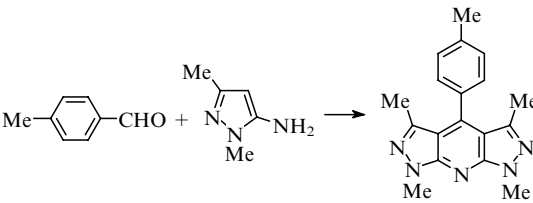
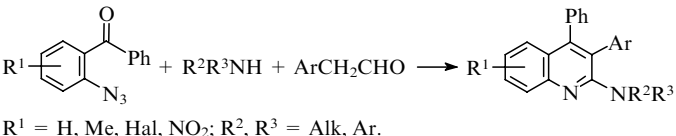
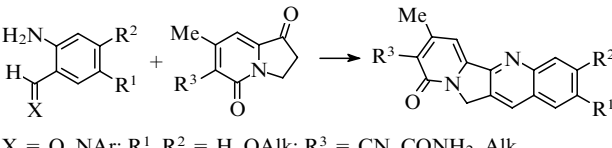
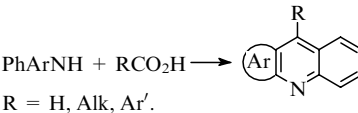
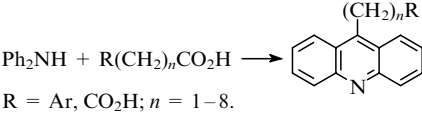
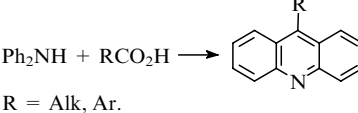
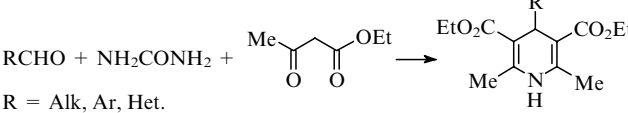
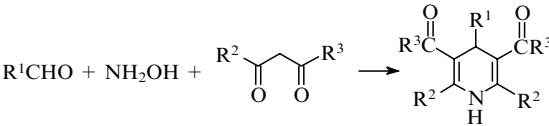
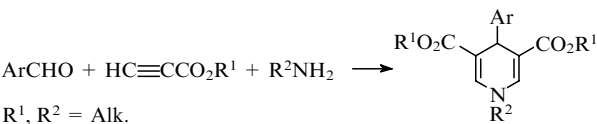
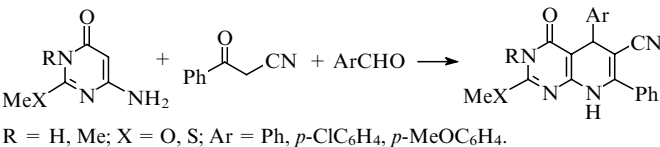
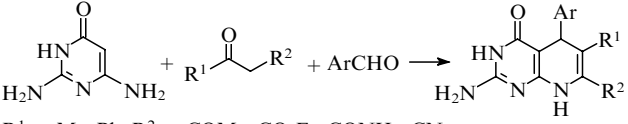
| No. | Reaction                                                                                                                                                                                                                                                                 | Conditions                                                                        | Number of exam-<br>ples | Yield (%)      | Ref.       |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-------------------------|----------------|------------|
| 5   |                                                                                                                                                                                         | MW, 15 min                                                                        | 1                       | 91             | 282        |
| 6   |  <p><math>R^1 = \text{H, Me, Hal, NO}_2</math>; <math>R^2, R^3 = \text{Alk, Ar}</math>.</p>                                                                                             | $\text{C}_2\text{H}_4\text{Cl}_2$ , MW, 10 min                                    | 7                       | 57–100         | 283        |
| 7   |  <p><math>X = \text{O, NAr}</math>; <math>R^1, R^2 = \text{H, OAlk}</math>; <math>R^3 = \text{CN, CONH}_2, \text{Alk}</math>.</p>                                                       | DMF, Et <sub>2</sub> O or EtOH, AcOH<br>a) MW, 15 min<br>b) $\Delta$ , 8 h        | 9<br>9                  | 57–91<br>31–51 | 284        |
| 8   |  <p><math>R = \text{H, Alk, Ar'}</math>.</p>                                                                                                                                            | $\text{ZnCl}_2$ , MW, 5–22 min                                                    | 16                      | 0–87           | 285        |
| 9   |  <p><math>R = \text{Ar, CO}_2\text{H}</math>; <math>n = 1–8</math>.</p>                                                                                                               | $\text{ZnCl}_2$ , MW, 4–8 min                                                     | 9                       | 50–80          | 286        |
| 10  |  <p><math>R = \text{Alk, Ar}</math>.</p>                                                                                                                                              | a) $\text{ZnCl}_2$ , MW, 2.5–12 min<br>b) $\text{ZnCl}_2$ , $\Delta$ , 2.5–12 min | 7<br>7                  | 57–98<br>18–53 | 287<br>287 |
| 11  |  <p><math>R = \text{Alk, Ar, Het}</math>.</p>                                                                                                                                         | a) $\text{SiO}_2$ , MW, 2–6 min<br>b) $\Delta$ , 12 h                             | 14<br>13                | 70–93<br>15–77 | 288<br>288 |
| 12  |  <p><math>R^1 = \text{Alk, Ar}</math>; <math>R^2 = \text{Me}</math>; <math>R^3 = \text{OEt, OBu}^t, \text{OBn}</math>; <math>R^2–R^3 = \text{CH}_2\text{CMe}_2\text{CH}_2</math>.</p> | a) MW, 4–10 min<br>b) $\Delta$ , 12 h                                             | 28<br>8                 | 21–89<br>15–72 | 289<br>289 |
| 13  |  <p><math>R^1, R^2 = \text{Alk}</math>.</p>                                                                                                                                           | $\text{SiO}_2$ , MW, 4 min                                                        | 8                       | 62–94          | 290        |
| 14  |  <p><math>R = \text{H, Me}</math>; <math>X = \text{O, S}</math>; <math>\text{Ar} = \text{Ph, } p\text{-ClC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4</math>.</p>                        | a) MW, 15–20 min<br>b) EtOH, $\Delta$ , 40–48 h                                   | 7<br>7                  | 70–75<br>21–25 | 291<br>291 |
| 15  |  <p><math>R^1 = \text{Me, Ph}</math>; <math>R^2 = \text{COMe, CO}_2\text{Et, CONH}_2, \text{CN}</math>.</p>                                                                           | a) DMSO, $\text{ZnBr}_2$ , MW, 20 min<br>b) $\Delta$ , 3 days                     | 10<br>10                | 55–91<br>14–86 | 292<br>292 |

Table 24 (continued).

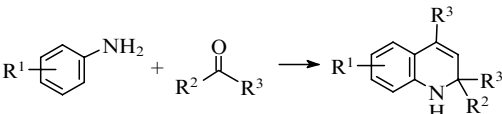
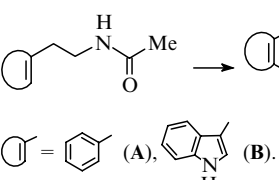
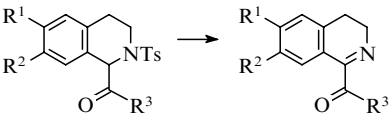
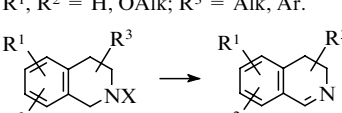
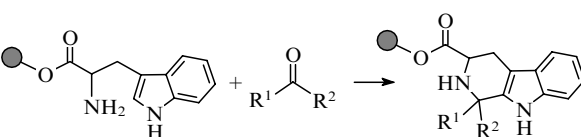
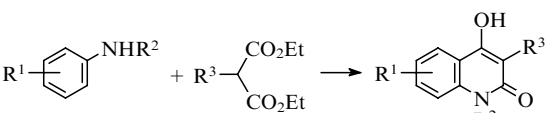
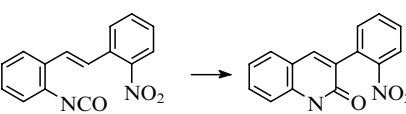
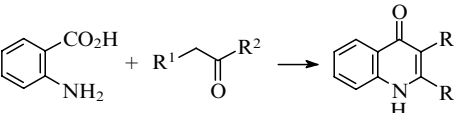
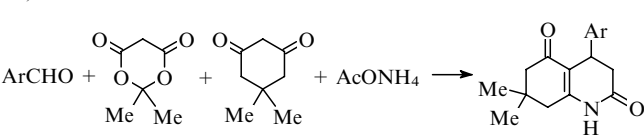
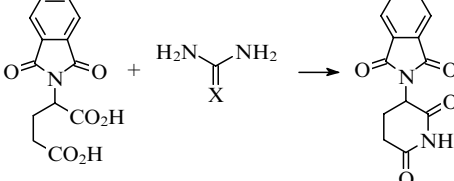
| No. | Reaction                                                                                                                                                                                   | Conditions                                                                                                                          | Number of exam-<br>ples | Yield (%)      | Ref. |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|-------------------------|----------------|------|
| 16  |  <p><math>R^1 = \text{H, Alk, Ar, Het, Hal, OMe}; R^2 = \text{Alk}; R^3 = \text{Alk, Ar}.</math></p>      | Sc(OTf) <sub>3</sub> , MeCN, MW, 50–60 min                                                                                          | 44                      | 30–98          | 293  |
| 17  |  <p><math>R^1, R^2 = \text{H, OAlk}; R^3 = \text{Alk, Ar}.</math></p>                                     | <p>a) POCl<sub>3</sub>, P<sub>2</sub>O<sub>5</sub>, MeCN (A) or PhMe (B), MW, 600 s (A) or 160 s (B)</p> <p>b) MeCN, Δ, 2 h (B)</p> | 2                       | 75 (A), 86 (B) | 294  |
| 18  |  <p><math>R^1, R^2 = \text{H, OAlk}; R^3 = \text{Alk, Ar}.</math></p>                                     | KF/Al <sub>2</sub> O <sub>3</sub> , MW, 10–20 s                                                                                     | 5                       | 60–92          | 295  |
| 19  |  <p><math>R^1, R^2 = \text{H, OMe, OBn}; R^3 = \text{Alk, Ar}; X = \text{Ts, SPh, COAr}.</math></p>       | KF/Al <sub>2</sub> O <sub>3</sub> , MW, 20–420 s                                                                                    | 12                      | 16–86          | 295  |
| 20  |  <p><math>R^1 = \text{Alk, Ar}; R^2 = \text{H, Alk, Ar}.</math></p>                                     | TsOH, CHCl <sub>3</sub> , MW, 15 min                                                                                                | 15                      | 87–99          | 296  |
| 21  |  <p><math>R^1 = \text{H, Hal, CF}_3, \text{OMe}; R^2 = \text{H, Alk}; R^3 = \text{Ph, OAlk}.</math></p> | MW, 15 min                                                                                                                          | 19                      | 0–94           | 297  |
| 22  |                                                                                                         | PhNO <sub>2</sub> , MW, 12 min                                                                                                      | 1                       | 80             | 298  |
| 23  |  <p><math>R^1, R^2 = \text{Alk}.</math></p>                                                             | DMA, MW, 6–10 min                                                                                                                   | 7                       | 56–81          | 299  |
| 24  |                                                                                                         | MW, 3–5 min                                                                                                                         | 7                       | 72–86          | 300  |
| 25  |  <p><math>X = \text{O, S}.</math></p>                                                                   | MW, 15 min                                                                                                                          | 2                       | 65–85          | 301  |



**Table 25.** Synthesis of six-membered heterocyclic compounds with one oxygen atom.

| No. | Reaction                                                                  | Conditions                                        | Number of examples | Yield (%) | Ref. |
|-----|---------------------------------------------------------------------------|---------------------------------------------------|--------------------|-----------|------|
| 1   |                                                                           | AcONH <sub>4</sub> , MW, 4–8 min                  | 7                  | 61–90     | 302  |
| 2   |                                                                           | AcONH <sub>4</sub> , MW, 1.5–4 min                | 7                  | 89–96     | 303  |
| 3   |                                                                           | Py–EtOH, MW, 2–8 min                              | 6                  | 61–91     | 304  |
| 4   | <br>R = Me, Et.                                                           | K-10, MW, 2–5 min                                 | 4                  | 65–90     | 305  |
| 5   | <br>R <sup>1</sup> = H, Me, Cl; R <sup>2</sup> , R <sup>3</sup> = H, OMe. | DBU, Na <sub>2</sub> SO <sub>4</sub> , MW, 20 min | 5                  | 0–27      | 306  |

were prepared by the cyclocondensation of the respective amides (No. 17) and direct oxidation of tetrahydroisoquinolines (Nos 18 and 19). The microwave-assisted cyclocondensation of amines (for instance, tryptophan derivatives) with compounds having a carbonyl group (No. 20) was achieved. Table 24 also gives some examples of syntheses of different quinolinones (Nos 21–23), octahydroquinoline-2,5-diones (No. 24) and hexahydropyridine-2,6-diones (No. 25).

Typically, the use of MWI substantially reduced the reaction times as compared to the thermal activation (Nos 7, 14 and 17); in some cases, an increase in the yields of heterocyclic products was registered (see, for instance, Nos 7, 10, 14, and 17), which indicated the MWE.

#### b. Six-membered heterocycles with one oxygen atom

Table 25 lists examples of applications of MWI to the synthesis of six-membered heterocyclic compounds with one oxygen atom,

*viz.*, substituted  $\gamma$ -pyrans through the condensation of Meldrum's acid with  $\beta$ -carboxy- $\beta$ -cyanostyrenes (No. 1) or benzylidenemalonodinitriles (No. 2) or three-component condensation of malonodinitrile, aromatic aldehydes and 3-methyl-1-phenyl-2-pyrazolin-5-one (No. 3), dihydropyrans through the intramolecular cyclisation of hydroxyketones (No. 4) and flavones through the intramolecular cyclocondensation of chalcones (No. 5).

For all of the above examples except for No. 5, the reaction times under the MWI conditions were 1.5–8 min and the yields of products were up to 90%, which confirms the high efficiency of this activation method.

#### c. Six-membered heterocycles with two heteroatoms

The microwave activation appeared equally efficient in the synthesis of heterocyclic compounds with two nitrogen atoms in a ring, such as pyrazine, pyridazine, pyrimidine (Table 26, Nos 1–11) and pyrimidopyrimidine (Nos 12–14). 1,3-Oxazin-2-

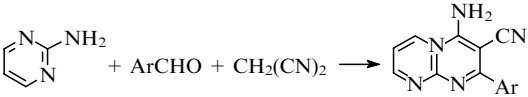
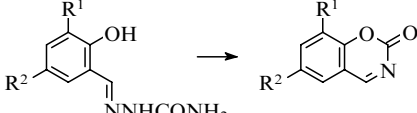
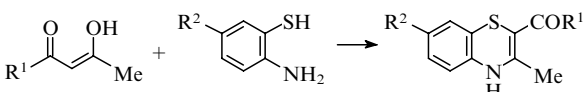
**Table 26.** Synthesis of six-membered heterocyclic compounds with two heteroatoms.

| No. | Reaction | Conditions   | Number of examples | Yield (%) | Ref. |
|-----|----------|--------------|--------------------|-----------|------|
| 1   |          | MW, 35–270 s | 5                  | 42–95     | 307  |
| 2   |          | MW, 62–270 s | 5                  | 28–70     | 307  |

Table 26 (continued).

| No. | Reaction                                                                                                  | Conditions                                                                                                 | Number of exam-<br>ples | Yield (%)      | Ref.       |
|-----|-----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|-------------------------|----------------|------------|
| 3   |                                                                                                           | SiO <sub>2</sub> or KSF, <sup>a</sup> or KH <sub>2</sub> PO <sub>4</sub> ,<br>H <sup>+</sup> , MW, 1–6 min | 17                      | 8–94           | 308        |
| 4   | <br>R = H, Alk.                                                                                           | SiO <sub>2</sub> , MW, 5 min                                                                               | 5                       | >85            | 309        |
| 5   | <br>R = H, Alk, Ar.                                                                                       | MW, 1.5–12 min                                                                                             | 9                       | 24–70          | 310        |
| 6   | <br>R <sup>1</sup> = Me, CH <sub>2</sub> Cl, Ph; R <sup>2</sup> = Me, Et.                                 | MW, 2–6 min                                                                                                | 7                       | 77–93          | 311        |
| 7   |                                                                                                           | FeCl <sub>3</sub> ·6H <sub>2</sub> O, MW, 4–6 min                                                          | 8                       | 87–95          | 312        |
| 8   | <br>n = 1–3.                                                                                              | MW, 6–8 min                                                                                                | 3                       | 89–92          | 313        |
| 9   | <br>R <sup>1</sup> = H, Alk, NO <sub>2</sub> , Br, OH, OMe; R <sup>2</sup> , R <sup>3</sup> = H, OMe, Br. | a) MW, 15–40 min<br>b) Δ, 6 h                                                                              | 10<br>1                 | 70–90<br>59    | 314<br>314 |
| 10  |                                                                                                           | a) Al <sub>2</sub> O <sub>3</sub> , MW, 7–8 min<br>b) Δ, 5–5.5 h                                           | 3<br>3                  | 89–95<br>65–71 | 245<br>245 |
| 11  |                                                                                                           | a) Al <sub>2</sub> O <sub>3</sub> , MW, 8–9 min<br>b) Δ, 3.5–4 h                                           | 3<br>3                  | 90–98<br>69–74 | 245<br>245 |
| 12  |                                                                                                           | a) MW, 20 min<br>b) EtOH, Δ, 4 h                                                                           | 5<br>5                  | >95<br>60–80   | 315<br>315 |
| 13  | <br>R = H, Me, Ph, Cl.                                                                                    | graphite, MW, 30 min                                                                                       | 4                       | 14–90          | 316        |

Table 26 (continued).

| No. | Reaction                                                                                                                                        | Conditions                                    | Number of examples | Yield (%) | Ref. |
|-----|-------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|--------------------|-----------|------|
| 14  |                                                                | piperidine, MW, 3 min                         | 1                  | 85        | 317  |
| 15  | <br>$R^1, R^2 = \text{H, Hal, OMe, NO}_2$                      | K-10, MW, 1.5–3 min                           | 10                 | 83–94     | 318  |
| 16  | <br>$R^1 = \text{Me, Ar, OEt; } R^2 = \text{H, Me, Hal, OAlk}$ | Al <sub>2</sub> O <sub>3</sub> , MW, 6–11 min | 14                 | 69–85     | 319  |

<sup>a</sup> Hereinafter, KSF is a support material.

ones were synthesised by the intramolecular cyclisation of substituted semicarbazones of salicylic aldehyde (Table 26, No. 15); the condensation of 2-aminothiophenols with  $\beta$ -diketones afforded 1,4-benzothiazines (No. 16).

The results compiled in Table 26 clearly demonstrate the superiority of the microwave activation over the thermal one.

#### d. Synthesis of six-membered heterocycles with three nitrogen atoms

Examples of the use of MWI in the synthesis of 1,2,4- and 1,3,5-triazines are given in Table 27.

One of the listed studies is worth a special note. Kidwai *et al.*<sup>320</sup> explicitly demonstrated the advantages of microwave activation as compared to thermal for 12 model reactions. Using alumina as a support they achieved quantitative yields of 1,2,4-triazines with simultaneous acceleration of the reactions by 3 orders of magnitude. This is a striking manifestation of the MWE action.

#### 5. Heterocyclic compounds with 7 or more atoms in a ring

Results of the application of MWI to the synthesis of heterocyclic compounds containing  $\geq 7$  atoms are summarised in Table 28. In particular, seven-membered heterocycles with two nitrogen atoms were prepared by the condensation of *o*-phenylenediamines with ketones in different catalytic environments (No. 1) and reaction of unsaturated amines with *N*-carboxyanthranilic anhydride (No. 2). The condensation of hydrazides with orthoesters yielded 4,7-dihydro-1,2,4-triazepin-8-one derivatives (No. 3). The reaction of *o*-aminothiophenols with  $\alpha,\beta$ -unsaturated ketones gave rise to 2,3-dihydro-1,5-benzothiazepines (No. 4). A 8-membered dibenzodiazocinoquinazolinone was synthesised from 3-hydroxyquinazolinones and *N*-carboxyanthranilic anhydride (No. 5). The cyclocondensation of benzaldehydes with pyrrole afforded tetraarylporphyrins (No. 6). The cyclocondensation of phthalic acid or its derivatives was employed for the synthesis of phthalocyanines (No. 7). Cationic cyclophanes were afforded by the cyclocondensation of precyclophanes with *m*-terphenyl dibromides (No. 8). Two types of binuclear phthalocyanines (Nos 9 and 10) were

Table 27. Synthesis of 1,2,4- and 1,3,5-triazines.

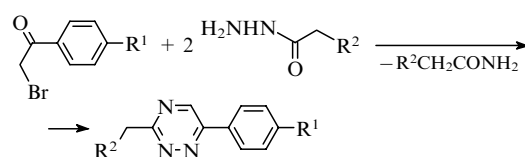
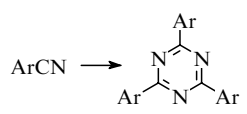
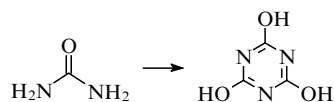
| No. | Reaction                                                                                                                                | Conditions                                                                                                                                                  | Number of examples | Yield (%) | Ref. |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------|------|
| 1   | <br>$R^1 = \text{H, Cl, NH}_2; R^2 = \text{Ar, OAr}$ | a) MW, 300–420 s<br>b) SiO <sub>2</sub> , MW, 90–120 s<br>c) K-10, MW, 95–120 s<br>d) Al <sub>2</sub> O <sub>3</sub> , MW, 60–95 s<br>e) $\Delta$ , 18–25 h | 12                 | 60–64     | 320  |
| 2   |                                                      | a) Yb(OTf) <sub>3</sub> or Si(M) (M = Al, Zn, Ti), MW, 30–60 min<br>b) $\Delta$ , 1–24 h                                                                    | 10                 | 0–95      | 321  |
| 3   |                                                      | a) graphite, MW, 1–3 min<br>b) $\Delta$ , 1–3 min                                                                                                           | 2                  | 10–61     | 322  |

**Table 28.** Synthesis of heterocyclic compounds with 7 or more atoms in a ring.

| No.                  | Reaction                                                                                  | Conditions                                                                          | Number of examples | Yield (%)            | Ref.       |
|----------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------|----------------------|------------|
| Seven-membered rings |                                                                                           |                                                                                     |                    |                      |            |
| 1                    | <p><math>R^1, R^2 = \text{H, Alk, Ar, Cl, PhCO}; R^3, R^4 = \text{H, Alk, Ar.}</math></p> | a) $\text{Al}_2\text{O}_3/\text{P}_2\text{O}_5$ , MW, 1 min<br>b) AcOH, MW, 2–7 min | 6<br>12            | 73–85<br>90–99       | 323<br>324 |
| 2                    | <p><math>R = \text{Me, Alk}; X = \text{H, Hal.}</math></p>                                | a) MW, 5 min<br>b) DMF, 60 min                                                      | 6<br>6             | 55–69<br>27–45       | 325<br>325 |
| 3                    | <p><math>R = \text{Alk, Ph.}</math></p>                                                   | a) EtOH, MW, 3 h<br>b) $\Delta$ , 22 h                                              | 2<br>3             | 38–47<br>8–74        | 326<br>326 |
| 4                    | <p><math>X = \text{Me, OMe, Hal.}</math></p>                                              | a) KSF, MW, 9–15 min<br>b) EtOH, HCl, $\Delta$ , 420–840 min                        | 6<br>6             | 59–71<br>50–62       | 327<br>327 |
| Eight-membered rings |                                                                                           |                                                                                     |                    |                      |            |
| 5                    | <p><math>R = \text{H, Me, Et.}</math></p>                                                 | montmorillonite, MW, 7 min                                                          | 2                  | 72–73                | 328        |
| 16-Membered rings    |                                                                                           |                                                                                     |                    |                      |            |
| 6                    | <p><math>R^1 - R^3 = \text{H, Me, Cl, OMe, NO}_2.</math></p>                              | EtCO <sub>2</sub> H, MW, 3–5 min                                                    | 8                  | 4–43                 | 329        |
| 7                    | <p><math>R = \text{H, Bu}^t; M = \text{Co, Zn, Cu, Ni, Cr, Mn.}</math></p>                | MW, 3–10 min                                                                        | > 15               | < 30–80 <sup>b</sup> | 330        |

Table 26 (continued).

| No. | Reaction                                                                      | Conditions                                                                                                                                                                                                                                                                                                        | Number of examples | Yield (%)        | Ref.              |
|-----|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|------------------|-------------------|
| 8   | <p>R = H, Br, CO<sub>2</sub>H, CO<sub>2</sub>Me; X = CR' (R' = H, Me), N.</p> | a) Na <sub>2</sub> SO <sub>4</sub> , MW, 13–15 min<br>b) Δ, 5 days                                                                                                                                                                                                                                                | 10<br>10           | 30–60<br>40–70   | 331<br>331        |
| 9   |                                                                               | a) Zn(OAc) <sub>2</sub> ·2 H <sub>2</sub> O (2 equiv.), <i>o</i> -Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub> , MW, 15 min<br>b) Zn(OAc) <sub>2</sub> ·2 H <sub>2</sub> O (20 equiv.), <i>o</i> -Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub> , MW, 3 min<br>c) iso-C <sub>5</sub> H <sub>11</sub> OH, Δ, 14 h | 1<br>1<br>1        | 6.8<br>33<br>1.8 | 332<br>332<br>332 |
| 10  |                                                                               | MW, 5 min                                                                                                                                                                                                                                                                                                         | 1                  | 22 <sup>c</sup>  | 333               |

<sup>a</sup> If lithium methoxide is used, a complex with two lithium atoms is formed; <sup>b</sup> if phthalic imide or anhydride or RC<sub>6</sub>H<sub>3</sub>(CO<sub>2</sub>H)<sub>2</sub> in the presence of urea is used instead of RC<sub>6</sub>H<sub>3</sub>(CN)<sub>2</sub>, the yields of products decrease; <sup>c</sup> the monosubstitution product is formed in a yield of 28%.

synthesised using the cyclocondensation of 1,2-bis(3,4-dicyanophenoxymethyl)benzene.

## XV. Organophosphorus compounds

Alkylphosphonates were prepared by the microwave-assisted reaction of trialkyl phosphites with alkyl halides (the Arbuzov rearrangement) (Table 29, Nos 1 and 2) or aldehydes (the modified Arbuzov reaction) (No. 3). The Kabachnik–Fields reaction was utilised to synthesise aminoalkylphosphonates either under solvent-free conditions on a solid support (Nos 4 and 5) or using a catalyst in an ionic liquid (No. 6) or 1,2-dichloroethane (No. 7). The interaction of triphenylphosphine with alkyl halides gave rise to phosphonium salts (No. 8). The MWE is manifested in an increase in the yields of products in the cases of microwave activation (Nos 4 and 5).

## XVI. Miscellaneous reactions

Table 30 lists several additional examples of microwave-assisted reactions not covered by Tables. 1–29.

## XVII. Conclusion

The history of the utilisation of microwave technology in organic synthesis extends only over two decades. We may consider that it is now mainly in the stage of gathering empirical results. Despite the fact that the number of papers reporting the use of MWI for heating and activation of chemical reactions exceeded 2000, there is still no solid theoretical background underlying the experimentally observed specific microwave effect.

The above analysis of the published data indicates that the microwave method for the activation of chemical processes is applicable to nearly all known types of organic reactions. The net result of a microwave chemical reaction depends primarily on the nature of reactants (*i.e.*, on their structural features and distribution of the electron density therein), the reaction mechanism (the

**Table 29.** Synthesis of phosphonates, aminophosphonates and phosphonium salts.

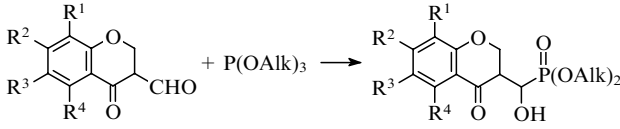
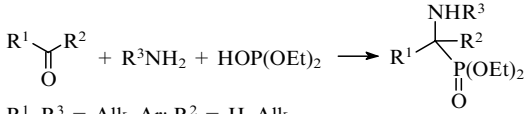
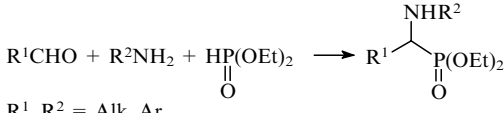
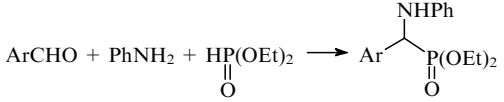
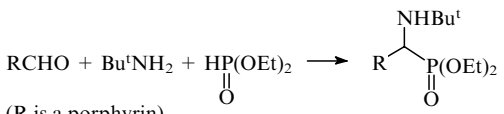
| No. | Reaction                                                                                                                                          | Conditions                                                        | Number of examples | Yield (%)      | Ref.       |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|--------------------|----------------|------------|
| 1   | $\text{AlkX} + \text{P}(\text{OEt})_3 \longrightarrow \text{Alk}-\text{P}(\text{OEt})_2$ $\text{X} = \text{Br, I.}$                               | MW, 15–30 s                                                       | 3                  | 95–97          | 334        |
| 2   | $\text{Alk}^1\text{Cl} + \text{P}(\text{OAlk}^2)_3 \longrightarrow \text{Alk}^1-\text{P}(\text{OAlk}^2)_2$                                        | $\text{Al}_2\text{O}_3$ , MW, 5–15 min                            | 10                 | 0–90           | 335        |
| 3   |  $\text{R}^1-\text{R}^4 = \text{H, Alk, Cl.}$                    | $\text{Me}_3\text{SiCl}$ , MW, 5–10 min                           | 13                 | 70–95          | 336        |
| 4   |  $\text{R}^1, \text{R}^3 = \text{Alk, Ar; R}^2 = \text{H, Alk.}$ | a) KSF, MW, 3–8 min<br>b) PhMe, $\Delta$ , 5–12 h                 | 18<br>18           | 75–91<br>65–80 | 337<br>337 |
| 5   |  $\text{R}^1, \text{R}^2 = \text{Alk, Ar.}$                      | a) $\text{Al}_2\text{O}_3$ , MW, 3–6 min<br>b) $\Delta$ , 4–8 h   | 13<br>14           | 65–95<br>59–80 | 338<br>338 |
| 6   |                                                                 | $\text{Yb}(\text{OTf})_3$ , (bmim) $\text{BF}_4$ , MW, 2 min      | 6                  | 83–100         | 339        |
| 7   |  $(\text{R} \text{ is a porphyrin})$                           | $\text{CdI}_2$ , $\text{C}_2\text{H}_4\text{Cl}_2$ , MW, 9–10 min | 4                  | 80–85          | 340        |
| 8   | $\text{AlkX} + \text{PPh}_3 \longrightarrow [\text{Ph}_3\text{AlkP}]^+\text{X}^-$ $\text{X} = \text{Br, I.}$                                      | xylene, MW, 30 s                                                  | 3                  | > 99           | 334        |

**Table 30.** Miscellaneous reactions.

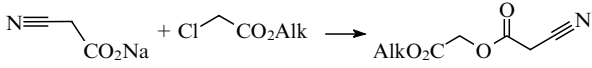
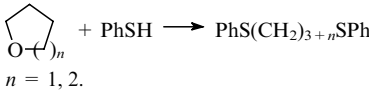
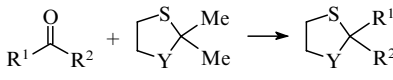
| No. | Reaction                                                                                                                                                 | Conditions                                                    | Number of examples | Yield (%)      | Ref. |
|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|--------------------|----------------|------|
| 1   |                                                                       | $\text{Bu}_4^{\text{n}}\text{NBr}/\text{SiO}_2$ , MW, 2–4 min | 8                  | 84–95          | 341  |
| 2   |  $n = 1, 2.$                                                          | $\text{InCl}_3/\text{SiO}_2$ , MW, 10–15 min                  | 18                 | 53–89          | 342  |
| 3   | $\text{AlkX} + \text{S} + \text{NaOH} \longrightarrow \text{AlkS}-\text{SAlk}$ $\text{X} = \text{Cl, Br.}$                                               | PEG-400, DMF<br>a) MW, 6–7 min<br>b) $\Delta$ , 4 h           | 9<br>9             | 65–91<br>50–97 | 343  |
| 4   |  $\text{R}^1 = \text{Alk, Ph; R}^2 = \text{H, Alk; Y} = \text{O, S.}$ | KSF or Amberlyst 15, MW, 15 min                               | 16                 | 0–98           | 344  |

Table 30 (continued).

| No. | Reaction                                                                                                          | Conditions                                                                                                                                                                                            | Number of examples  | Yield (%)      | Ref.       |
|-----|-------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|----------------|------------|
| 5   | <p><math>R^1 = \text{Alk, Ar}; R^2 = \text{Alk}; R^3 = \text{OTs, OC}_6\text{H}_4\text{NO}_2\text{-}p.</math></p> | PhI(OAc) <sub>2</sub> , MW, 10–40 s                                                                                                                                                                   | 32                  | 75–95          | 345        |
| 6   | <p><math>R = \text{H, Me}; n = 1, 2.</math></p>                                                                   | a) Pd(OAc) <sub>2</sub> , Bu <sub>4</sub> NBr, K <sub>2</sub> CO <sub>3</sub> ,<br>H <sub>2</sub> O–PhMe, MW, 5 min<br>b) [Pd], <sup>a</sup> KF/Al <sub>2</sub> O <sub>3</sub> , KOH,<br>MW, 4–10 min | 2<br>8 <sup>b</sup> | 65–70<br>73–81 | 346<br>347 |

<sup>a</sup> Various Pd catalysts were used; <sup>b</sup> the synthesis of other polythiophenes with a common formula  $X-\text{S}_n-\text{Y}$  (X, Y = H, Br; R = H, Me; n = 2–6) was also reported.

stronger the change in the polarity of the medium during the reaction, the more evident is the microwave effect), the duration and power of MWI, the types of supports, catalysts and solvents utilised. Therefore, the factors listed above have to be considered as a whole for any specific reaction type.

Numerous attempts have been undertaken (see, for instance, Refs 5–7,9,12,42) to reconcile the current theoretical concepts regarding the physics of microwave processes with the experimental results on organic syntheses performed under microwave activation. However, by no means all the factors affecting the overall output of a specific chemical reaction have been properly taken into account. In particular, the effects of MWI wavelength and power and support type on the direction, chemical and stereochemical yields of a chemical reaction are unknown up to date. Several studies emphasising these issues were published after 2002. In particular, Nüchter *et al.*<sup>348</sup> considered the best practices of microwave experiments, Kappe<sup>349</sup> and de la Hoz *et al.*<sup>350</sup> gave examples of successful applications of controlled MWI-heating to organic synthesis and Romanova *et al.*<sup>351</sup> described the influence of MWI on the direction and stereochemistry of reactions.

The rapidly increasing number of publications devoted to microwave syntheses clearly confirms the growing perception of MWI as a powerful tool in hands of organic chemists. The first monographs on MWI synthesis have already appeared.<sup>352–354</sup> Without doubt, the near future will witness expanding application of the method both on the laboratory and industrial scales, especially provided that its theoretical substantiation is elaborated. The efforts put into the optimisation of conditions of microwave organic syntheses will be definitely rewarded by the quickness and simplicity of experimental implementations, energy saving and cost efficiency intrinsic to MWI.

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# Analysis of high-purity solids by atomic emission spectroscopy and mass spectrometry with atom excitation and ionisation in inductively coupled plasma

I R Shelpakova, A I Saprykin

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**Abstract.** Studies on procedures for the analysis of high-purity solids by inductively coupled plasma atomic emission spectroscopy and mass spectrometry published over the last decade are considered. The analytical scope of the methods is outlined. Specific features of sampling procedures, matrix effects and possibilities of decreasing the detection limits of impurities based on their preconcentration are discussed. The bibliography includes 95 references.

## I. Introduction

The problem of substance purity control is always topical, because pure substances are used in the preparation of materials with special properties, which in turn determine parameters of devices constructed from these materials. At present, the influence of the trace element and its concentration, especially in the presence of other impurities, on the aim parameters of the device is often unknown. Therefore, the purpose of technological processes is to purify substances from all possible contaminants to the highest extent, which makes it necessary to monitor the purification process by analytical methods. These are characterised by the number of elements that can be detected and the detection limits of impurities (analytes). Up to the end of the previous century, spectrochemical techniques with arc excitation irradiation and mass spectrometry with spark or laser ionisation were widely used for the determination of the composition of impurities in high-purity substances. At present, these methods are virtually superseded by the methods of atom excitation and ionisation in inductively coupled plasma (ICP). Inductively coupled plasma atomic emission spectroscopy (ICP-AES) and mass spectrometry (ICP-MS) are the most important of them. In these methods, atom excitation and ionisation are induced by an electrode-less discharge generated in an inductor high-frequency field in an argon atmosphere. As a rule, the capacity of generators employed in analytical instruments with ICP is up to 5 kW and the working

frequency is 27.12 MHz. The capacity achieved in ICP is 1–2 kW. The electron temperature reaches 6000–8000 K, while the concentration of electrons is  $10^{13}$ – $10^{16}$  cm<sup>-3</sup>. Under such conditions, virtually total dissociation of molecules occurs, and atoms are effectively excited and ionised (the degree of ionisation of > 75% of the elements in the Periodic Table is ~90%), and the portion of multiply ionised atoms is very low (~1%). This type of discharge has stable parameters, which ensures high (up to tenth parts of percent) reproducibility of the analytical signal. There are several ways to introduce samples into the ICP. Together with the traditional dispersion of solutions (either pneumatic or ultrasonic), vaporisation can be effected using an electrothermal atomiser (ETA) or by laser- or spark-induced dispersion (ablation). The low starting energy of ions (10–15 eV) and high stability of the plasma parameters enable the use of ICP ionisation in combination with relatively simple mass analysers of quadrupole or time-of-flight types.

## II. Instrumentation

The instruments for inductively coupled plasma atomic emission spectroscopy and mass spectrometry (ICP-AES and ICP-MS, respectively) are commercially available.

As regards the number of instruments for multielement analysis, those for ICP-AES produced by the instrument-making companies in the last decades play a leading role. Wide distribution of this equipment is due to low matrix effects, high reproducibility of the results, low detection limits for elements (down to  $10^{-2}$  ng ml<sup>-1</sup> or  $10^{-7}$  mass % for solid samples) and relatively low cost (from USD 60 000 to 100 000). In the modern instruments for ICP-AES, linear detectors (as in spectrometers of the Pashen–Runge type) or matrix detectors (as in spectrometers with diffraction echelle gratings) with charge coupling and with charge carrier injection are used for recording the spectra. These detectors provide simultaneous photoelectric recording of the entire working range of wavelengths and allow complete automation of spectra processing using personal computers. The latest models of ICP spectrometers contain an option to perform axial measurement of plasma along with radial, which allows further reduction of the element detection limits (from two- to five-fold) due to an increase in the signal-to-noise ratio.<sup>1,2</sup>

Recently, ICP-MS has acquired wide use due to excellent analytical characteristics, viz., the possibility of simultaneous detection of up to 70 elements as contaminants in mineral acid solutions, including rare-earth elements (REE) and transuranium

**I R Shelpakova, A I Saprykin** A V Nikolaev Institute of Inorganic Chemistry, Siberian Branch of the Russian Academy of Sciences, prosp. Akad. Lavrent'eva 3, 630090 Novosibirsk, Russian Federation. Fax (7-383) 330 94 89, tel. (7-383) 336 69 65, e-mail: shelp@che.nsk.su (I R Shelpakova), saprykin@che.nsk.su (A I Saprykin)

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elements, in a wide (up to 9 orders of magnitude) range of concentrations and with high (up to 99%) reproducibility. In the majority of publications devoted to mass spectrometric analysis of high-purity solids with the use of ICP, quadrupole mass spectrometers 'Plasma Quad' (Vacuum Generator, UK), 'ELAN' (Perkin Elmer, USA) and a magnetic sector field high resolution mass spectrometer 'ELEMENT' (Finnigan MAT, Germany) have been used most often. Note the higher cost of these instruments (from USD 80 000 to 300 000) as compared to those for ICP-AES.

An advantage of ICP-MS is the possibility of performing an isotope analysis.<sup>3–5</sup>

The resolution of a mass spectrometer is a crucial parameter determining the element detection limits. As a rule, the lowest detection limits (1–2 orders of magnitude lower than those achievable with quadrupole mass spectrometers) are provided by Finnigan MAT double-focusing instruments, due to the higher sensitivity, lower detector noise and the possibility of overcoming problems associated with overlap, in the analytical signal, of molecular ion lines and analyte lines generated in the ICP.<sup>3, 6, 7</sup>

One of the problems of using ICP-MS is the memory effect caused by deposition of a sample material on the introduction system and on parts of the separation and ion-beam formation devices. This effect can be reduced by high dilution of the sample solution (10<sup>3</sup>-fold and larger), preliminary cleaning of the entrance cones (sampler and skimmer), prolonged (up to 2–3 h) washing of the sample introduction system with 2%–5% solutions of high-purity nitric or hydrochloric (sometimes sulfuric) acid.

The sample introduction system consists of a peristaltic pump, a nebuliser and a dispersion chamber. The peristaltic pump regulates the rate of solution feeding. The nebuliser and the dispersion chamber produce aerosol drops with sizes of 1–2  $\mu\text{m}$ , which ensure equilibrium loading of the plasma and prevent its overcooling. Different constructions of dispersion chambers provide the uniformity of aerosol drop sizes or the sample particles in the case of laser ablation, thus reducing the element detection limits and random errors of the analysis.<sup>8–10</sup> With the use of pneumatic nebulisers, only ~1% of the analytical sample is transferred to the plasma, which decreases the efficiency of the sample usage. Ultrasonic nebulisers are about an order of magnitude more efficient.

### III. Sampling procedures

Sampling procedures are determined, on the one hand, by the nature of the analysed material and, on the other hand, by the method of analysis and sample introduction into the ICP. One of the main steps in the analysis of high-purity solids by ICP-AES and ICP-MS is the dissolution of the sample. Dissolution eliminates the problems of non-uniformity of the sample, but instead brings a problem of importation of contaminants from the solvent. Those methods are preferred that require the least quantity of reagents. For example, dissolution in an autoclave was used for the analysis of indium,<sup>11</sup> and microwave-assisted dissolution for the analysis of pure carbon.<sup>9</sup> In certain cases, complete dissolution of analysed substances requires their preliminary fusion with alkali metal salts. For example, carbon ash samples were fused with lithium metaborate.<sup>9</sup> While choosing the solvent, it is necessary to keep in mind that this can damage the equipment parts. In particular, hydrofluoric, hydrochloric or sulfuric acid, even diluted to ~1% concentration, may cause corrosion of the metallic parts of the ion-beam forming system of the mass spectrometer.

For the ICP-AES, the admissible content of a matrix element in a solution is 1%–5%. In the case of ICP-MS, the concentration of a solid sample in a solution (preferably, in 1 M HNO<sub>3</sub>) should not exceed 0.1%–0.05% to protect the instrument's entrance cones from the probe material deposition.<sup>12</sup> Such a dilution reduces the matrix effect. Due to the extremely low detection limits of analytes in solutions (up to several femtograms per ml)

attainable with the double-focusing spectrometers, the detection limits of non-common contaminants in solids can reach 10<sup>–9</sup> mass %–10<sup>–7</sup> mass %.

When analysing high-purity substances using ICP-AES and ICP-MS, advantage is taken of introducing of sample into the ICP in the form of a vapour from an electrothermal atomiser.<sup>13–16</sup> The preliminary dissolution of the sample is still necessary for this method, however, the solution may not be highly diluted. Optimisation of the pyrolysis and evaporation temperatures and the use of matrix modifiers allows selection of the conditions for the separation of analytes from the matrix. In the determination of contaminants in high-purity phosphorus, arsenic, antimony, sulfur, tellurium and iodine, ICP-MS and ETA were used with preliminary thermal separation (80%–97%) of the sample matrix.<sup>13</sup> In simultaneous determination of 45 contaminants, detection limits of 10<sup>–7</sup> mass % were reached, while in the case of optimised conditions for analysis for each element separately, they were as low as 10<sup>–8</sup> mass %.

In a number of studies, the electrothermal analyser was fed with a homogeneous (for example, ultrasonicated) aqueous slurry of a finely dispersed sample rather than with its solution.<sup>17–19</sup> On the one hand, this method reduces the risk of contamination or analyte loss during the sampling, but on the other hand, it complicates the process due to the necessity of very fine desintegration of the sample (< 5–45  $\mu\text{m}$ ). Such a dispersity is achieved by treatment in special apparatuses for many hours. In the analysis of alumina, a dry sample mixed with a matrix modifier was introduced into the graphite atomiser.<sup>20</sup> In the determination of contaminants in coals by ICP-AES and ICP-MS, Ebdon *et al.*<sup>21, 22</sup> introduced the samples directly into the ICP in the form of an aqueous suspension using the PTFE nebuliser for highly concentrated solutions.<sup>23</sup> Obviously, such a sampling procedure requires high dispersity of the sample and high uniformity and stability of the suspension. The sample content in the suspension was 0.2%–0.002% (ICP-MS) and 0.5% (ICP-AES). The same procedure was employed for the analysis of silicon nitride.<sup>24</sup>

At present, the search for new ways of introducing of powder samples into ICP without dissolution is in progress. For the direct introduction of powders into an instrument for ICP-AES, Bukar' <sup>25</sup> has used a special device. It is of note that certain difficulties are thus inevitable due to the low capacity of the ICP. The calibration problem becomes more serious due to the absence of standard samples adequate to the analytical ones. In our view, a more powerful (10–15 kW) plasma of double-jet arc plasmotron<sup>26</sup> is more promising for the direct analysis of powder samples.

The direct analysis of bulk solids by ICP-AES and ICP-MS is possible with the use of laser ablation (LA). The vaporisation of the material occurs under the action of a UV-laser ( $\lambda = 266 \text{ nm}$ ) focused on the sample surface to a spot 10–100  $\mu\text{m}$  in diameter. With a plasma power density of 10<sup>8</sup>–10<sup>9</sup> W cm<sup>–2</sup>, non-selective sample vaporisation occurs. The aerosol is transported to the plasma by an argon flow. This method is especially efficient in the cases where solubilisation of the analytes without losses or contamination is complicated or for an express semi-quantitative analysis. The time- and labour-consuming steps of sample dissolution or desintegration are eliminated, and there is the possibility of local analysis. However, the non-uniformity of the sample and especially its surface can import essential errors into the results. LA-ICP-MS was used for the analysis of pure coal and graphite,<sup>9, 27</sup> aluminium and copper<sup>28</sup> and a quartz glass.<sup>29, 30</sup> Unfortunately, the detection limits in this method are usually not lower than 10<sup>–7</sup> mass %–10<sup>–5</sup> mass %.<sup>27, 31</sup> Lower values (10<sup>–10</sup> mass %–10<sup>–7</sup> mass %) were reached only by Becker and Tenzler<sup>29</sup> in the analysis of a quartz glass with the use of a powerful IR-laser at a wavelength of 1064 nm. In this case, as opposed to the UV-laser case, the sample was decomposed by the plasma formed from the surrounding gas (argon), so it was unnecessary to focus the laser beam.<sup>32</sup>

Both laser and spark ablation are used in combination with the ICP-AES. By the examples of ICP atomic emission analysis of

a series of metals and alloys,<sup>33</sup> it was shown that the detection limits of analytes with the use of spark and laser ablation are comparable and have values of  $10^{-6}\%$ – $10^{-4}\%$ . These limits depend on the matrix and the nature of the element under study. In this method, it is possible to spend substantially more sample material (as compared with the LA-ICP mass spectrometric method) without the risk of its deposition on the equipment parts.

It is possible to substantially reduce the detection limits of contaminants in solid high-purity substances by preconcentration. This refers in particular to the mass spectrometric method. For the preconcentration coefficient  $K > 10^3$ , *i.e.*, where the sample matrix is virtually completely separated, the detection limits, for non-common impurities can reach values comparable to those in pure water, *viz.*, of about  $10^{-11}$  mass %– $10^{-10}$  mass % (and even lower). It is substantial that preconcentration allows one to level the matrix effect, to avoid deposition of sample material on the entrance cones of the mass spectrometer, to eliminate the 'memory effect'<sup>34</sup> and to diminish the probability of overlap of lines of molecular ions of the matrix element and the analyte lines in the output signal. Numerous methods of preconcentration used in conjunction with ICP-AES and ICP-MS are sorption, chromatographic separation, extraction, distillation of the probe matrix (also in the form of a volatile compound) and its precipitation. A column for anion-exchange chromatography to separate the matrix (tantalum) from impurities was built directly into the system of sample introduction into the ICP.<sup>10</sup> Determination of contaminants in silicon and germanium on the ICP-MS spectrometer ELEMENT achieved their preconcentration by halogenation and distillation of the probe matrix from the solution.<sup>35</sup> The detection limits for the contaminants were  $10^{-11}$  mass %– $10^{-6}$  mass %. With the same mass spectrometer, the detection limits of fourteen rare-earth elements as impurities in lanthanum oxide of  $10^{-10}\%$ – $10^{-8}\%$  were reached following preliminary separation of the matrix from impurities by high-performance liquid chromatography.<sup>36</sup> The detection limits of the same order of magnitude were obtained with the use of the 'Plasma Quad3' mass spectrometer for fifteen contaminants in cadmium separated from the matrix by sorption.<sup>37</sup> Chromatographic separation of impurities from the matrix has been used<sup>14,15</sup> in combination with ICP-AES and ETA for the analysis of lanthanum and cerium oxides.

The lowest possible detection limits of the common impurities could be achieved using minimum volumes of specially purified reagents, 'clean rooms', disposable glassware and special precautions to prevent contamination during sampling.<sup>9,10</sup> The contaminants introduced during sampling were taken into account in a control experiment. It can be noted that the reagent-free methods of preconcentration are the most effective, since the extent of contamination in this case is a minimum. One of these methods is the vacuum distillation of the sample matrix. The preconcentration methods based on sample dissolution and its reaction with other reagents (in particular, with solid and liquid extractants) do not provide low detection limits for common impurities even at high preconcentration coefficient.<sup>35</sup>

#### IV. Matrix effects

Matrix effects related to ICP-AES and ICP-MS manifest themselves in the control of the aerosol droplet size and its transport to plasma, thermal properties of plasma, and spectral overlaps.<sup>38</sup> An efficient method of compensating non-spectral matrix effects is the use of an internal standard.<sup>39</sup> Usually, the role of the internal standard introduced into the sample solution is played by a chemical element not to be determined and is absent from the sample and from the control experiment (most often, indium, rhodium and single-isotope rare-earth elements are used). In the LA-ICP-MS, the working gas components (krypton, xenon) and molecular ions of the matrix ( $\text{MAr}^+$ ,  $\text{MO}^+$  where M is the matrix element) serve as the standards. In the analysis of a quartz glass by this method, the compensation of the signal instability by virtue of

the internal standard  $\text{SiAr}^+$  allowed one to decrease four- to five-fold the random error.<sup>30</sup>

Spectral overlaps of the analyte lines, mainly with the molecular ions, are among the main limitations of the mass spectrometric method. Steep gradients of the plasma density and temperature in the plasma beam formation area favour the formation of different molecular ions, the mass spectra of which override the spectra of the analytes. In particular, components of the solvent ( $\text{H}_2\text{O}$ ,  $\text{HNO}_3$ ,  $\text{H}_2\text{SO}_4$ ,  $\text{HClO}_4$ ,  $\text{HCl}$ ) can serve as one of the sources of molecular ions,<sup>9,40</sup> which combine with the sample matrix element and with argon to form  $\text{MCl}^+$ ,  $\text{MO}^+$ ,  $\text{MN}^+$ ,  $^{40}\text{Ar}^{35}\text{Cl}^+$ ,  $^{40}\text{Ar}^{16}\text{O}^+$ ,  $^{40}\text{Ar}^{14}\text{N}^+$ , and also argides ( $\text{MAr}^+$ ), oxides ( $\text{MO}^+$ ), hydrides ( $\text{MH}^+$ ) and other compounds of the matrix elements with the plasma components. Elements from the matrix modifiers also participate in molecular ion formation.<sup>18</sup> The sample introduction into the ICP by laser ablation allows elimination of these interference sources (except for  $\text{MAr}^+$ ). The problem of molecular ion line overlap is especially vital for the light elements with atomic masses  $< 80$  a.m.u. Possible overlaps of the molecular ion lines and atomic ones from  $^{24}\text{Mg}^+$  to  $^{76}\text{Ge}^+$  are documented.<sup>41</sup> The paper cited also contains a discussion of the problems of element determination in different matrices using a double-focusing mass spectrometer with a resolution up to 10 000.

Systematic studies of molecular ion formation have been carried out.<sup>42–45</sup> The problem of molecular ion overlap in the mass spectrometric analysis of dissolved coal samples with the use of ICP and LA was considered in detail.<sup>9</sup> Possible approaches to avoid these overlaps are also discussed. It is obvious that the ability to solve the problem of overlaps depends on the resolution of the instrument. They can largely be avoided by the use of double-focusing mass spectrometers with medium (3000–4000) and high (10000) resolution. However, the use of high resolution in these instruments leads to an increase in the element detection limits due to the reduced ion transfer efficiency.<sup>3</sup> The intensity of molecular ion lines can be reduced by their 'desolvation' in special collision cells. Molecular ions decompose in these cells due to collisions with the filler gas. For example, a collision cell was used<sup>46</sup> in the analysis of pure graphite by LA-ICP-MS on a quadrupole mass spectrometer. By the example of the reduction of intensity of  $^{40}\text{Ar}^{16}\text{O}^+$  and  $^{40}\text{Ar}^{14}\text{N}^+$  lines, which complicate the determination of iron in graphite, the efficiency of a collision cell with hydrogen and helium as filler gases is shown. The fundamental aspects and the practical usage of collision cells in mass spectrometric analysis have been considered.<sup>47</sup> It should be noted that the so-called isobaric interferences, *i.e.*, overlap of the lines of the matrix element oxides and those of the analyte isotopes with equal masses still present an unsolved problem. This problem is especially critical in the case of the determination of REE contaminants in rare-earth-containing matrix materials, for example,<sup>159</sup> of Tb in neodymium oxide ( $^{143}\text{Nd}^{16}\text{O}^+$ ).

Usually, in the ICP-AES method it is possible to find analytical lines free from overlap. Otherwise, chemometric methods and the subtraction of control spectra from the sample spectra are used to account for the overlap.<sup>48</sup> Fractional evaporation of impurities and the matrix in the form of fluorides from a graphite atomiser was used in the analysis of alumina by ICP-AES in order to suppress the non-spectral matrix effects.<sup>48</sup>

#### V. Quantitative analysis

The advantages of the use of ICP as a tool for excitation and ionisation of atoms in the analysis of solutions of high-purity solids include the possibility of using aqueous solutions of analytes as standards and the ease of using the methods of additives and isotopic dilution. For example, the method of additives in atomic emission spectroscopy was successfully used for the determination of impurities in alumina, gallium and scandium oxides.<sup>20,49,50</sup> The influence of the matrix on the analytical signal value is levelled owing to the use of an internal

standard.<sup>8,9,51–56</sup> Reliable results were obtained in the mass spectrometric analysis with use of the isotopic dilution method and introduction of a suspension into the ICP<sup>19</sup> and the method of additives with aqueous solutions of the analytes.<sup>18,20,31</sup>

It is much more difficult to obtain quantitative results from the LA-ICP-MS due to the absence (as a rule) of certified standards. Some researchers employ calibration by analyte solutions for determination of the relative sensitivity coefficients using the standards with the similar matrix.<sup>27</sup> With internal standards, the correction of different sensitivity of mass spectrometric methods based on ICP only or LA-ICP is also possible.<sup>31,57</sup> Specially synthesised standards based on the material to be analysed are also employed. For example, such samples were used<sup>58</sup> in the LA-ICP mass spectrometric analysis of GaAs. Becker<sup>46</sup> proposed an original method of calibration by LA-ICP-MS in the analysis of graphite: an aqueous solution of the analyte passed through the nebuliser is mixed with high-purity graphite atomised by laser ablation, and the graphite sample atomised in the same way is mixed with the pure solvent. In the author's opinion, this method allows one to obtain reliable results and to reduce the detection limits for a series of elements due to the reduction of the background level and the increase in the sensitivity coefficient.

For the verification of the correctness of the result of analysis, the method 'added–found' is often used,<sup>59–61</sup> together with comparison with the results from independent analytical methods<sup>18,20,62</sup> and with those obtained for synthetic standards. The most reliable results are obtained where the certified standards are used. Unfortunately, their list for the high-purity substances is short. Standards of the SARM, BCR and NIST series (SRM 1635, SRM 1630a, SRM 1632b and SRM 1633b) are used for the ICP-MS analysis of coal and ash,<sup>9,17,19</sup> NIST (SRM 8171) for the analysis of silver,<sup>63</sup> NIST (SRM 681) for platinum,<sup>31,46</sup> NIST

(SRM 699) for alimina,<sup>18,20</sup> State Standard Sample 7287-96 for gold,<sup>64</sup> JCRM (R004) and JCRM (R005) for Si<sub>3</sub>N<sub>4</sub>,<sup>24</sup> CRM (JSS 003-2) for iron,<sup>65</sup> and silicate glasses NIST (SRM 610-615) for the analysis of oxide crystals.<sup>66–68</sup> According to the results of the inter-laboratory measurements, these glasses contain ~50 elements as impurities in the  $1 \times 10^{-4}$  mass % –  $5 \times 10^{-2}$  mass % concentration range.

As a rule, in all versions of ICP-AES and ICP-MS, the random error of element determination is not larger than 10%, and sometimes it is much lower.

## VI. Specific analytical procedures

Properties of materials used in semiconductor and nuclear engineering, as well as in micro- and optoelectronics, are extremely sensitive to the content of impurities. Therefore, analytical monitoring in all steps of the purification technology of these materials is very important. At present, the methods discussed above are the leaders in the field of such monitoring.

It is of note that numerous procedures are devoted to the determination of contaminants in REE oxides, the majority of them being developed and published in China. The problems of atomic-emission spectroscopic analysis of REE are related to the multilinear character of their emission spectra. A general approach to the development of procedures for the quantitative determination of contaminants in pure REE and their oxides was proposed,<sup>60</sup> which is based on the preliminary quantitative determination of the matrix effect on the analytical signal.

The main data on the specific analytical procedures for pure substances using atomic emission spectroscopy and mass spectrometry are summarised in Tables 1 and 2.

**Table 1.** Methods of analysis of some pure metals, semiconductors and other substances by ICP-AES and ICP-MS.

| Matrix                                                             | Method | Instrument                |                    | Sampling procedure                                                                                                                                                                                                                                                    | Contaminants determined                                   | $C_{\min}$                                                        | Ref. |
|--------------------------------------------------------------------|--------|---------------------------|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-------------------------------------------------------------------|------|
|                                                                    |        | name                      | manufacturer       |                                                                                                                                                                                                                                                                       |                                                           |                                                                   |      |
| Cadmium, zinc, copper, gallium                                     | MS     | ELEMENT                   | Finnigan MAT       | dissolution in HNO <sub>3</sub> + HCl, 2 g litre <sup>-1</sup>                                                                                                                                                                                                        | 34 elements                                               | 10–16 ng litre <sup>-1</sup> ,<br>(5–8) × 10 <sup>-7</sup> mass % | 12   |
| Cadmium                                                            | MS     | Plasma Quad 3             | VG Elemental       | dissolution in HNO <sub>3</sub> + HCl, sorption of impurities on Dowex 50W-X8, dissolution of sorbed impurities in HNO <sub>3</sub>                                                                                                                                   | Ti, V, Cr, Ni, Mn, Co, Cu, Zn, Sr, Cs, Ba, La, Gd, Lu, Pb | (0.3–5) × 10 <sup>-8</sup> mass %                                 | 37   |
|                                                                    | MS     | —                         | —                  | ion-exchange preconcentration                                                                                                                                                                                                                                         | Cu, Zn, Pb, Fe                                            | —                                                                 | 69   |
| Tellurium                                                          | MS     | POEMS                     | Thermo Jarrell Ash | dissolution in HNO <sub>3</sub> , co-precipitation of impurities with Fe(OH) <sub>3</sub> , dissolution of the precipitate in HNO <sub>3</sub> , dilution with water                                                                                                  | Bi, Sn, Pb, In, Tl, Cd, Cu, Co, Ni, Zn, Ti, Be, Zr        | $n \times 10^{-5}$ mass % and lower, except for Pb and Zn         | 34   |
| Phosphorus, sulfur, arsenic, selenium, antimony, tellurium, iodine | MS     | Plasma Quad 2+, ETV Mk II | VG Elemental       | dissolution in H <sub>2</sub> O <sub>2</sub> (portion of 1 g, 10% solution of the sample), evaporation from a graphite atomiser. Thermal separation of the matrix from impurities                                                                                     | 57 elements                                               | $n \times 10^{-7}$ mass % –<br>$n \times 10^{-6}$ mass %          | 13   |
| Silicon, germanium                                                 | MS     | ELEMENT                   | Finnigan MAT       | dissolution of a sample (1 g) in a closed beaker in a mixture of acids (HF + HNO <sub>3</sub> for silicon and HCl + HNO <sub>3</sub> for germanium) at 70–75 °C, concentration of a solution to ~50 µl, dissolution of the precipitate in 1 M HNO <sub>3</sub> (5 ml) | 64 elements                                               | $n \times 10^{-11}$ mass % –<br>$n \times 10^{-6}$ mass %         | 35   |

Table 1 (continued).

| Matrix           | Method | Instrument                                                                                     |                      | Sampling procedure                                                                                                                                                                                                                   | Contaminants determined                                                                           | $C_{\min}$                                                                                               | Ref. |
|------------------|--------|------------------------------------------------------------------------------------------------|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|------|
|                  |        | name                                                                                           | manufacturer         |                                                                                                                                                                                                                                      |                                                                                                   |                                                                                                          |      |
| Quartz glass     | MS     | Elan 6000 laser<br>Nd: YAG,<br>$\lambda = 1064$ nm,<br>$W = 10^9 - 10^{10}$ W cm <sup>-2</sup> | Perkin Elmer         | laser ablation                                                                                                                                                                                                                       | Li, B, Na, Mg, Al, K, Ca, Ti, V, Cr, Fe, Mn, Cu, Zr, Ba, Pb                                       | $n \times 10^{-7}$ mass % –<br>$n \times 10^{-5}$ mass %                                                 | 29   |
|                  | MS     | HP 4500 laser<br>Nd: YAG,<br>$\lambda = 1064$ nm,<br>$W = 10^9 - 10^{10}$ W cm <sup>-2</sup>   | Agilent Technologies | the same                                                                                                                                                                                                                             | Na, Al, Ca, Ti, Cr, Mn, Zr, Ba, Pb                                                                | $n \times 10^{-6}$ mass % –<br>$n \times 10^{-5}$ mass %                                                 | 30   |
| Quartz           | AES    | JY 2000                                                                                        | Jobin Yvon           | simultaneous dissolution in an autoclave of 17 samples (1 g portions) in HF vapour, distillation of the sample matrix in the form of SiF <sub>4</sub> , dissolution of the precipitate in 2% HNO <sub>3</sub>                        | Na, K, Ca, Fe, Ti                                                                                 | $n \times 10^{-6}$ mass %                                                                                | 70   |
|                  | MS     | VG Plasma Quad PQ 3                                                                            | VG Element           | the same                                                                                                                                                                                                                             | Li, Mg, Al, V, Cr, Mn, Co, Ni, Cu, Zn, Mo, Cd                                                     | $n \times 10^{-8}$ mass % –<br>$n \times 10^{-7}$ mass %                                                 | 70   |
| Silicon nitride  | AES    | Mono-chromator JY138                                                                           | Jobin Yvon           | dissolution in an autoclave in a mixture of HF, H <sub>2</sub> SO <sub>4</sub> and HNO <sub>3</sub> or preparation of 1% suspension                                                                                                  | Ca, W, Co, Al, Fe, Mg, Na                                                                         | —                                                                                                        | 24   |
| Gallium          | MS     | Plasma Quad 3                                                                                  | VG Elemental         | partial dissolution of 2 g of gallium in HCl + HNO <sub>3</sub> (more noble impurities are concentrated in the insoluble residue). The dissolved impurities (Al, Cd, Mn), are concentrated by extraction with isobutyl methyl ketone | Ag, Bi, Co, Cu, Fe, Ni, Pb, Al, Cd                                                                | $n \times 10^{-7}$ mass % –<br>$n \times 10^{-8}$ mass %                                                 | 71   |
|                  | MS     | —                                                                                              | —                    | extraction of the sample matrix with diisopropyl ether                                                                                                                                                                               | —                                                                                                 | 0.006–0.082 mg litre <sup>-1</sup>                                                                       | 39   |
|                  | AES    | JY-2000                                                                                        | Jobin Yvon           | dissolution in HNO <sub>3</sub> , treatment with HF for the separation of the matrix by precipitation of GaF <sub>3</sub> . Electrothermal atomisation                                                                               | Au, Ba, Bi, Cd, Co, Cr, Cu, Mg, Mn, Pb, Pd, Pt, Rh, Tl, Zn                                        | $10^{-7}$ mass % –<br>$10^{-6}$ mass %                                                                   | 49   |
| Arsenic          | MS     | Plasma Quad 3                                                                                  | VG Elemental         | dissolution of a 250 mg sample in aqua regia vapour. Separation of the sample matrix by distillation of bromide from a solution in H <sub>2</sub> SO <sub>4</sub> + HBr or by sorption on Dowex 50W-X 8                              | Mg, Al, V, Cr, Mn, Fe, Ni, Co, Zn, Cu, Ga, Sr, Zr, Mo, Cd, In, Ba, Cs, Tl, Pb, Bi, La, Ce, Gd, Lu | $n \times 10^{-8}$ mass % –<br>$n \times 10^{-7}$ mass %                                                 | 40   |
| Gallium arsenide | MS     | ELEMENT                                                                                        | Finnigan-MAT         | chlorination of GaAs by gaseous Cl <sub>2</sub> at 280 °C with simultaneous distillation of gallium and arsenic as chlorides, dissolution of the residue in 1 M HNO <sub>3</sub>                                                     | B, Mg, Al, Si, Ca, V, Cr, Mn, Fe, Ni, Zn, Sn                                                      | $3 \times 10^{-8}$ at. % –<br>$1 \times 10^{-6}$ at. %                                                   | 58   |
|                  |        |                                                                                                |                      | laser ablation                                                                                                                                                                                                                       | Tc, I, Th, U                                                                                      | $< 1 \times 10^{-7}$ mass %                                                                              | 58   |
| Indium           | AES    | ICAP 61                                                                                        | Thermo Jarrell Ash   | dissolution in an autoclave in HCl, 1% indium solution                                                                                                                                                                               | 21 elements                                                                                       | $n \times 10^{-5}$ mass % –<br>$n \times 10^{-3}$ mass %                                                 | 11   |
|                  |        |                                                                                                |                      | precipitation of indium in the form of oxychloride                                                                                                                                                                                   |                                                                                                   | lowering by 5–100 times                                                                                  |      |
|                  | MS     | Plasma Quad                                                                                    | VG Elemental         | dissolution in an autoclave in HCl, 0.1% indium solution                                                                                                                                                                             | 40 elements                                                                                       | $n \times 10^{-6}$ mass % –<br>$n \times 10^{-3}$ mass %                                                 | 11   |
| Graphite         | AES    | Nippon, model ICAP-55                                                                          | Thermo Jarrell Ash   | decomposition of 0.5 g of graphite in a mixture of HNO <sub>3</sub> + H <sub>2</sub> SO <sub>4</sub> in a microwave oven                                                                                                             | Li, Na, K, Mg, Ca, Sr, Al, Fe, Ni, Cr, Ti, V                                                      | $n \times 10^{-5}$ mass % –<br>$n \times 10^{-4}$ mass % (under the optimum conditions for each element) | 72   |



Table 1 (continued).

| Matrix          | Method | Instrument                |                                  | Sampling procedure                                                                                                                                                                                                                                      | Contaminants determined                              | $C_{\min}$                                                                                                              | Ref. |
|-----------------|--------|---------------------------|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|------|
|                 |        | name                      | manufacturer                     |                                                                                                                                                                                                                                                         |                                                      |                                                                                                                         |      |
| Graphite        | AES    | ICPS 2000                 | Shimadzu                         | decomposition of a 0.5 g portion in a mixture of $\text{H}_2\text{SO}_4$ , $\text{HClO}_4$ and $\text{HNO}_3$ (5 : 3 : 1) at 200 °C, removal of the excess $\text{HClO}_4$ and $\text{HNO}_3$ at 150 °C, dilution with water to 100 ml                  | Ca, Fe, Ni, Sr, Ti, V                                | $n \times 10^{-5}$ mass % –<br>$n \times 10^{-4}$ mass %                                                                | 73   |
|                 | MS     | Elan 6000, CETAC LSX-200  | Perkin Elmer, Cetac Technologies | laser ablation                                                                                                                                                                                                                                          | Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Y, Lu, U | $n \times 10^{-7}$ mass % –<br>$n \times 10^{-6}$ mass %                                                                | 27   |
| Coal            | MS     | HR-ICP-MS                 | Finnigan MAT                     | fusion with lithium metaborate, dissolution in a mixture of $\text{H}_2\text{O}_2$ , $\text{HNO}_3$ and HF in a microwave oven                                                                                                                          | 70 elements                                          | $n \times 10^{-8}$ mass % –<br>$n \times 10^{-4}$ mass %                                                                | 9    |
|                 | MS     | UV Laser Probe            | Finnigan MAT                     | blending with a coal powder, containing an internal standard (In), pressing into pellets                                                                                                                                                                |                                                      | $n \times 10^{-7}$ mass % –<br>$n \times 10^{-4}$ mass %                                                                |      |
|                 | AES    | ARL 3580                  | ARL                              | fusion with lithium metaborate, dissolution in a mixture of $\text{H}_2\text{O}_2$ , $\text{HNO}_3$ and HF in a microwave oven                                                                                                                          | —                                                    | —                                                                                                                       | 9    |
|                 | MS     | ELAN 6000                 | Perkin Elmer                     | suspension ( $1.3 \text{ mg ml}^{-1}$ ) in 5% nitric acid                                                                                                                                                                                               | As<br>Mn                                             | 0.06 pg<br>0.06 pg                                                                                                      | 17   |
|                 | MS     | HGA 600 MS                | Perkin Elmer                     | electrothermal atomisation in the presence of NaCl (physical carrier) and matrix modifier (Pd)                                                                                                                                                          | Pb<br>Se                                             | 0.12 pg<br>0.36 pg                                                                                                      | 17   |
| Coal, coal ash  | MS     | ELAN 6000, HGA 600 MS     | Perkin Elmer                     | uniform suspension, electrothermal atomisation in the presence of matrix modifiers. Isotopic dilution                                                                                                                                                   | Cd<br>Hg<br>Tl<br>Pb                                 | $6 \times 10^{-6}$ mass %,<br>$1.4 \times 10^{-5}$ mass %,<br>$1 \times 10^{-6}$ mass %,<br>$1.2 \times 10^{-4}$ mass % | 19   |
| Aluminium       | MS     | —                         | —                                | separation of a matrix from impurities by sorption                                                                                                                                                                                                      | Fe, Ni, Co, Cu, Zn, Ag, Cd, Ga, In                   | $n \times 10^{-9}$ mass % –<br>$n \times 10^{-7}$ mass %                                                                | 74   |
|                 | AES    | Philips PV 8210           | Philips                          | dissolution in HCl (1 : 1) in the presence of a catalyst (Pd) with addition of $\text{HNO}_3$ at 45–55 °C,                                                                                                                                              | 21 elements                                          | $10^{-6}$ mass % –<br>$10^{-4}$ mass %                                                                                  | 75   |
|                 |        |                           |                                  | extraction of analytes with bis(2-ethyl-hexyl) dithiophosphate and bis(2-ethyl-hexyl)phosphate after dissolution of a 1 g sample at 45–55 °C in HCl (1 : 1) in the presence of a catalyst (Pd) with addition of $\text{HNO}_3$                          | Ti, Ga, Ni, Se, Te, Cd, Co, Bi, Pb, Cu               | $n \times 10^{-7}$ mass % –<br>$n \times 10^{-6}$ mass %                                                                | 75   |
|                 | AES    | IRIS Advantage, SSEA      | Thermo Jarrell Ash               | spark ablation                                                                                                                                                                                                                                          | 26 elements                                          | $n \times 10^{-6}$ mass % –<br>$n \times 10^{-4}$ mass %                                                                | 76   |
|                 | MS     | ELAN 5000, HGA 600        | Perkin Elmer                     | preparation of a uniform suspension, electrothermal atomisation in the presence of a matrix modifier ( $\text{PdCl}_2$ )                                                                                                                                | Na, Mg, Ca, V, Mn, Fe, Ni, Ga                        | $n \times 10^{-6}$ mass % –<br>$n \times 10^{-3}$ mass %                                                                | 18   |
| Aluminium oxide | AES    | Spectroflame, ETY 4000    | Spectro, Spectral System         | blending of a sample with a matrix modifier (AgCl) in a 1 : 1 ratio, electrothermal atomisation                                                                                                                                                         | Fe, Ga, Mg, Mn, V, Zn                                | $n \times 10^{-6}$ mass % –<br>$n \times 10^{-4}$ mass %                                                                | 20   |
|                 | AES    | Monochromator WDG 500-1A, | Beijing Second Optics            | 1% emulsion of $\text{Al}_2\text{O}_3$ in an aqueous solution of Triton X-100, $\text{HNO}_3$ and PTFE                                                                                                                                                  | Cr, Cu, Fe, V                                        | $n \times 10^{-6}$ mass % –<br>$n \times 10^{-5}$ mass %                                                                | 48   |
|                 |        | ICP HGA 500               | BBE Factory <sup>a</sup>         | fluorination of the matrix and impurities in a graphite atomiser                                                                                                                                                                                        |                                                      |                                                                                                                         |      |
|                 | AES    | ICAP 61                   | Thermo Jarrell Ash               | autoclave decomposition (4 atm) in a microwave oven in a mixture of HF and $\text{HNO}_3$ (6 : 1), addition of $\text{H}_2\text{SO}_4$ , concentration, dissolution of the residue in 1%–4% ammonium oxalate. Sorption preconcentration on Polyorgs VII | 22 elements                                          | without preconcentration<br>$n \times 10^{-4}\%$                                                                        | 77   |

Table 1 (continued).

| Matrix                                                          | Method | Instrument                         |                                  | Sampling procedure                                                                                                                                                                                                                                                                 | Contaminants determined                               | $C_{\min}$                                                                                                         | Ref. |
|-----------------------------------------------------------------|--------|------------------------------------|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|------|
|                                                                 |        | name                               | manufacturer                     |                                                                                                                                                                                                                                                                                    |                                                       |                                                                                                                    |      |
| Tantalum, Ta <sub>2</sub> O <sub>5</sub> , Ta(OEt) <sub>5</sub> | MS     | SPQ 8000                           | Seiko Instruments Company        | dissolution in a mixture of HF and HNO <sub>3</sub> , for tantalum oxide, in an auto-clave, dilution with H <sub>2</sub> O. Separation of the sample matrix on an ion-exchange column (Dowex 1-X 8)                                                                                | Be, Al, Ti, Cr, Ni, Nb, Mo, Sn, W, Th, U              | 0.003–0.02 ng ml <sup>-1</sup>                                                                                     | 10   |
| Platinum                                                        | AES    | ICPQ-1015                          | —                                | dissolution in aqua regia, concentration with addition of HCl, dissolution of the dry residue in 10% HCl                                                                                                                                                                           | Mg, Mn, Cu, Ag, Fe, Zn, Au, Ir, Ni, Pb, Rh, Al, Pd    | 1 × 10 <sup>-4</sup> mass %, 3 × 10 <sup>-4</sup> mass %, 5 × 10 <sup>-4</sup> mass %, 8 × 10 <sup>-4</sup> mass % | 8    |
|                                                                 | MS     | ELAN 6000, CETAC LSX-200           | Perkin Elmer, Cetac Technologies | laser ablation                                                                                                                                                                                                                                                                     | Rh, Ag, Pd, Hf, Ir, Pb, U, Co, Ni, Cu, Zr, Ru, In, Sn | $n \times 10^{-7}$ mass %, $n \times 10^{-6}$ mass %, $n \times 10^{-5}$ mass %                                    | 31   |
|                                                                 | MS     | ELAN 5000                          | Perkin Elmer                     | dissolution of sample (1g) in 7 M HNO <sub>3</sub> , matrix precipitation in the form of AgCl                                                                                                                                                                                      | Al, Co, Pb, Mg, Mn, Ni, Cu, Cd, Sn, Au, Fe            | $n \times 10^{-10}$ mass %, $n \times 10^{-9}$ mass %, $n \times 10^{-8}$ mass %                                   | 63   |
| Gold                                                            | MS     | ELAN 6000, Laser Sampler Model 320 | Perkin Elmer                     | laser ablation                                                                                                                                                                                                                                                                     | Zn, Cd, Sn, Sb, Au, Pb, Bi                            | $n \times 10^{-4}$ mass %                                                                                          | 57   |
|                                                                 | MS     | ELAN 5000                          | Perkin Elmer                     | dissolution in aqua regia, electro-chemical precipitation of the sample matrix                                                                                                                                                                                                     | Be, Mg, Cr, Mn, Ni, Cu, Zn, Ag, Pd, Sn, Pb            | $n \times 10^{-6}$ mass % – $n \times 10^{-5}$ mass %                                                              | 78   |
|                                                                 | AES    | JY385                              | Jobin Jvon                       | dissolution in aqua regia, concentration, dissolution of the residue in 6 M HCl                                                                                                                                                                                                    | Ag, Cd, Cr, Cu, Fe, Mn, Ni, Bi, Co, Pb, Pd, Sb        | $n \times 10^{-5}$ mass % – $n \times 10^{-4}$ mass %                                                              | 62   |
|                                                                 | MS     | —                                  | —                                | —                                                                                                                                                                                                                                                                                  | 44 contaminants                                       | 0.0006–0.21 mg litre <sup>-1</sup>                                                                                 | 51   |
| Zinc                                                            | MS     | Model 7500                         | Agilent Technologies             | dissolution in aqua regia. Dilution to 0.1% gold solution                                                                                                                                                                                                                          | 29 contaminants                                       | $n \times 10^{-8}$ mass % – $n \times 10^{-5}$ mass %                                                              | 64   |
|                                                                 | AES    | —                                  | —                                | microcolumn preconcentration with DCS-arsenazo in a flow system                                                                                                                                                                                                                    | REE                                                   | $n$ /ng ml <sup>-1</sup>                                                                                           | 79   |
|                                                                 | AES    | —                                  | —                                | dissolution of sample (1g) in a mixture of H <sub>2</sub> SO <sub>4</sub> and HNO <sub>3</sub> , extraction of analytes into xylene, as diethyldithiocarbamate complexes, reextraction into HNO <sub>3</sub>                                                                       | Cu, Ag, Cd                                            | 7 × 10 <sup>-6</sup> mass % – 1 × 10 <sup>-5</sup> mass %                                                          | 80   |
| Uranium                                                         | MS     | ELAN 6000                          | Perkin Elmer                     | sample of 0.5 g. Separation of uranium on an extraction chromatographic column with the use of tributyl phosphate                                                                                                                                                                  | 26 contaminants                                       | $n \times 10^{-8}$ mass % – $n \times 10^{-5}$ mass %                                                              | 81   |
| Iron                                                            | AES    | Mono-chromator P-5200              | Hitachi                          | dissolution of a sample (2g) in HCl, co-precipitation of analytes with cupferon, dissolution of the precipitate in a mixture of H <sub>2</sub> SO <sub>4</sub> , HNO <sub>3</sub> and HClO <sub>4</sub> , addition of HF, concentration, dissolution of the salts in tartaric acid | V, Hf, Mo, Nb, Ga, Zr, Ti                             | 3 × 10 <sup>-6</sup> mass % – 9 × 10 <sup>-5</sup> mass %                                                          | 56   |
|                                                                 | AES    | —                                  | —                                | dissolution in a mixture of H <sub>2</sub> O <sub>2</sub> and HF, ion-exchange preconcentration                                                                                                                                                                                    | Mo, W, Nb, Ta                                         | —                                                                                                                  | 82   |
|                                                                 | AES    | —                                  | —                                | dissolution of a sample (1g) in a mixture of HNO <sub>3</sub> and HCl with addition of acetic acid. Sorption of contaminants on DDTC. Elution with a mixture of HNO <sub>3</sub> and H <sub>2</sub> O <sub>2</sub>                                                                 | Bi, Pb, Ni, Co                                        | 3 × 10 <sup>-8</sup> mass % – 9 × 10 <sup>-7</sup> mass %                                                          | 83   |

**Table 1** (continued).

| Matrix | Method | Instrument                    |                                     | Sampling procedure                                                                                                                                                            | Contaminants determined | $C_{\min}$                                            | Ref. |
|--------|--------|-------------------------------|-------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------------------------------------|------|
|        |        | name                          | manufacturer                        |                                                                                                                                                                               |                         |                                                       |      |
| Iron   | AES    | UOP-2                         | Kyoto Koken                         | dissolution of a sample (1g) with heating in HCl (1 : 4). Co-precipitation of analytes with cupferon, separation of the precipitate, dissolution in HNO <sub>3</sub> (100 ml) | Ti, V, Zr, Nb, Mo, Ta   | $3 \times 10^{-7}$ mass % – $1 \times 10^{-5}$ mass % | 65   |
|        |        | MARK II, ultrasonic nebuliser | Precision Instruments Incorporation |                                                                                                                                                                               |                         |                                                       |      |

<sup>a</sup> Beijing Broadcast Equipment Factory (China) self-made similar to HGA 500 (Perkin Elmer).

**Note.** Here and in Table 2, the papers originally published in Chinese or Japanese are cited from the abstracts in *Chemical Abstracts*. The dash means that the abstract contains no data.

**Table 2.** Methods of analysis of rare-earth oxides by ICP-AES and ICP-MS.

| Matrix                   | Method | Instrument                      |                                      | Sampling procedure                                                                                                                                                                        | Contaminants determined              | $C_{\min}$                                             | Ref.           |
|--------------------------|--------|---------------------------------|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|--------------------------------------------------------|----------------|
|                          |        | name                            | manufacturer                         |                                                                                                                                                                                           |                                      |                                                        |                |
| Yttrium oxide            | AES    | LABTEST                         | Labtest Equipment Company and others | dissolution in HNO <sub>3</sub> . Extractive chromatographic separation of the matrix from the analytes, preconcentration of the solution                                                 | up to 30 contaminants, including REE | $n \times 10^{-5}$ mass % – $n \times 10^{-1}$ mass %  | 16, 60, 84, 85 |
|                          |        |                                 |                                      | fluorination of a sample with polytetrafluoroethylene in ETA                                                                                                                              | the same                             | $n \times 10^{-2}$ – $n$ ng                            | 16             |
| Lanthanum oxide          | AES    | Spectrograph                    | Beijing Instruments Factory          | dissolution in HNO <sub>3</sub> + H <sub>2</sub> O <sub>2</sub> . Chromatographic separation of the matrix and the analytes, introduction of the eluate into the ETA                      | REE                                  | 0.8 – 48 ng ml <sup>-1</sup>                           | 14             |
|                          | AES    | Chromatograph                   | Shimadzu                             | preconcentration of impurities on a C – Si-gel in a flow microcolumn system                                                                                                               | Non-REE impurities                   | $n \times 10^{-1}$ mass%                               | 86             |
|                          | MS     | POEMS II                        | Thermo Jarrell Ash                   | dissolution in HNO <sub>3</sub> . Separation of the matrix from impurities by high-performance liquid chromatography                                                                      | REE                                  | $n \times 10^{-10}$ mass % – $n \times 10^{-8}$ mass % | 36, 87         |
| Cerium oxide             | AES    | Spectrograph PGS-2, HPLC system | Karl Zeiss Jena                      | dissolution of a sample (0.1g) in HNO <sub>3</sub> + H <sub>2</sub> O <sub>2</sub> . Chromatographic separation of the sample matrix and the analytes, introduction into the graphite ETA | REE                                  | 0.8 – 36 ng ml <sup>-1</sup>                           | 15             |
|                          | AES    | LABTEST                         | Labtest Equipment Company            | extractive chromatographic separation of the matrix and the analytes                                                                                                                      | REE                                  | $5 \times 10^{-5}$ mass % – $5 \times 10^{-3}$ mass %  | 61             |
|                          | MS     | —                               | —                                    | dissolution in HNO <sub>3</sub>                                                                                                                                                           | Gd, Tb, La, Pr                       | 0.008% overall                                         | 88             |
| Neodymium oxide          | MS     | HP 4500                         | Agilent Technologies                 | 0.01% solution of neodymium oxide in 0.1% HNO <sub>3</sub>                                                                                                                                | La, Ce, Pr, Sm, Eu, Gd               | $n \times 10^{-5}$ mass % – $n \times 10^{-4}$ mass %  | 59             |
| Samarium oxide           | AES    | —                               | —                                    | dissolution in HNO <sub>3</sub> . The concentration of Sm <sub>2</sub> O <sub>3</sub> in the solution is 5 mg ml <sup>-1</sup>                                                            | Cu, Fe, Ca, Ni                       | $3 \times 10^{-4}$ mass % – $3 \times 10^{-3}$ mass %  | 89             |
| Europium oxide           | AES    | —                               | —                                    | microcolumn preconcentration in a flow system                                                                                                                                             | Al, Cr, Cu, Fe, Pb, V, Zn            | $n$ ng ml <sup>-1</sup>                                | 90             |
|                          | AES    | —                               | —                                    | concentration on an active Si – C-gel in a flow regime                                                                                                                                    | Al, Cr, Cu, Fe, Pb, V, Zn            | —                                                      | 91             |
|                          | AES    | —                               | —                                    | extraction of impurities                                                                                                                                                                  | REE, Cu, Pb, Co, Ni                  | $7 \times 10^{-4}$ mass % – $7 \times 10^{-2}$ mass %  | 92             |
| Europium, europium oxide | MS     | —                               | —                                    | dissolution in HNO <sub>3</sub>                                                                                                                                                           | Cr, Mn, Co, Ni, Cu, Cd, Pb           | 0.12 – 0.3 mg litre <sup>-1</sup>                      | 53             |
|                          | MS     | —                               | —                                    | —                                                                                                                                                                                         | REE                                  | 0.005 – 0.02 ml litre <sup>-1</sup>                    | 55             |
|                          | MS     | —                               | —                                    | chromatographic separation                                                                                                                                                                | REE                                  | 0.001 mass % – 0.015 mass %                            | 93             |

Table 2 (continued).

| Matrix           | Method | Instrument         |                 | Sampling procedure                                                                                                                                         | Contaminants determined                            | $C_{\min}$                                            | Ref. |
|------------------|--------|--------------------|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|-------------------------------------------------------|------|
|                  |        | name               | manufacturer    |                                                                                                                                                            |                                                    |                                                       |      |
| Gadolinium oxide | MS     | VG Plasma Quad     | VG Elemental    | dissolution in 50% HCl. Concentration. Dissolution of the residue in 1% HCl. Chromatographic separation of La, Ce, Pr, Nd, Sn, Eu and the major part of Gd | Tb, Tm, Yb, Lu                                     | $2 \times 10^{-7}$ mass % – $5 \times 10^{-6}$ mass % | 54   |
| Terbium oxide    | AES    | —                  | —               | separation of the matrix from the analytes by HPLC                                                                                                         | Ca, Cu, Mg, Mn, Ni, Si, La, Ce, Pr, Nd, Sn, Eu, Gd | 0.04 mass % – 0.4 mass %                              | 94   |
| Dysprosium oxide | MS     | —                  | —               | dissolution in $\text{HNO}_3$                                                                                                                              | REE                                                | 0.01–0.09 mg litre $^{-1}$                            | 52   |
| REE oxides       | AES    | Spectrograph PGS-2 | Karl Zeiss Jena | dissolution. Concentration of impurities on an active C—Si-gel in a flow microcolumn system                                                                | Al, Cr, Cu, Fe, Pb, V, Zn                          | 1–10 ng ml $^{-1}$                                    | 95   |

## VII. Conclusion

The main advantages of ICP as the ion source in mass spectrometry and the radiation source in atomic emission spectroscopy for the analysis of high-purity solids are as follows:

- relatively easy combination with different sample introduction systems (solution nebulisers, graphite atomisers, laser and spark ablation);
- multielement analysis with low element detection limits;
- plasma stability, which provides the reproducibility of the analytical signal;
- simple calibration (in the analysis of solutions);
- small non-spectral matrix effects.

Let us also denote the drawbacks of ICP:

- the necessity of dissolution of a sample, which may lead to uncontrolled introduction of contaminants, especially common ones, and to the risk of losses of the analytes;
- low capacity, usually not higher than 2 kW, which results in plasma instability in the case of direct introduction of powders and suspensions;
- formation of a great variety of molecular ions, which increases the element detection limits by ICP-MS due to interferences, especially in the mass range from 25 to 80 a.m.u.;
- high cost of the equipment, especially for mass spectrometric analysis.

The record-breaking low absolute detection limits (down to  $10^{-14}$  g) that can be provided by multielement ICP-MS on a double-focusing instrument with introduction of 0.05%–0.2% solution of a sample (or a concentrate) into the plasma, make it possible to reach detection limits of  $10^{-9}\%$ – $10^{-7}\%$  without concentration and down to  $10^{-11}\%$ – $10^{-9}\%$  with virtually complete sample matrix separation for non-common contaminants the analytical lines of which are free from molecular ion overlap. The detection limits for the elements in the mass range from 24 to 80 a.m.u. and for a number of rare-earth elements in REE-containing matrices (neodymium, europium, cerium) are several orders of magnitude larger ( $10^{-6}\%$ – $10^{-3}\%$ ). The element detection limits in the direct analysis of solids by LA-ICP-MS lie generally in the range  $10^{-7}\%$ – $10^{-5}\%$ , and the use of powerful IR laser reduces the limits to  $10^{-10}\%$ – $10^{-7}\%$ . It should be noted that ICP-MS covers a broad range of analyte detection limits.

In the majority of published works, the analyte detection limits with ICP-AES on echelle spectrometers with introduction of 1% solutions into the plasma are no lower than  $10^{-6}\%$ – $10^{-4}\%$  for direct analysis and  $10^{-8}\%$ – $10^{-5}\%$  for the method with preconcentration. It is obvious that low detection limits of trace-elements in the matrices with multilinear spectra (d-

and f-elements) require the sample matrix to be separated. The use of ultrasonic nebulisers, instruments with an axial observation of plasma<sup>65</sup>, and ETA also reduces the detection limits.

Considering multielement analysis, both methods allow simultaneous determination of several tens of contaminants in pure substances. However, according to the published works, usually no more than ten elements were determined. Determination of several tens of impurities simultaneously at the level of  $10^{-7}$  mass %– $10^{-6}$  mass % and non-common elements with a detection limits as low as  $10^{-11}$  mass % (see<sup>35</sup>) by ICP-MS represents an exception.<sup>9, 11–13, 35</sup> The limited number of contaminants that can be determined is often explained by the purposes of the study (for example, in the graphite nuclear reactor, only neutron-absorbing REE were determined),<sup>27</sup> and by the capacities of the concentration procedures.

Inductively coupled plasma atomic emission spectroscopy and mass spectrometry supplement each other, and their parallel use for the characterisation of high-purity substances allows verification of the correctness of the analysis by methods different in principle, and determination of the elements the analytical lines of which in one of the methods are hidden by spectral overlaps.<sup>9, 11, 70</sup> In other words, due to the multielement nature and low detection limits, the combination of the two methods makes it possible to fully characterise a high-purity substance regarding virtually all elements from the Periodic Table, excluding the gaseous ones. For the analysis of certain high-purity compounds by ICP-MS, see also Refs 3, 6, 7 and 46.

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# Quantum-chemical methods for the construction of wave functions of many-electron systems alternative to the Hartree – Fock approximation

N D Chuvylkin, E A Smolenskii, N S Zefirov

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**Abstract.** Modern quantum-chemical methods for the construction of approximate many-electron wave functions differing from the traditional Hartree–Fock approximation are considered. Attention is focused on the methods based on the use of symmetric groups and nodal surfaces of many-electron wave functions. A new interpretation of the Pauli exclusion principle is discussed. The bibliography includes 75 references.

## I. Introduction

The latest achievements in theoretical chemistry are largely related to quantum chemistry. The advent of computers with vector processors such as CRAY and CYBER in the late-1970s–early-1980s affected appreciably the status of quantum-chemical calculation.<sup>1</sup> Even more pronounced changes in computational quantum chemistry were induced by the appearance of computers with parallel processors.

The applications of computational quantum-chemical methods have now gone far beyond the limits of traditional fields of chemistry (organic, inorganic, physical) and have extended into many fields of physics, biology, pharmacology, materials science, *etc.* The range of these applications is being extended because more and more problems can be tackled by the techniques of computational chemistry, which has become a generally recognised source of valuable information. Computers can supplement (and in some cases replace) conventional laboratory techniques if experimental information is either insufficient or cannot be gained due to temperature, concentration or procedural restrictions.

Reliable quantum-chemical predictions of the electronic structure and physicochemical parameters of molecular systems are based on *ab initio* methods, which are more rigorous than the single-electron Hartree–Fock (HF) approximation and take into account electron correlation. The development of these methods receives most attention.<sup>1–5</sup> Numerous computer programmes taking account of the electron correlation effects, to some extent, have now been developed.

Owing to all-round computerisation and the availability of major quantum-chemical software programmes to chemists, some of these programmes have lately been regarded as routine. Whereas 30 years ago the predictions of quantum chemists were met, at best, with scepticism, now there is rather a risk of overestimating the reliability of quantum-chemical results. It should be borne in mind that the magical words *ab initio* do not always ensure high accuracy computations.

One can hardly be confident that quantum-chemical predictions are correct, if, for example, the errors in determining the system energy, which are involved in any *ab initio* computation due to the neglecting of or incomplete allowance for the electron correlation effects, prove to be much greater than the estimated activation energies, barriers to internal rotation and inversion, chemical bond dissociation energies, *etc.* Therefore, to obtain reliable physicochemical information using *ab initio* methods, effective ways of taking account the electron correlation are required. It is not by chance that the problems of accurately calculating correlation effects based on primary principles are regarded as highly important in quantum chemistry.

Unfortunately, computational procedures for the elimination of correlation errors are not embedded in all routine quantum-chemical programmes. Until chemists who run modern computing machinery realise its limited scope, even the most expensive *ab initio* computations will be fraught with artifacts and illegitimate conclusions.

A critical analysis<sup>1–3</sup> of the trends and prospects for the development of modern quantum chemistry has shown that traditional *ab initio* calculations have reached a sort of limit. This calls for searching for new ways of solving the Schrödinger equation for many-electron systems, other than those based on the HF approximation. While working along this line, we proposed an approximate method for solving this equation and called it the many-electron wave function (MWF) method.<sup>6</sup>

The MWF technique is based on in-depth mathematical analysis of the generally accepted interpretation of the fundamental Pauli exclusion principle, which actually forbids not only ‘trivial’, but also many other seemingly quite allowable electron configurations. A specific feature of the proposed method is that, in conformity with the views of the founders of quantum mechanics — W Heisenberg, P Dirac and E Schrödinger — paramount importance is ascribed to analysis of the properties of the nodal surfaces of antisymmetric MWFs.

The foundation of the MWF method is composed of two fundamental statements.

N D Chuvylkin, E A Smolenskii, N S Zefirov N D Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prosp 47, 117913 Moscow, Russian Federation. Fax (7- 495) 135 53 28, tel. (7- 495) 135 90 89 (N D Chuvylkin, E A Smolenskii), e-mail: smolensk@cacr.ioc.ac.ru (E A Smolenskii), tel. (7- 495) 939 16 20 (N D Zefirov)

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1. Generalisation<sup>7</sup> of the Courant–Hilbert theorem for the case of precise non-relativistic many-electron wave function  $\Psi$  for the electronic state with a specified spin.

2. An original hypothesis,<sup>8</sup> according to which the Pauli exclusion principle should be interpreted as the prohibition for two electrons with identical spins to occur on the same equipotential surface in a given configuration space.

The MWF method has now been tested using a number of ‘test systems’ most representative of quantum mechanics.

## II. Retrospective view on the development of *ab initio* methods in quantum chemistry

Since the HF method in *ab initio* approximation is free from experimental or adjustable parameters, and allows a simple and vivid interpretation of the calculated properties, many quantum chemists do not see the point in developing alternative approaches, referring to the sharp increase in the degree of computerisation of theoretical investigations observed in the last decade and to the progress in computer engineering already attained (and expected in the future). Indeed, the last ~50 years have seen the transition from scalar computers (three successive generations) to modern vector computers and computing potential has sharply increased.

Chemists already have powerful computers of a new architecture at their disposal. Perhaps, not only supercomputers but also sets of computers operating in parallel with hundreds or thousands of simultaneously operating units could play an important role in the further development of quantum chemistry and could initiate a new avalanche of more accurate *ab initio* calculations based on the HF approximation. However, most likely, this would have an adverse effect on the development of theoretical quantum chemistry, as it is much easier to apply well-developed theoretical methods to new systems than to develop absolutely new approaches.

One should bear in mind that apart from the obvious advantages, the Hartree–Fock approximation has substantial drawbacks. These drawbacks are due to the fact that in the use of this approximation, the number of two-electron integrals grows as  $m(m+1)/2$ , where  $m = n(n+1)/2$ , and  $n$  is the number of the basis functions. This sharp ( $\sim n^4$ ) dependence imposes natural restrictions on high-precision *ab initio* calculations for large molecular systems. In addition, the electron correlation effects are often great. For example, the HF approximation does not describe adequately the dissociation of even diatomic molecules, especially  $\text{Be}_2$  and  $\text{F}_2$  (Table 1). Usually, such drawbacks can be eliminated only partially on switching to Configuration Interaction (CI) methods, despite the impressive number ( $\sim 10^6$ ) of configurations additionally taken into account.

However, the popularity of the CI methods is held up by the fact that the *ab initio* calculation, which reaches in accuracy the

‘Schrödinger’ limit, is not physically obvious, its results requiring interpretation like experimental data. The point is that in high-precision *ab initio* methods, taking into account the configurational interaction, the total wave function is ‘smeared’ over many thousand determinants, whose clear interpretation is impossible. It is noteworthy that the implementation of CI methods for complex molecular systems currently does not provide even a 90% allowance for the electron correlation energy.

At first glance, this is surprising. Indeed, for  $N = 2$  ( $N$  is the number of electrons) for example, for a helium atom or a hydrogen molecule, the problem is solved by a high-precision *ab initio* method using an advanced computer with an accuracy in energy down to  $10^{-8}$  a.u. in fractions of a second. Meanwhile, for  $N = 3$  (Li atom) or  $N = 4$  (LiH molecule), the same computer can ensure, at best, an accuracy of  $\sim 0.001$  a.u. after running for several hours, *i.e.*, the duration of an equivalent high-precision calculation increases on passing from  $N = 2$  to  $N = 4$  by approximately ten (!) orders of magnitude. This is accompanied by a catastrophic complication of the problem, to such an extent that equally high-precision *ab initio* calculations are absolutely impracticable for complex electron systems.

This means that on passing to systems with  $N = 3$ , the computational situation changes in principle. This brings about the viewpoint that, due to the substantial growth of the number of mathematical operations involved in the use of the Self Consistent Field (SCF) scheme, even for an insignificant increase in the number of electrons, high-precision *ab initio* calculations have no prospects in most fields of chemistry and materials science, because they are forcibly meant for relatively small molecules. Therefore, researchers still pay considerable attention to further development of semi-empirical methods. However, this is not a priority line of research, although it is still important. At present, the problem of searching for fundamentally new methods to solve the Schrödinger equation for many-electron systems is being brought to the forefront.<sup>1</sup>

The specialists engaged in quantum chemistry refuse more and more often basis concepts related to the model of independent particles, which are fairly well known to most of physical chemists. Instead, they have started to borrow diverse theories from solid-state physics, nuclear physics and related fields,<sup>1–3</sup> in which  $N$ -particle problems are solved for  $N \rightarrow \infty$ . The mathematical apparatus used to solve these problems, which had been developed for ideal translationally invariant systems, was modified in the last decade; first of all, the simplifications related by translational symmetry were eliminated, because this is not inherent in finite molecular systems.

*Ab initio* methods using the concept of Atomic Pseudopotential or Effective Core Potential (ECP) have been developed. The introduction of this notion made the computation much simpler and reduced it to considering only valence electrons. Due to the ‘passivity’ of the core electrons of the inner electron shells, their influence on the valence electrons is often not taken into account explicitly, but is modelled by the ECP. Therefore, the work content of *ab initio* quantum-chemical calculations sharply decreases. In addition, it becomes possible to include, without much difficulty, the relativistic effects created mainly by the core electrons.<sup>9</sup>

Many pseudo-potential methods imply the presence of  $N_v$  valence active and  $N_c$  core passive electrons. The full Hamiltonian (in atomic units) for a system of  $N = N_v + N_c$  electrons is represented in the form

$$\hat{H}_v = \sum_{i=1}^{N_v} \left[ -\frac{1}{2} \nabla_i^2 + \sum_A \hat{W}^A(r_i) \right] + \sum_{i < j} \frac{1}{r_{ij}} + \sum_{A < B} \frac{Z_v^A Z_v^B}{R_{AB}}, \quad (1)$$

where  $\hat{W}^A(r_i)$  is the model pseudo-potential describing the interaction of valence electrons with the nucleus and with core electrons of atom  $A$ ;  $r$  is the distance between the electrons,  $Z_v^A$  is the shielded charge of the atomic nucleus ( $Z_v^A = Z^A - N_c^A$ ),  $R$  is the distance between the nuclei;  $A$  and  $B$  are the numbers of atom

**Table 1.** Dissociation energy (in eV) of diatomic molecules.<sup>1</sup>

| Molecule      | HF calculation   | Experiment |
|---------------|------------------|------------|
| $\text{H}_2$  | 3.64             | 4.75       |
| $\text{Li}_2$ | 0.17             | 1.07       |
| $\text{Be}_2$ | see <sup>a</sup> | 0.10       |
| $\text{B}_2$  | 0.89             | 3.09       |
| $\text{C}_2$  | 0.79             | 6.32       |
| $\text{N}_2$  | 5.20             | 9.91       |
| $\text{O}_2$  | 1.28             | 5.22       |
| $\text{F}_2$  | –1.37            | 1.66       |
| LiH           | 1.49             | 2.52       |
| HF            | 4.38             | 6.10       |

<sup>a</sup> The HF approximation gives a purely ‘repulsive’ curve for the dependence of energy on the distance between the nuclei.



nuclei, and  $i$ , and  $j$  are the numbers of electrons. For any chemical element,  $\hat{W}^A(r_i)$  is a fixed and transferable operator that is usually determined from calculations of atomic wave functions in the HF approximation.

The authors of many publications have used, not without success, by analogy with ECP, schemes of effective single-fragment potentials that simulate the presence of chemically inactive functional groups in molecular systems. The intuitive reasons in favour of these schemes look rather convincing, although they can hardly be called substantiated.

In view of the above, one can plainly see why some researchers<sup>10–20</sup> have started bringing Density Functional Theory (DFT) to the forefront of quantum chemistry. The idea of using DFT to calculate the ground-state total energies of many-electron systems was put forward by Thomas and Fermi.<sup>21,22</sup> Their model implies a completely uncorrelated electron motion. A real  $N$ -electron object is matched to some fictitious system of non-interacting electrons, which is not identical but equivalent to this object. This system has the same electron density  $\rho(r)$  as the initial system, consisting of interacting electrons.

Initially, the Thomas–Fermi model was perceived as a useful simplification based on the assumption that the energy of this quantum system can be expressed in terms of the electron density. This hypothesis has been formally proven by the Hohenberg–Kohn theorem,<sup>10</sup> according to which the ground-state energy of a system of electrons in an external field is the functional (moreover, the only) of the single-particle density  $\rho(r)$ . After the appearance of this theorem, the interest of researchers in the DFT has sharply grown.

Modifications of DFT have been described in numerous publications (see, for example, the studies<sup>12–14</sup>). It is worthy to note that the early Slater model, borrowed from the solid-state physics, actually reduces the problem of solving the many-particle Schrödinger equation to the solution of the one-particle differential equation

$$\left[ -\frac{1}{2}\nabla_i^2 + V_c^{X_z}(r) + V_e^{X_z}(r) \right] \Psi_i^{X_z}(r) = \varepsilon_i^{X_z} \Psi_i^{X_z}(r), \quad (2)$$

where  $V_c^{X_z}(r)$  is the Coulomb potential (including the contribution of the electron self-action),  $V_e^{X_z}(r)$  is the exchange Slater potential

$$V_e^{X_z}(r) = -3\alpha \left[ \frac{3}{4\pi} \rho(r) \right]^{1/3} = \alpha V_e^S(r), \quad (3)$$

$\Psi_i^{X_z}$  is a single-electron orbital and  $\varepsilon_i^{X_z}$  is its energy.

Expressions (2) and (3) reflect the essence of the so-called  $X_z$  method. A scaling parameter  $\alpha$  appeared historically during the development of the  $X_z$  method and is included in its name. An  $\alpha$  value, chosen from the 2/3 to 1 range, is usually accepted for the calculations.

The Slater potential has been successfully used in quantum chemistry for many years, despite the lack of a strict theoretical substantiation of its use for inhomogeneous electron density. A lot of effort was concentrated on the problem of improving of potential (3), which favoured to a considerable extent the successful development of general DFT methods involving the exchange-correlation potential

$$V_{ec} = \frac{dE_{ec}}{d\rho}, \quad (4)$$

where  $E_{ec}$  is the exchange-correlation energy functional.

Among the variants of DFT, the Kohn–Sham (KS) variant is currently the most popular and best developed.<sup>11</sup> This version can, in principle, be considered as a quantum-mechanical generalisation of the Thomas–Fermi model. In this scheme, the solution of the many-electron Schrödinger equation is reduced to the solution of a single-electron equation of type (2), in which the full effective potential is the sum of three potentials: nuclear  $V_{nuc}(r)$ , the classical Coulomb electron  $V_{el}(r)$ , and the exchange-correlation  $V_{ec}(r)$  potentials. The magnitude of the exchange-correlation potential at point  $r$  is assumed to depend only on the

electron density  $\rho(r)$  at this point. The resulting single-electron equation is solved by iterations; hence, this scheme is self-consistent.

The KS equation closely resembles the Hartree–Fock equation. The difference is that in the KS equation, the orbital-dependent exchange HF operator is formally replaced by the exchange-correlation (taking into account the electron correlation) operator  $V_{ec}(r)$ , which depends on  $\rho(r)$  (and on the spin density in the spin-polarised DFT versions). Therefore, the form of the matrix elements of the ‘modified Fockian’ become simpler and, in practice, single-electron molecular orbitals (MO)  $\psi_i$  can be represented by linear combinations of not only Gaussian type functions (GTF) but also other functions such as Slater type orbitals (STO), numerical Hartree–Fock atomic orbitals, planar waves, *etc.* The use of GTF in the KS, as in the Hartree–Fock theory, accelerates the computation of multicentre integrals, opens up the way for constructing efficient and precise basis sets that are still relatively small, simplifies the analytical determination of the energy gradients, *etc.* Moreover, all the experience accumulated in the HF theory regarding the selection of basis sets can be used in the DFT calculation of molecular systems.

As applied to molecules with large numbers of atoms, some variants of the SCF approach based on DFT prove to be much more attractive than *ab initio* methods, because the number of arithmetic operations in DFT increases as  $\sim N^3$ , rather than  $\sim N^4$  as in the HF approximation or  $\sim N^5$  as in the CI scheme. At present, DFT is a rapidly developing field of quantum chemistry. The popularity of DFT is largely determined by the fact that it allows one to study complicated and real rather than model objects, while requiring much fewer resources and less computer time than the HF calculations. Moreover, DFT usually provides much better agreement with experiment, especially for transition element compounds.<sup>15</sup>

In the KS model, the equality of the densities  $\rho(r)$  in the real and equivalent systems is provided by the functional  $V_{KS}(r)$ . If this functional was known exactly, it would be possible to determine the energy of a real system by solving a model single-particle KS equation. Unfortunately, the exact form of this functional is most often unknown; therefore, the only way forward than is to use model forms.

The exchange-correlation functional should be defined in such a way as to ensure the required accuracy of property calculations. As a rule, it exhibits an appreciable dependence on the accepted geometry of the system and the set of basis functions chosen; the convergence of the results is often deteriorated upon increasing the size of the basis set.<sup>23</sup> Therefore, it is not always clear whether the recommended functionals tested for determination of particular characteristics would be suitable for accurate prediction of other, qualitatively different characteristics of chemical compounds.

A number of expressions for  $V_{ec}(r)$  have now been proposed within the framework of the Local Density (LD) approximation.<sup>12–15</sup> Almost all these expressions can formally be reduced to the following formula

$$V_{ec}(r) = \alpha(r) V_e^S(r), \quad (5)$$

whose form emphasises the relationship between the LD approximation and the  $X_z$  method [*cf.* Eqn (3)]. Note also that numerous Local Spin Density (LSD) and Gradient-Corrected Local Spin Density (GCLSD) functionals have been developed; in addition to the spin densities  $\rho^\alpha$  and  $\rho^\beta$ , these contain their gradients  $\nabla\rho^\alpha$  and  $\nabla\rho^\beta$ , which take into account the non-uniformity of spin distributions in real systems compared to the spin distributions in the homogeneous electron gas models, in which the motion of electrons is uncorrelated.<sup>18</sup> Gradient-corrected functionals have markedly increased the reliability of the DFT-based methods.

It should be especially emphasised that the LD approximation plays more or less the same role in modern DFT as ascribed to the HF approximation in the theory of many-electron systems. Meanwhile, the LD approach has a substantial benefit as it is less

labour-consuming, despite the partial allowance for electron correlation (within the electron gas model). The main difficulty in using LD approximation is the lack of strict systematic methods for correcting errors, *i.e.*, the corrections applied often rely on the researcher's flair.

Apart from the inclusion of gradient corrections into the energy functional, the idea of combining the HF and LD approximations has been implemented beyond the LD scheme,<sup>19</sup> giving rise to a more labour-consuming but more efficient method. This method makes use of a special three-parameter hybrid B3LYP functional (Becke–Lee–Yang–Parr) that contains three semi-empirical coefficients ( $a_0 = 0.80$ ,  $a_e = 0.72$ ,  $a_c = 0.81$ ), selected by experimental data adjustment of 56 atomisation energy, 42 ionisation potential, 8 proton affinity and 10 atomic energy values for a specially selected set of molecules. Currently, the B3LYP approximation is universally used to perform high-precision calculations of thermochemical and spectroscopic parameters for relatively simple molecular systems. The B3LYP functional in combination with specially constructed basis sets of a moderate size have also proved applicable for studying structure–property relationships (see the references cited in Ref. 23).

Analysis of the use of local approximation for the exchange contribution<sup>24,25</sup> has shown that the most serious errors are due to the changes that take place to the ‘angular’ nodal surfaces of wave functions.

The Quantum Monte Carlo (QMC) methods brought to quantum chemistry in the 1970s–1980s from nuclear physics may appear quite promising.<sup>26–28</sup> The most widely used QMC approaches are the Variational Quantum Monte Carlo (VQMC), Diffusion Quantum Monte Carlo (DQMC) and Green's Function Quantum Monte Carlo (GFQMC) methods. These methods are closely related to one another, but each has its own specific features, advantages and disadvantages.

The main approximations of VQMC are, in principle, the same as those of the traditional analytical variational approach; however, the required integrals should be found using special Monte Carlo methods. In this approximation, the expected total electron energy  $\langle E \rangle$  is estimated using the local energies ( $E_{\text{loc}} = \hat{H}\Psi_0/\Psi_0$ ) for the trial wave function  $\Psi_t$  and using its square as the weight factor

$$\langle E \rangle = \frac{\int \Psi_t^2 (\hat{H}\Psi_t/\Psi_t) d\tau}{\int \Psi_t^2 d\tau} = \lim_{n \rightarrow \infty} \frac{\sum_{i=1}^n \Psi_t^2 (\hat{H}\Psi_t/\Psi_t)}{\sum_{i=1}^n \Psi_t^2}. \quad (6)$$

In expression (6), summation is usually carried out over the arbitrary points in the electron configuration space, which is characterised by probabilities proportional to  $\Psi_t^2$ . As in analytical variational computations, the  $\langle E \rangle$  value is an upper estimate of the Schrödinger energy.

With this approach there is no need to carry out numerical integration; to determine  $E_{\text{loc}}$ , one only has to calculate the  $\hat{H}\Psi_t/\Psi_t$  values at specified points. Therefore, this function can acquire any form and even contain the electron–electron distances  $r_{ij}$  in an explicit form. Hence, by using relatively simple trial functions, one can take into account the electron correlation effects with much higher accuracy, which would result in a much lower expected energy for a molecular system than that corresponding to the Hartree–Fock limit.<sup>26,27</sup>

The so-called diffusion version of the QMC method is physically explicit and provides high accuracy to the energetic characteristics of atoms and molecules, because the correlation energy is often taken into account to 80%–100%. The expediency of using the DQMC method to solve the stationary Schrödinger equation

$$-\sum_i \frac{\hbar^2}{2m_e} \nabla_i^2 \Psi(\mathbf{R}) + \hat{V} \Psi(\mathbf{R}) = E \Psi(\mathbf{R}) \quad (7)$$

can be easily understood by paying attention to the formal similarity between the non-stationary Schrödinger equation for a single electron of mass  $m_e$  in imaginary time  $\tau = it$

$$\hbar \frac{\partial \Psi(\mathbf{r}, \tau)}{\partial \tau} = \frac{\hbar^2}{2m_e} \nabla^2 \Psi(\mathbf{r}, \tau) - \hat{V}(\mathbf{r}) \Psi(\mathbf{r}, \tau) \quad (8)$$

and the branching diffusion equation

$$\frac{\partial C(\mathbf{R}, t)}{\partial t} = D \nabla^2 C(\mathbf{R}, t) - k C(\mathbf{R}, t), \quad (9)$$

where  $\mathbf{R}$  is a  $3N$ -dimensional vector that specifies the coordinates of  $N$  electrons in a molecular system. The potential energy operator for the system has the form

$$\hat{V}(\mathbf{R}) = \sum_{i>j}^N \sum_{l=1}^N \frac{e^2}{r_{ij}} - \sum_{i=1}^N \sum_{A=1}^M \frac{Z_A e^2}{r_{iA}} + \sum_{A>B}^M \sum_{l=1}^M \frac{Z_A Z_B e^2}{r_{AB}}. \quad (10)$$

As previously, the  $i$  and  $j$  subscripts designate the electrons,  $A$  and  $B$  correspond to the nuclei,  $e$  is the charge of the electron and  $Z_A$  is the charge of nucleus  $A$ . The second term in the right-hand part of Eqn (9) describes the concentration  $C$  of particles that diffuse with probability  $k$  (the first-order rate constant for a chemical reaction), the random path  $\Delta r$  they effectively travel in time  $\Delta t$  being determined through the diffusion coefficient  $D$  using the Einstein relation

$$D = \frac{1}{2} \frac{(\Delta r)^2}{\Delta t}. \quad (11)$$

It is assumed that the  $\Psi(\mathbf{R}, \tau)$  value corresponds to  $C(\mathbf{R}, t)$ ,  $V(\mathbf{R})$  to  $k$  and  $\hbar^2/2m_e$  to  $D$ .

In the diffusion version of the QMC method, the function  $\Psi(\mathbf{R}, \tau)$  acquires the meaning of the density of imaginary ‘walkers,’ the search for the solution of stationary Eqn (7) is equivalent to the search for the solution of a type (8) equation for an equilibrium stable state. When simulating the Schrödinger equation in imaginary time,  $\Delta r$  and  $\Delta t$  in relation (11) are chosen in such a way as to ensure that  $D$  is close to  $\hbar^2/2m_e$ . In particular, for the  $\text{H}_2$  molecule with fixed  $A$  and  $B$  nuclei (the Born–Oppenheimer approximation), the Schrödinger equation in imaginary time has the following form (in atomic units):

$$\frac{\partial \Psi}{\partial \tau} = \frac{1}{2} \nabla_1^2 \Psi + \frac{1}{2} \nabla_2^2 \Psi - V \Psi, \quad (12)$$

the potential energy operator ( $\hat{V}$ ), without allowance for the internuclear repulsion, being determined using the formula

$$\hat{V} = -\frac{1}{r_{1A}} - \frac{1}{r_{1B}} - \frac{1}{r_{2A}} - \frac{1}{r_{2B}} + \frac{1}{r_{12}}, \quad (13)$$

where  $r_{1A}$  is the distance between electron 1 and the proton  $A$ , and  $r_{12}$  is the interelectron distance. Then, in designations of the diffusion equation, we have  $D = 1/2$  and  $k = V$ .

Along with DQMC, the GFQMC technique is often used;<sup>26</sup> this is underlain by the fact that the time-independent Schrödinger equation can be written in the form

$$-\sum_i \nabla_i^2 \Psi(\mathbf{R}) + k^2 \Psi(\mathbf{R}) = k^2 \frac{V(\mathbf{R})}{E} \Psi(\mathbf{R}), \quad (14)$$

where  $k^2 = -2mE/\hbar^2$ . For the  $k^2$  value to be positive, the energy value should be negative. Hence, it is necessary to specify an appropriate reference level of the potential energy. The Green function for Eqn (14) that satisfies the required boundary conditions ( $\Psi \rightarrow 0$  for  $\mathbf{R} \rightarrow \infty$ ) can be represented as follows

$$G(\mathbf{R} \rightarrow \mathbf{R}') = \frac{K_{3N/2-1}}{(2\pi)^{3N/2}} \frac{k|\mathbf{R}' - \mathbf{R}|}{k|\mathbf{R}' - \mathbf{R}|^{3N/2-1}}, \quad (15)$$

where  $K$  is the modified Bessel function and  $N$  is the number of electrons.

The search for  $\Psi(\mathbf{R})$  within the framework of the GFQMC method is accomplished by iterations using the arbitrary initial wave function  $\Psi_0(\mathbf{R})$

$$\Psi_{n+1}(\mathbf{R}') = \int G(\mathbf{R} \rightarrow \mathbf{R}') \frac{V(\mathbf{R})}{E} \Psi_n(\mathbf{R}) d\mathbf{R}. \quad (16)$$

The iteration procedure is carried out until the verification shows that the process convergence has been attained. In essence,  $G(\mathbf{R} \rightarrow \mathbf{R}')$  in Eqn (16) is the probability of transforming one electron configuration ( $\mathbf{R}$ ) into the other ( $\mathbf{R}'$ ) through arbitrary motion of each electron.

The solution of the Schrödinger equation for molecules by the GFQMC method is faced with substantial difficulties caused, first of all, by the properties of the Coulomb potential and the antisymmetry requirement. The time-dependent many-electron wave function  $\Psi(\mathbf{R}, t)$  is represented at the initial instant [ $\Psi(\mathbf{R}, 0)$ ] as a set of  $3N$  coordinates of electrons. For example, for LiH, this ensemble would consist of 12 Cartesian coordinates that determine the spatial arrangement of each of the four electrons. Any specified electron configuration defines one point ( $\mathbf{R}$ ) in a  $3N$ -coordinate space, the set of these allowed configurations is considered as a configurational ensemble.

If the second addend in the right-hand part of Eqn (8) were missing, this would correspond to the usual diffusion equation with coefficient  $D$ , and would describe particle ‘walk’ in the configuration space. However, only in the presence of this addend, is Eqn (8) applicable to branching processes, for example radioactive decay, or the exponential development of populations. This branching is due to a decrease in the probability density in the regions with greater values for the  $V(\mathbf{R})$  potential and its increase in the regions with a low potential energy.

The interpretation of Eqn (8) as a diffusion equation implies that the ‘walker’ density [i.e.,  $\Psi(\mathbf{R}, t)$ ] should always be positive. Since the phase of the function  $\Psi(\mathbf{R}, t)$  is arbitrary, the function can also always be negative; it must have one sign. This requirement is equivalent to the absence of nodes in the  $\Psi(\mathbf{R}, t)$  function.

However, in the case of Fermi systems, the MWF can have nodes or a change in the sign. Therefore, to retain the analogy with the diffusion equation, the regions of positive and negative MWF values should be considered separately. The exclusion of the ‘walk’ between these regions is called the fixed-node approximation of the QMC method. Equation (8) is solved by the variational method separately for each node-free region, with application of the conditions  $\Psi(\mathbf{R}, t) = 0$  only at the boundary of this region. As applied to the branching diffusion process, this means that as soon as a ‘walker’ reaches the boundary of its region, it is destroyed.

Until recently, researchers have paid relatively little attention to the topological structure and other properties of MWF nodal hypersurfaces. In practice, the QMC method was used most often to upgrade the existing MWFs with known nodal hypersurfaces.

The trial function  $\Psi_t(\mathbf{R}, t)$  should possess the following properties:

- (1) be rather simple, which would allow fast calculation of the value of the function and its derivatives;
- (2) be a smooth and well-defined function of the argument  $\mathbf{R}$ , in order to avoid difficulties in the calculation of the local energies ( $\hat{H}\Psi_t/\Psi_t$ );
- (3) have nodal surfaces close to the Schrödinger ones, in order to ensure a sufficiently high accuracy calculated to the energy.

The last two requirements are better fulfilled when  $\Psi_t$  is close to the exact solution of the Schrödinger equation. Therefore, when determining  $\Psi_t$ , it is expedient to invoke everything that is known about the sought-after exact solution (symmetry conditions, boundary conditions, etc.).

It has been recommended<sup>27,28</sup> to divide the electron configuration space into two parts by means of a hypersurface in which  $\Psi(\mathbf{R}) = 0$  for any electron pair with parallel spins. Then, the resulting MWF would possess the required antisymmetry if it is specified to be positive on one side and negative on the other side

of the nodal hypersurface. For describing excited electron states, a larger number of such hypersurfaces are required.

However, it is no confidence that the above arbitrary division of the electron configuration space would give a wave function corresponding to the ground state. Moreover, a mathematically feasible solution of the Schrödinger equation does not always have a physical meaning. Without strict rules for defining the nodal hypersurfaces, finding a sufficiently accurate upper estimate of the desired energy may require variation of the chosen nodal hypersurfaces.

The application of Eqn (8) to the branching walk is faced with certain difficulties. The point being that the branching rate, proportional to the Coulomb potential, can become very high when the ‘walkers’ closely approach each other, which would entail a pronounced fluctuation of their number. However, such fluctuations and hence the statistical uncertainty in solving equations such as Eqn (8), can be substantially reduced by using the so-called Importance Sampling (IS) procedure proposed ~35 years ago.<sup>29</sup> The essence of IS is the use of preliminary knowledge of the properties of MWF in order to make quantum-chemical calculations more accurate; the procedure involves the introduction of a ‘controlling’ function  $g(\mathbf{R})$ , meant to meet the symmetry requirements of the desired function  $\Psi(\mathbf{R}, t)$ . This allows one to operate with  $\Phi(\mathbf{R}, t) = \Psi(\mathbf{R}, t)g(\mathbf{R})$  rather than with  $\Psi(\mathbf{R}, t)$ . This markedly enhances the accuracy of QMC estimates of the mean values of physical quantities.<sup>26–28</sup>

In order to be interpretable as the probability density corresponding to the Schrödinger equation, the function  $\Phi(\mathbf{R}, t)$  should be non-negative [ $\Phi(\mathbf{R}, t) \geq 0$ ]. This means that the functions  $\Psi(\mathbf{R}, t)$  and  $g(\mathbf{R})$  have identical signs. However, they change the sign on permutation of electrons with identical spins, i.e., they are positive in some regions of the configuration space and negative in other regions; the dimensions and shapes of these regions being entirely determined by the nodal surfaces. Thus, the requirement for non-negative definiteness of the function  $\Phi(\mathbf{R}, t)$  is equivalent to the requirement of coincidence for the nodal surfaces of  $\Psi(\mathbf{R}, t)$  and  $g(\mathbf{R})$ .

The condition of the presence of identical nodes for MWF and  $g(\mathbf{R})$  restricts the arbitrariness in choosing the function  $\Psi(\mathbf{R}, t)$ . Due to the use of the fixed-node approximation, any electron configuration should be excluded from the configuration ensemble (see above) if it crosses the nodal surface for  $\Psi(\mathbf{R}, t)$  upon shifting from  $\mathbf{R}$ . This requirement is equivalent to the presence of an infinitely high barrier (potential) at  $g(\mathbf{R}) = 0$ . With this formalism, the ‘controlling’ function  $g(\mathbf{R})$  fixes the nodes of the MWF and thus influences the accuracy of calculations. The closer the nodal surfaces of the ‘controlling’ and the proper (exact) functions, the more accurate the obtained solution of the Schrödinger equation.<sup>26–28</sup>

The choice of optimal trial MWF is dictated by a compromise between two criteria. On the one hand, it is desirable that the function  $\Psi_t$  in the QMC calculation be as simple as possible, because this markedly shortens the time it takes to calculate its first and second derivatives at points  $\mathbf{R}$  of the spinless configuration space (this computation has to be repeated up to  $10^7$  times).<sup>26–28</sup> On the other hand, it would be better if the trial function  $\Psi_t$  were as close as possible to the Schrödinger one, because in this case, the statistical deviations decrease and the MWF nodes are located more correctly.

The results of particular computations (see the references cited in Ref. 26) have shown that a plausible compromise results from using an expression for  $\Psi_t$  equal to the product of the Slater determinant  $\det(Q_{kl})$  ( $k, l$  are the numbers of lines and columns in the determinant), and the electron–electron and electron–nuclear Jastrow’s factors (see the references in Refs 26, 28), which impose the required conditions on  $\Psi_t$  for  $r_{ij} \rightarrow 0$  and  $r_{iA} \rightarrow 0$ ,

$$\Psi_t(\mathbf{R}) = \det(Q_{kl}) \exp \left( \sum_{i>j} \frac{a_{ij}r_{ij}}{1 + br_{ij}} - \sum_{i,A} \frac{Z_A a_{i,A}r_{i,A}}{1 + br_{i,A}} \right). \quad (17)$$

Jastrow's factors allow one to explicitly take into account the correlation in the electron motion. Usually, it is taken that  $a_{ij} = 1/8D$  for electrons  $i$  and  $j$  with parallel spins,  $a_{ij} = 1/4D$  in the case of antiparallel spins and  $a_{i,A} = 1/2D$ ; the parameter  $b$  is considered as a variable parameter during energy minimisation [ $D$  is the diffusion coefficient, see expression (11)].

Since the Jastrow's factors are positive, they do not affect the trial function (17) nodes, which are totally dictated by the Slater determinant. The molecular orbitals  $\phi_k(\mathbf{r})$  are usually linear combinations of exponential functions (linear combinations of atomic orbitals), determined by the SCF procedure. Attempts at using multideterminant SCF trial functions instead of one Slater determinant are still few and far between.<sup>26–28</sup>

The energy characteristics calculated by the QMC method for both small and large molecules and for clusters are usually much more accurate than those obtained when using other quantum-chemical approaches. During recent years, substantial progress has been made by using QMC methods.<sup>28</sup> QMC methods have proved highly efficient in studies of rather complex molecules, electron–positron systems, vibronic effects and so on. However, the difficulties encountered in their use are still great, especially for many-electron compounds containing atoms heavier than fluorine. In these cases, the accuracy of the QMC methods decreases sharply. The statistical error inherent in QMC calculations is, most often, proportional to  $t^{-1/2}$  ( $t$  is the computer time spent).<sup>30</sup>

Currently, QMC methods are used most of all, for the improvement of the existing wave functions of which the nodal hypersurfaces are known. Unfortunately, a strict definition of MWF nodal hypersurfaces is problematic.

The testing of various QMC versions (see the references cited in Ref. 31) has shown that most of them are unstable. This accounts for the inadmissible expenses of computer provision needed to attain high accuracy. Among the innovations discussed in detail in the literature, mention should be made of the uncoupled node procedure with subspace design<sup>32</sup> and a version of the mirror potential method<sup>33</sup> meant for electron systems. Some known approaches have been modified rather successfully.<sup>34,35</sup>

Unfortunately, in most cases, it is only possible to evaluate the correctness of choice of MWF nodal hypersurfaces that separate the configuration space into the regions with constant sign by solving the Schrödinger equation with a plausible accuracy. To have physical meaning, the MWF thus found should satisfy the general principles of quantum mechanics (spin and symmetry ones), which were defined back in 1925–1926 by Pauli, Dirac and Heisenberg.<sup>36–38</sup> In 1927–1928, Wigner, Hund and Heitler formulated these principles in terms of group theory.<sup>39–41</sup> In the 1920s, researchers paid much attention to a thorough investigation into the properties of MWF nodal surfaces.

After Slater<sup>42</sup> had introduced (in 1929) a determinant representation for the MWF, the problem of nodal surfaces receded into the background for a long period. Indeed, when Slater determinants are used, the antisymmetry of trial many-electron functions is ensured automatically. In addition, according to the theorem proven by Levdin,<sup>43</sup> an exact MWF for the ground or excited state of an  $N$ -electron system can be represented as a linear combination of all sorts of Slater determinants (with  $N \times N$  dimensionality), which include single-electron spin orbitals that constitute the mathematically full set of basis functions.

Probably, due to the above, the interest in detailed investigations of the structures of MWFs in solving the Schrödinger equation by the variational method has been lost. In the MWF method being developed, this problem has acquired again a prime importance (thus illustrating the well-known proverb that new is well-forgotten old).

### III. Many-electron wave functions

Antisymmetry and diversity of the nodal surfaces are fundamental characteristics of the MWF. If the potential possesses the sym-

metry property, the Hamiltonian eigen functions  $\Psi_i$  (solutions of the stationary Schrödinger equation  $\hat{H}\Psi = E\Psi$ ) can be classified according to irreducible representations of an appropriate symmetry group. Unlike single-electron orbitals, a physically acceptable MWF reflects not only the point symmetry of the Hamiltonian but also its invariance with respect to permutations of the spin and space electron coordinates; in addition, it vanishes on nodal surfaces predetermined by permutation symmetry. It is obvious that even for  $N = 3$  and for the ground state of an  $N$ -electron system, it is impossible to construct a many-electron wave function  $\Psi_0$  without nodes.

The nodal surfaces divide the whole coordinate space in which the MWF is specified into the regions in which its sign is constant (positive on one side and negative on the other side of each nodal surface). Since the MWF is  $3N$ -dimensional, one can hardly rely on intuition in attempts to visualise the nodal hypersurfaces. Visual representation of these, even for very simple systems (He and  $\text{H}_3$ ), is possible only by constructing 3D cross-sections of the  $3N$ -dimensional space with fixed positions for all particles, except for one electron.<sup>44,45</sup>

The antisymmetry requirements of the function  $\Psi_i$  relative to the permutations of the spatial coordinates of electrons with parallel spins, except for systems such as He ( $^3\text{S}$ ), do not suffice for correct determination of the coordinates of the nodal surfaces, although this strongly restricts the arbitrariness of the *a priori* selection of the shape of these surfaces.<sup>31</sup> In essence, the Wigner approach (discussed in a publication<sup>46</sup>) is unable to provide efficient assistance, as it does not contain any practical recommendations on constructing the coordinate (spinless) MWF with the required symmetry properties. The method outlined below takes into account the limitations of the generally accepted interpretation of the fundamental Pauli exclusion principle.

The canonical interpretation of the Pauli principle for a many-electron atom states that two electrons with identical spins cannot exist in the same state specified by four quantum numbers. In the HF approximation, the sought-after MWF is represented by the Slater determinant, thus ensuring fulfilment of the Pauli principle and antisymmetry with respect to the corresponding electron permutations.

The antisymmetry requirement for the MWF means the presence of a definite set of nodal surfaces in the multidimensional configuration space. The probability of finding an electron configuration on this surface is equal to zero. It is beyond doubt that for any many-electron system, solution of the stationary Schrödinger equation should vanish on a nodal surface. Among the possible diverse multidimensional nodal surfaces, there exist some that determine the configurations corresponding to the occurrence of a pair of electrons with the same orientation of spins at the same point in space. The exclusion of such configurations by the Pauli principle is taken into account automatically when the antisymmetric MWF is constructed. However, in reality, apart from these configurations, the Pauli principle forbids a multitude of other, seemingly quite acceptable configurations.<sup>47</sup>

The main feature distinguishing this approach from the Hartree–Fock one is the investigation of the possible form of nodal surfaces. This essentially narrows down the excessively broad set of acceptable antisymmetric functions by distinguishing the functions that satisfy the boundary conditions derived from the modern interpretation<sup>47</sup> of the Pauli principle. It can be demonstrated, for example, that the Slater determinants corresponding to different electron configurations turn to zero on non-coincident surfaces. Therefore, the CI calculations converge slowly, as one has to consider a very large number of determinants with different nodal surfaces in order to approach the true (Schrödinger) MWF and corresponding nodal surface. If it was possible to determine *a priori* the nodal surfaces and use them for constructing the trial MWF, the convergence of quantum-chemical calculations would be substantially faster and the accuracy higher.

In addition, owing to the use of a symmetric group in the MWF construction, the computational procedure becomes much simpler, because for a system of  $N$  electrons, the initial problem is finally reduced, without loss of accuracy, to  $N!$  identical problems, but with a smaller integration region.<sup>47,48</sup> Indeed, if a system with spin  $S$  has  $K = (N/2) + S$  electrons with the spin coordinates  $s_i = +1/2$  (set  $I$ ) and  $N - K = (N/2) - S$  electrons with  $s_j = -1/2$  (set  $J$ ), then among the total group of permutations  $S_N$ , one can distinguish the subgroups  $S_K$  and  $S_{N-K}$  acting on the elements of sets  $I$  and  $J$ , respectively. The direct product of these subgroups  $S_K \times S_{N-K} \equiv S(I, J)$  can be reasonably termed as a ‘spin-invariant subgroup’, as its elements act only on the electrons with the same projections of the spin.<sup>49</sup>

The use of ‘spin-invariant subgroups’ for solving the Schrödinger equation allows one to handle only the part of the wave function which is antisymmetric with respect to electron permutations contained in  $S(I, J)$  rather than the whole many-electron wave function  $\Psi(r_1, s_1; \dots; r_N, s_N)$ . The full MWF is easily restored from this part by means of appropriate symmetry operations. With this approach, the number of integrals needed to calculate the matrix elements of the Hamiltonian decreases by a factor of  $M = N! / \{[(N/2) + S]![(N/2) - S]!\}$ .

The problem of methods suitable for the practical construction of the functions  $\Psi(r_1, s_1; \dots; r_N, s_N)$  having a different physical meaning from spinless functions, which depend only on spatial coordinates  $r_i$  and possess the required symmetry properties, has been studied comprehensively by Fok.<sup>46</sup> Both the Pauli principle and the equation for the full spin angular momentum

$$\hat{S}^2 \Psi(x_1, \dots, x_N) = S(S+1) \Psi(x_1, \dots, x_N) \quad (18)$$

( $x_i$  designates the set of spatial coordinates and the spin variable for  $i$ th electron) were taken into account<sup>46</sup> by strict mathematical techniques. By representing the operator  $\hat{S}^2$  as

$$\hat{S}^2 = N - \frac{N^2}{4} + \sum_{i < j} \hat{P}_{ij}, \quad (19)$$

where  $\hat{P}_{ij}$  is the permutation operator for spin variables  $s_i$  and  $s_j$ , Fok expressed the full MWF for a system of  $N$  electrons through only the spinless wave function [for  $k$  electrons with parallel spins and  $(N-k)$  electrons with antiparallel spins]

$$\Psi = \Psi(r_1, r_2, \dots, r_k | r_{k+1}, r_{k+2}, \dots, r_N) \quad (20)$$

and formulated the following necessary and sufficient symmetry properties for the latter:

(1) antisymmetry with respect to  $k$  arguments on the left of the vertical line in series (20), for example,

$$\Psi(r_2, r_1, \dots, r_k | r_{k+1}, \dots, r_N) = -\Psi(r_1, r_2, \dots, r_k | r_{k+1}, \dots, r_N);$$

(2) antisymmetry with respect to  $(N-k)$  arguments on the right of the vertical line in series (20), for example

$$\Psi(r_1, \dots, r_k | r_{k+2}, r_{k+1}, \dots, r_N) = -\Psi(r_1, \dots, r_k | r_{k+1}, r_{k+2}, \dots, r_N);$$

(3) so-called cyclic symmetry, expressed by the following equalities:

when  $(N-k)$  is even

$$(1 + P + P^2 + \dots + P^{N-k}) \Psi = 0, \quad (21)$$

when  $(N-k)$  is odd

$$(1 - P + P^2 - \dots - P^{N-k}) \Psi = 0, \quad (22)$$

where  $P$  designates the cyclic permutation of the arguments  $(r_k, r_{k+1}, \dots, r_N)$ , i.e., the permutation in which each term of the cycle  $(r_k, r_{k+1}, \dots, r_N)$  is replaced by the next one, and the last term by the first one.

It follows from expressions (21) and (22) that a system of two electrons with a total spin of zero ( $S = 0$ ,  $N = 2$ ,  $k = 1$ ) is described by a symmetric Schrödinger function, while its triplet state ( $S = 1$ ,  $N = 2$ ,  $k = 0$ ) is described by an antisymmetric function relative to the spatial coordinates of the electrons. The

Schrödinger wave function does not depend on spin variables; however, in this case, the resultant spin is reflected in its properties by governing the symmetry and the nodal surface.

An example of a many-electron function that satisfies the three above-indicated conditions of symmetry, exceptionally important for quantum chemistry, is the product of two determinants<sup>46</sup>

$$\Psi = |A| \times |B|, \quad (23)$$

where

$$|A| = \begin{vmatrix} \varphi_1(r_{k+1}) & \dots & \varphi_{N-k}(r_{k+1}) \\ \dots & \dots & \dots \\ \varphi_1(r_N) & \dots & \varphi_{N-k}(r_N) \end{vmatrix}, \quad |B| = \begin{vmatrix} \varphi_1(r_1) & \dots & \varphi_k(r_1) \\ \dots & \dots & \dots \\ \varphi_1(r_k) & \dots & \varphi_k(r_k) \end{vmatrix}$$

and  $2k \leq N$ .

These determinants are composed of one set of single-electron orbitals  $\{\varphi_1(r), \varphi_2(r), \dots, \varphi_{N-k}(r)\}$ , the greater of them containing all  $(N-k)$  orbitals, and the smaller of them containing only the first  $k$  wave functions present in the set.

A similar consideration<sup>48,50–55</sup> of the symmetry properties and nodal MWF having a physical meaning, and taking into account the most meaningful properties of nodal surfaces, has resulted in the formulation of a theorem<sup>7</sup> that is a generalisation of the Courant–Hilbert<sup>56</sup> theorem, concerning the nodes of the eigen functions of elliptical operators, and the theorem proven by Zhislin<sup>57</sup> on the nodes of the eigen functions of the Schrödinger operator, without the requirement of their permutation antisymmetry. According to the formulation of this theorem in the study,<sup>7</sup> there exists an eigen function  $\Psi_0(r_1, r_2, \dots, r_N)$  of an  $N$ -electron Schrödinger operator

$$\hat{H} = -\frac{1}{2} \sum_{i=1}^N \nabla_i^2 + \sum_{i=1}^N \sum_{j>i}^N \frac{1}{r_{ij}} - \sum_{A=1}^M \sum_{i=1}^N \frac{Z_A}{r_{Ai}}, \quad (24)$$

that corresponds to the ground electronic state with the spin  $S$ , and whose nodal surfaces divide the Euclidean space  $|R^{3N} = \{r_1, r_2, \dots, r_N\}$  into at least

$$L = (N/2 + S)! (N/2 - S)!$$

regions  $\Omega_1, \dots, \Omega_L$  with constant sign. Any of these  $\Omega_i$  regions can be regarded as fundamental, while the others are regarded as its copies. The total many-electron wave function  $\Psi_0$  can be restored, based on the distinguished part, by using symmetry operations.

The continuous function  $\Psi_0$  within each constant-sign region is not equal to zero but becomes zero at the boundary. Due to the splitting of the whole space  $|R^{3N}$  into  $L$   $\Omega_i$  regions, the determination of MWF becomes  $\sim L$  times simpler, without a loss of accuracy due to the transition from the integration over  $|R^{3N}$  to the  $\Omega_i$  region. In the case of a large value of  $N$ , the number  $L$  is great. Moreover, in this case, there is no need to consider the symmetry of the desired function or its spin part, isolated as a multiplier; instead, it is sufficient that the function is equal to zero at the boundary of the fundamental region.

The possibility of restoring the full MWF by means of symmetry operations should certainly facilitate high-precision calculation of the observed values and the construction of a trial MWF for the stationary states of given multiplicity. In view of the possibility of replacing the antisymmetrisation over the whole group of permutations  $S_N$  by antisymmetrisation over the spin-invariant subgroup  $S(I, J)$  of this group (see above), strictly substantiated mathematically, the degree of computation involved in the numerical solution of the Schrödinger equation is expected to be reduced by a factor of  $L \times M = N!$ . For example, for the molecule LiH ( $N = 4$ ), one can expect a 24-fold increase in the calculation performance compared to that used traditionally; for the CH<sub>4</sub> molecule ( $N = 10$ ), this increase may be up to 3 628 800-fold.

For any atomic or molecular system, each electronic state is matched by the MWF nodal surfaces. The antisymmetry of the MWF with respect to particle permutations is inherent only in

many-electron systems. Many-electron wave functions differ appreciably from the single-electron functions familiar to chemists, namely AOs or MOs. (Note that the MWF is represented in the CI method as the sum of antisymmetrised derivatives of single-electron functions.<sup>43</sup>) For example, the spatial part of the MWF for the triplet state of a helium atom in the HF approximation has the form

$${}^3\Psi(\mathbf{r}_1, \mathbf{r}_2) = \frac{1}{\sqrt{2}} [\varphi_1(\mathbf{r}_1)\varphi_2(\mathbf{r}_2) - \varphi_1(\mathbf{r}_2)\varphi_2(\mathbf{r}_1)], \quad (25)$$

where  $\varphi_1$  and  $\varphi_2$  are the Hartree-Fock AOs. Even if the coordinates of, for example, electron 1 are such that they correspond to the node of the  $\varphi_1$ -AO, *i.e.*,  $\varphi_1(\mathbf{r}_1) = 0$ , the function  ${}^3\Psi(\mathbf{r}_1, \mathbf{r}_2)$  still does not necessarily become zero, because the term  $[-\varphi_1(\mathbf{r}_2)\varphi_2(\mathbf{r}_1)]$  can be non-zero. The condition  ${}^3\Psi(\mathbf{r}_1, \mathbf{r}_2) = 0$  is attained only when both constituents in the right-hand part of Eqn (25) coincide. Similarly, it can be considered that (except for the ground states of two-electron systems, for which spatial antisymmetry is completely ruled out) an antisymmetrised MWF has nodes even when it is constructed from nodeless AOs or MOs.

In the case of the  ${}^3S$  state of helium, the MWF can be expressed exactly through the electron–nuclear ( $r_1, r_2$ ) and electron–electron ( $r_{12}$ ) distances.<sup>58</sup> The MWF should be antisymmetric with respect to the permutation of electrons 1 and 2, *i.e.*,

$$\Psi(r_1, r_2, r_{12}) = -\Psi(r_2, r_1, r_{21}); \quad (26)$$

hence, taking into account that  $r_{12} = r_{21}$ , we get the condition  $r_1 = r_2$ , at which the MWF vanishes.

Unfortunately, the cases in which the exact form of the  $(3N-1)$ -dimensional MWF nodal surface can be established *a priori* from symmetry considerations alone are very scarce. As a rule, this task cannot be solved, first of all due to the large number of variables.

In view of the special significance of the MWF nodes, it appears expedient to introduce a special factor into the expression for the trial wave function, which could specify explicitly the form of its nodal surface. One more factor should be defined only in one of the constant-sign MWF regions (see above). According to a hypothesis,<sup>8,47</sup> the eigen functions of the  $N$ -electron Schrödinger operator have nodal surfaces defined by the equation with the potential functions of form

$$U_{ij} = \sum_{k \neq i, j}^N \left( \frac{e^2}{r_{ki}} - \frac{e^2}{r_{kj}} \right) - \sum_{A=1}^M \left( \frac{Z_A e}{r_{Ai}} - \frac{Z_A e}{r_{Aj}} \right) \equiv 0. \quad (27)$$

It is assumed that electrons ( $i, j$ ) have the same spin orientation. This means that any two electrons with parallel spins are prohibited from occurring on the same equipotential surface (the equipotential surface prohibition principle).

In the general case, one should expect that for isoelectronic compounds of different types, the forms of the equipotential surfaces would be different, first of all, due to differences between their nuclear configurations. According to the equipotential surface prohibition principle, the function  $\Psi(\mathbf{r}_1, \dots, \mathbf{r}_N)$  must have the same nodes as found for the set of potential functions  $U_{ij}$  of the electron–nuclear system. This requirement specifies the form and the minimum number of nodal surfaces related to the coordinate permutations for any electron pair. This eliminates the necessity of solution antisymmetry, because, as noted above, it is ensured automatically by the procedure of further construction of the full MWF.

The sought-after function  $\Psi(\mathbf{r}_1, \dots, \mathbf{r}_N)$  can, of course, have additional nodal surfaces, which are missing from the set of potential functions  $U_{ij}$ . Moreover, it cannot be ruled out that the proposed hypothesis would not find a reasonable substantiation; however, it appears expedient to verify this hypothesis by means of high-precision *ab initio* calculations for simple test objects.

## IV. Testing of many-electron wave functions

The statements outlined above form the basis of the MWF method. They can be validated using a simple example — the calculation of the ground triplet state of helium ( ${}^3S$ ). Experimental chemists usually treat the ‘quantum chemistry of helium’ as useless and dull. However, the unique opportunity to obtain results of exceptionally high accuracy has become the reason why the helium atom is most often chosen as the test system to verify many-electron theories.

In 1959, Pekeris<sup>59</sup> used a 1078-term trial function and obtained the best, at that time, value for the total energy of the  $1s^2$  ( ${}^1S$ ) state of helium

$$E_0 = -2.903724375 \text{ a.u.}$$

Later,<sup>60</sup> using the approach proposed by Fok,<sup>61</sup> the basis set was reduced to 246 functions and the accuracy of calculations was increased, giving the value

$$E_0 = -2.9037243770326 \text{ a.u.}$$

The same procedure, together with additional analysis<sup>62</sup> using only a 230-term function of the same form, gave the value

$$E_0 = -2.90372437703407 \text{ a.u.}$$

Note that according to some estimates,<sup>63</sup> attaining a comparable accuracy in the CI method would require  $\sim 10^4$  terms in the Legendre expansion and  $\sim 10^{12}$  electron configurations.

Calculations for the  $1s2s$  ( ${}^3S$ ) state should be better performed by a different technique.<sup>64</sup> Formally, the permutation of particles in the configuration space  $\{r_1, r_2, r_{12}\}$  implies the interchange of  $r_1$  and  $r_2$  for  $r_{12} = r_{21}$ . Thus, the  $r_1 = r_2$  surface divides the configuration space into two regions, and in one of them ( $r_1 \geq r_2$  or  $r_2 \geq r_1$ ), one has to find the solution of the Schrödinger equation that takes into account the boundary condition imposed on the wave function

$$\Psi(r_1, r_2, r_{12})|_{r_1=r_2} = 0.$$

With this approach, it is possible to use trial wave functions of two types

$$\Psi(r_1, r_2, r_{12}) = (e^{-\alpha r_1} - e^{-\alpha r_2})e^{-\beta(r_1+r_2)}\Psi_n^s(r_1, r_2, r_{12}), \quad (28)$$

$$\Psi(r_1, r_2, r_{12}) = (e^{-\alpha r_1} - e^{-\alpha r_2})e^{-\beta(r_1+r_2)}\Psi_n^u(r_1, r_2, r_{12}), \quad (29)$$

where  $\Psi_n^s$  is symmetric and  $\Psi_n^u$  is an arbitrary polynomial containing  $n$  terms. The first exponential factor in these functions corresponds to the antisymmetry condition, while the second one corresponds to the requirement of fast vanishing at large distances between the nucleus and the electrons. Function (28) is antisymmetric, unlike function (29); however, it can be reflected on the other half of the configuration space antisymmetrically, relative to the  $r_1 = r_2$  surface.

A practical advantage of expression (29) is that the class of functions used to approximate the solution of the Schrödinger equation is much broader, as the set of symmetric polynomials  $\{\Psi_n^s\}$  is a subset of the arbitrary polynomials  $\{\Psi_n^u\}$ ; therefore, the polynomial expansion (29) converges much faster than the expansion of (28). Rejection of the symmetry restrictions allows one to construct a broader class of trial functions using arbitrary polynomials. For example, in the case of a second-order polynomial, expressions (28) and (29) acquire the form

$$\Psi_7^s = a_0 + a_1(r_1 + r_2) + a_2r_{12} + a_3(r_1^2 + r_2^2) + \quad (30)$$

$$+ a_4r_1r_2 + a_5(r_1 + r_2)r_{12} + a_6r_{12}^2 \quad (n = 7),$$

$$\Psi_{10}^u = b_0 + b_1r_1 + b_2r_2 + b_3r_{12} + b_4r_1^2 + b_5r_2^2 + \quad (31)$$

$$+ b_6r_1r_2 + b_7r_1r_{12} + b_8r_2r_{12} + b_9r_{12}^2 \quad (n = 10).$$

For the  $^3S$  state of the helium atom and with an arbitrary five-order  $\{\Psi_{47}^u\}$  polynomial (47 variable linear coefficients<sup>64</sup>), the energy value  $^3E = -2.1752288$  a.u. was obtained; this is  $5 \times 10^{-7}$  a.u. lower than the value calculated by Pekeris<sup>59</sup> using a function containing 715 parameters (the experimental  $^3E$  value is  $-2.175230$  a.u.). This example is indicative of the advantage of the MWF method in applied quantum-chemical calculations.

This is exemplified in Fig. 1, which shows the nodal surface of the triplet helium atom, complying with the equipotential surface prohibition principle, in Cartesian coordinates. The Figure clearly illustrates the fact that in this state, irrespective of the distance between the electrons, their location in one sphere, centred in the atom nucleus, should be prohibited.

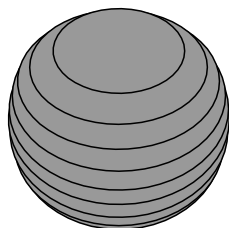


**Figure 1.** Spherical shape of the nodal surface for the triplet state of a helium atom.

Apart from helium, lithium is often used as the test system. The lithium atom has three electrons and can serve as the simplest model species for which the electron correlation effects are, firstly, rather substantial (due to the incomplete electron shell) and, secondly, include contributions from both the core and valence electrons. Therefore, it is not by chance that in recent years, a number of high-precision quantum-mechanical calculations for the  $^2S$  ground state of this atom have been carried out.

It is noteworthy in this context that in the case of three-electron systems with one unpaired electron, the structure of the three 9-dimensional subspaces and the action of  $P_{ij}$  transpositions (pair permutations belonging to the spin-invariant  $S_3$  group) on them can be depicted, as shown in Fig. 2. It can be seen that each of the three 9-dimensional subspaces is divided into two regions of constant MWF sign (wavy line). Any point of the configuration space  $(r_1s_1; r_2s_2; r_3s_3)$  with specified coordinates  $(r)$  and spins  $(s)$  of the three electrons is allocated one of these subspaces. Obviously, the three spatial functions corresponding to the scheme shown in Fig. 2 are interrelated, and it is sufficient to find the solution of the stationary Schrödinger equation for only one of the subspaces.<sup>7</sup>

Among the most accurate is the detailed variational calculation<sup>65</sup> of the lithium atom carried out using the trial wave function

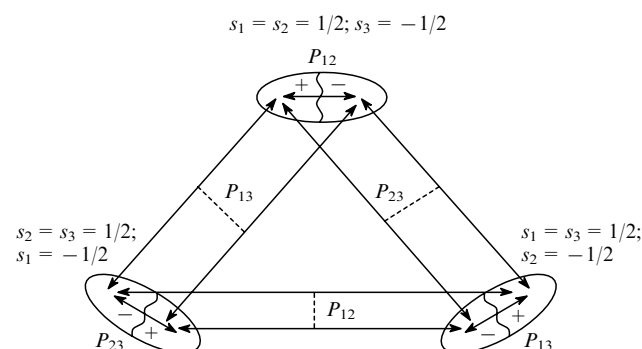


**Figure 2.** Scheme of the configuration space for the ground state of a three-electron system (see text).

$$\Psi_t = A \sum_{\mu=1}^M C_{\mu} \varphi_{\mu} \chi_{\mu}, \quad (32)$$

where  $A$  is the antisymmetriser,  $M$  is the number of basis functions,  $C_{\mu}$  are the expansion coefficients determined by the variational method

$$\varphi_{\mu} = R_{\varphi}(r_1, r_2, r_3, r_{12}, r_{13}, r_{23}) \exp(-\alpha_{\mu}r_1 - \beta_{\mu}r_2 - \gamma_{\mu}r_3), \quad (33)$$

[ $R_{\varphi}(r_1, r_2, r_3, r_{12}, r_{13}, r_{23})$  is the product of the distances  $r$  raised to relatively small powers,  $\alpha_{\mu}, \beta_{\mu}, \gamma_{\mu}$  are the varied parameters],  $\chi_{\mu}$  are the eigen doublet spin functions (all identical)

$$\chi_{\mu} = \chi = \alpha(1)\beta(2)\alpha(3) - \beta(1)\alpha(2)\alpha(3), \quad (34)$$

and  $\alpha$  and  $\beta$  are functions dependent on the spin coordinates of the electron.

In the case of polynomial trial function (32), the number of variable power exponents is excessively high. Therefore, this function was constructed term-by-term, only the exponents of newly added terms being optimised. Without this restriction, the calculation on a CRAY-1M type computer proved impossible. However, it should be emphasised that for a 296-term function, a new attempt at optimising the power exponents for the first five basis functions ( $\varphi_1, \dots, \varphi_5$ ) resulted in a negligibly minor correction to the total energy; therefore, the researchers<sup>65</sup> no longer performed the new optimisation procedure.

Analysis of the 296-term function<sup>65</sup> for the lithium atom, taking into account its component distribution among the three subspaces (see Fig. 2), has shown<sup>66</sup> that a substantial part of these components have  $r_i = r_j$  nodal surfaces corresponding to the hypothesis stated in a publication.<sup>8</sup> The other components possess nodal surfaces whose differences from the  $r_i = r_j$  surfaces are insignificant. The results of this analysis can also be interpreted as an argument supporting the equipotential surface prohibition principle.

In addition, special comparative calculations on the lithium ground state ( $^2S$ ) have been carried out<sup>67</sup> in identical basis sets [function of type (33)], but using either a standard antisymmetrisation procedure ( $E_1$ )<sup>65</sup> or boundary conditions corresponding to the equipotential surface prohibition principle ( $E_2$ ). The values for the total energy obtained by IBM PC-486 (in a.u.) are as follows:

| $n$ | $m$ | $E_1$    | $E_2$    |
|-----|-----|----------|----------|
| 1   | 5   | 7.421257 | 7.444296 |
| 2   | 17  | 7.465906 | 7.470490 |

[ $n$  is the maximum order of the type (33) function in the basis set,  $m$  is the number of functions in the basis set]. Comparison of the energies presented above with the experimental value  $E = -7.478069$  a.u.<sup>65</sup> has shown that on application of the boundary conditions corresponding to the above-mentioned principle, one can obtain better agreement with the experimental value by using small and moderately-sized basis sets. For the lithium atom, as for the helium atom, convergence has been substantially improved.<sup>67</sup>

For the ground state of the lithium atom, the equipotential surfaces and their cross-sections have more complex shapes than those of the excited triplet state of the helium atom. Nevertheless, a clear idea of the nodal surfaces for electrons 1 and 2, with parallel spins, can be gained by fixing the position of electron 3, with the opposite spin at some distance  $r_3$  from the lithium nucleus. According to the equipotential surface prohibition principle [see Eqn (27)], one should analyse the expression

$$\frac{3}{r_1} - \frac{1}{r_{13}} = C, \quad (35)$$

in which  $C$  can be represented by any real number. For example, a set of equipotential lines is formed in the  $(x, y)$  plane when the Cartesian coordinates of the lithium nucleus are  $(0, 0)$  and those of the third electron are  $(2, 0)$ . One of these lines, corresponding to

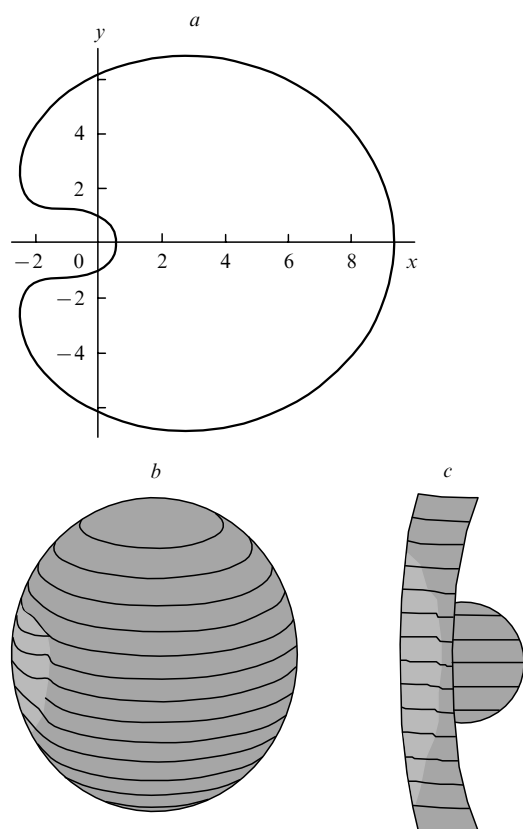


**Figure 3.** Equipotential surface ( $C = 0.3$ ) for the ground state of a lithium atom.

(a) Vertical cross-section, (b) three-dimensional image, (c) enlarged concave part of the nodal surface.

$C = 0.3$ , is shown in Fig. 3a. Its rotation around the  $x$  axis yields a slightly distorted spherical surface with a rather small cavity (Fig. 3b,c). For  $C \sim 0.25$ , the cavity becomes closed and is located inside the closed, somewhat distorted spherical surface.

The role of pre-determination of the nodal surfaces in the quantum-chemical calculations of molecular systems should be even more weighty, because for these, almost every basis function has its own nodal surface, often markedly different from the surfaces of other functions.

Thus a calculation of the  $^3\Sigma_u^+$  triplet state of the hydrogen molecule by the DQMC method for a nuclear–nuclear distance of 1.4 a.u. had been carried out<sup>31</sup> assuming that the trial wave function  $\Psi_t$  should be symmetric with respect to rotation around the internuclear axis  $z$  and antisymmetric with respect to the inversion centre on axis  $z$ . The following trial wave function, satisfying these conditions, was used:<sup>31</sup>

$$\Psi_t = \{\exp[-a(r_{1A} + r_{2B})] - \exp[-a(r_{2A} + r_{1B})]\} \exp\left[\frac{br_{12}}{(1 + cr_{12})}\right], \quad (36)$$

where  $a = 1.0$ ,  $b = 0.25$  and  $c = 0.25$  (a.u.)<sup>−1</sup>. It can be seen that  $\Psi_t = 0$  for  $r_{1A} - r_{1B} = r_{2A} - r_{2B}$ . The use of function (36) gave  $E = -0.7838 \pm 0.0007$  a.u., which is in good agreement with a value of  $-0.7830$  a.u. found<sup>68</sup> by the variational method.

For the triplet state of the hydrogen molecule, with allowance for the equipotential surface prohibition principle [see Eqn (27)], the following expression should be analysed

$$\frac{1}{r_{1A}} + \frac{1}{r_{1B}} = C; \quad (37)$$

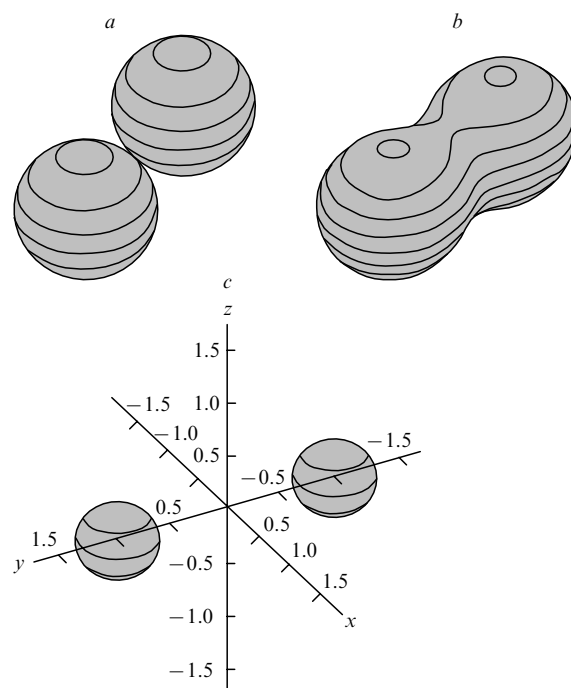


**Figure 4.** Form of the equipotential surfaces for the triplet state of a hydrogen molecule for  $C = 2$  (a),  $C < 2$  (b) and  $C > 2$  (c).

here  $C$  is any positive number, and  $r_{1A}$  and  $r_{1B}$  are the distances from electron 1 to each of the two protons located at distances  $R$  from each other. The nodal surfaces for the triplet state of the hydrogen molecule are shown in Fig. 4. When  $C = 2$  (see Fig. 4a), the equipotential surface has a dumbbell shape.

When  $C < 2$ , the point of contact between the two distorted spheres disappears and, as  $C$  successively approaches zero, every outer equipotential surface in the set under consideration becomes more and more like a sphere flattened from above and below (see Fig. 4b). This was to be expected, bearing in mind the ‘limiting transition’ of the helium atom into the triplet state with an increase in  $r_{1A}$  and  $r_{1B}$  to such an extent that the distance  $R$  between the protons can be neglected.

When  $C > 0$ , the dumbbell becomes broken into two closed topologically separate parts of the equipotential surface, the centre of each being occupied by its own proton (see Fig. 4c). When the first electron is located on one fragment of this separated surface, e.g., that concentrated around nucleus  $A$ , the positions of the second electron, not only on the same surface, but also on the other part of this surface, i.e., that centred at nucleus  $B$ , are forbidden.

## V. Conclusion

The subject matter of today’s conferences on quantum chemistry and its computational applications include theoretical sections devoted to molecular spectroscopy, intermolecular interactions, quantum molecular dynamics, the modern theory of valence bonding, methods for taking into account electron correlation, achievements of density functional theory, computational quantum-chemical prediction of the properties of new materials for emerging technologies, the biological activity of compounds, the results of the analysis of elementary processes in condensed media, calculation of potential energy surfaces, elucidation of the mechanisms of chemical reactions, and the development of new quantum chemical methods for studying the electronic structures of molecular systems in their ground and excited states. The method of many-electron wave functions belongs to the last of these lines of research.



The current state of high-precision *ab initio* calculations cannot be considered satisfactory, despite the progress achieved. The problems of taking account of electron correlation in molecular systems with partially filled electron shells and quasi-degenerate states still have not been solved. Problems related to the mathematics also exist. If they are solved, the development of the MWF method will be substantially accelerated.

In recent years, interest in the Valence Bond (VB) method has been revived, and has been clearly depicted in a small review.<sup>69</sup> The inevitability of the revival of the VB method, which had once lost its primary position in theoretical chemistry, is a result of the fact that it is based on the chemical bond concept.

The VB theory became widespread in the 1930s owing to L. Pauling's work. However, by the 1950s, MO theory, which has developed successfully since, became more popular. Among other reasons, the loss in popularity of the VB method was due to the fact that it predicts a diamagnetic ground state with a Lewis pairing of electrons for the oxygen molecule rather than the paramagnetic state (established experimentally and reproduced by the MO method). The results of this and some other applications of the VB method were responsible for it being regarded as a failure.

The reason for the lack of success was the imperfection of an early variant of this method: at that time, the method was actually reduced to a simplified resonance variant with a non-productive counting of resonance structures. Compared with the resonance theory, even the simple MO method looked much more fruitful. Firstly, it has attracted the attention of spectroscopists (owing to a unified interpretation of optical, IR and UV spectra), radiospectroscopists (who started interpreting their EPR spectra using the new notion of 'spin density') and finally organic chemists (who recognised the reliability of the proposed qualitative explanation of the stability of diverse systems and, hence, the possibility of deliberate planning of new purpose-directed experiments).

Analysis of the reactivity of organic compounds at the time of rapid development of MO theory was carried out almost exclusively within the framework of this theory, as indicated by the exceptional popularity of the Woodward–Hoffmann rules. The MO schemes were universally preferred in the interpretation of spectroscopic data.

Undoubtedly, the skew towards MO theory has been due, among other reasons, to advances in computing machinery. In particular, the versatile quantum-chemical software package GAUSSIAN, with exceptionally high computation potential, has become universally available. Therefore, experimental chemists started to resort, more and more often, to specialists who were able to perform at least semi-quantitative quantum-chemical calculations for the systems they were interested in.

However, it has become clear with time that the MO method with full allowance for the configuration interaction is equivalent to the VB method taking into account all ionic structures. The relationship between the MO and VB methods is reflected in the growing trend to localise the calculated MO, although consideration of localised orbitals implies the VB theory.

The use of the MO method is more expedient in cases where electron delocalisation is essential. In calculations on large molecules, the MO method is preferred, as the obtained wave functions are less cumbersome than those of the VB method.

However, using the VB theory, one can more easily represent the electron redistribution during chemical transformations or mechanisms of forming of activation barriers in diverse chemical processes by means of correlation diagrams of valence bonds. These diagrams allow one to predict the activation barriers proceeding from the structural parameters, ionisation potentials and electron affinities of the reactants, the singlet–triplet splitting energies of the chemical bond being cleaved, the substituent and solvation effects, *etc.* Resorting to VB models resulted in the discovery of a new type of bonding in metal clusters (ferromagnetic bonding), determination of the structures of unusual transition metal complexes, and so on. The above is indicative of the

significant role played by the VB method in theoretical chemistry.<sup>69</sup>

Experimental chemists are unlikely to do away with using vivid resonance structures. However, it should be borne in mind that two approaches to the description of the electronic structure and physicochemical properties of molecules exist that fruitfully supplement rather than exclude each other.

In order to increase the reliability of the results of any quantum-chemical method, a more adequate description of the electron motion is required. From general considerations, taking account of the correlation in motion of 'separate' electron pairs is expected to be most important. This assumption is based on the fact that the Pauli principle generally forbids three or more electrons from being at the same point in the configuration space, thus decreasing the correlation error for such electron groups (conglomerates). Therefore, many modern techniques for investigation correlation effects imply the 'intuitive concept' of electron pairs in some form.

The exclusion by the Pauli principle of ternary electron collisions clearly demonstrates that this principle has something in common with nodal surfaces. We attempted to reflect the correspondence between the Pauli exclusion principle and nodal surfaces, which can hardly provoke serious objections, by means of a simple physical hypothesis, according to which two electrons with parallel spins cannot occur on the same equipotential surface.

Undoubtedly, this hypothesis requires comprehensive verification and further development. It might prove untenable for complex molecular systems, or perhaps, it will have to be corrected or modified. In any case, the problem definition will remain topical. Successful solution of this problem will open up new prospects for the elaboration of high-precision quantum-chemical methods. Indeed, of the multitude of sets of antisymmetrical MWFs that can serve as the basis for finding approximate solutions to the Schrödinger equation, this method allows one to choose reliably the optimal solution for each particular system.

Some MWF nodal surfaces (including those for the degenerate states) can be established *a priori* by a generalised graph-theoretical method, according to which the MWF nodes are classified to an accuracy of equivalence and the configuration space is split into the smallest number of regions of constant sign.<sup>70</sup> The Fermi correlation of electrons with parallel spins, caused by the Pauli principle and related to the geometry of the MWF nodal surfaces, has a special significance.<sup>71,72</sup> Of interest are a new type of correlation effect, called geometrical,<sup>71</sup> which are closely related to electron density minima in the excited states of a two-electron atom. These effects result in the prohibition of seemingly quite plausible electronic configurations, as one of the electrons is 'ejected' from the inner three-dimensional region of the coordinate space when another electron is located at a definite distance from the atomic nucleus.

Detailed analysis of the wave functions of the beryllium atom in a Hartree–Fock approximation has shown<sup>73</sup> that particular quantum-chemical calculations may give rise to false nodes for the functions obtained due to the incompleteness and specificity of the basis set, limited convergence of the iteration procedure, and so on. It should also be borne in mind that even if the search for fundamentally new avenues in modern quantum chemistry does not always prove successful, this field of science would still gain new valuable experience.

The Pauli exclusion principle seems to be common knowledge, so no comments on this point are needed. However, in actual fact, it turns out that even the question 'what does the Pauli principle exclude in a particular many-electron system?' has not been answered as yet. The difficulty of understanding the Pauli principle was noted a long time back by L. de Broglie: '... currently, it is almost impossible to understand how two identical particles forbid each other to occupy the same state'.<sup>74</sup> R. Feynman expressed an even more categorical opinion concerning this principle: 'Probably, this is one of the few items in physics where

the rule formulation is very simple, but no equally simple explanation has been found. Apparently, this means that we do not fully understand the principle that underlies it. Let us consider it, as yet, to be a Law of the Universe'.<sup>75</sup>

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<sup>d</sup> — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*

<sup>e</sup> — *Russ. J. Phys. Chem. (Engl. Transl.)*

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# Heterogeneous catalytic redox reactions in the chemistry and technology of the nuclear fuel cycle

A V Ananiev, I G Tananaev, V P Shilov

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**Abstract.** The published data on heterogeneous catalytic redox reactions involving uranium, neptunium, plutonium and americium ions in acidic and alkaline media as well as on catalytic decomposition of some organic and nitrogen-containing inorganic components of liquid inorganic wastes are generalised. The results of kinetic studies of these reactions are analysed and possible mechanisms are considered. The bibliography includes 93 references.

## I. Introduction

The perfection of technological processes aimed at increasing the productivity and reducing production costs is of particular interest in the realisation of any industrial chain. The overgrowing environmental demands call for minimisation of industrial wastes, development of non-waste technologies and a switch, in a more remote perspective, to completely closed operation cycles.

In the chemical industry, these problems have long and successfully been solved by resort to technologies based on the use of catalytic reactions. To date, it is next to impossible to find an area of 'great' chemistry, be it sulfuric acid production, ammonia synthesis, petroleum cracking, fundamental organic synthesis or any other field, where catalysts are not employed. It is not incidental therefore that the branch of chemistry concerned with the study of catalytic reactions and properties of catalytic materials long ago became an independent science.

Radiochemical technology, which is an integral part of the nuclear fuel cycle, includes the fabrication of nuclear fuel compositions, reprocessing of the used nuclear fuel aimed at isolation of a fissile material for its reuse and separation of nuclear wastes for storage and safe disposal. The majority of existing technologies of hydrometallurgy of nuclear fuel and aqueous methods for reprocessing of the used heat-releasing elements are based on redox reactions intended for the stabilisation of components of the

dissolved fuel in predetermined oxidation states suitable for their separation, isolation and purification.

Manufacture of uranium, neptunium and americium in predetermined oxidation states is sometimes complicated by low rates of redox reactions, especially if non-salt-forming molecular reducing agents are used. Heterogeneous catalysts are used to increase the rates of these reactions.

In practical terms, final reprocessing of radioactive wastes, which includes fractionation and vitrification in glass or ceramic matrices as the back end of the fuel cycle, cannot successfully be implemented without preliminary removal of organic and nitrogen-containing inorganic impurities (*e.g.*, oxalic acid, complexons, urea, hydrazine, ammonium nitrate, excess nitric acid, *etc.*) from the so-called 'water-tail' fractions. The problem of their removal can also be solved using heterogeneous catalysis as a means to increase the rates of oxidative decomposition of hazardous impurities as components of liquid radioactive wastes.

To date, a large body of experimental results has been accumulated concerned with the studies of heterogeneous catalytic redox reactions of actinide ions and the use of catalysts for the decomposition of some organic and nitrogen-containing inorganic compounds in aqueous media. However, the literature data are often fragmentary and incomplete. Therefore, the present review is an attempt at systematic generalisation of the published data on heterogeneous catalytic redox reactions already applied, or potentially applicable, for radiochemical technological wet processes.

## II. Heterogeneous catalytic redox reactions of actinide ions in aqueous solutions

Heterogeneous catalytic processes can successfully be used for the stabilisation of predetermined valent forms of actinides in technological solutions at radiochemical plants. Activated charcoal or finely dispersed platinum on an inert support with a well-developed surface are commonly employed as heterogeneous catalysts. The role of a support is played by activated charcoal, alumina, silica gel or ion-exchange resins. Catalytic systems based on nickel, PdS, Re<sub>2</sub>S<sub>7</sub>, *etc.*, have also been investigated.

### 1. Uranium

The reduction of U(VI) to U(IV) is the most important process in the hydrometallurgy of the nuclear fuel cycle. Several methods for the conversion of U(VI) into U(IV) in a solution exist, *viz.*, electrochemical, photochemical and heterogeneous catalytic. The latter makes use of molecular hydrogen, hydrazine, formic acid and other compounds as reducing agents.

**A V Ananiev, V P Shilov** A N Frumkin Institute of Physical Chemistry and Electrochemistry, Russian Academy of Sciences, Leninsky prosp. 31, 119991 Moscow, Russian Federation. Fax (7-495) 952 53 08, tel. (7-495) 335 17 30, e-mail: ananiev@ipc.rssi.ru (A V Ananiev), tel. (7-495) 330 41 70, e-mail: shilov@ipc.rssi.ru (V P Shilov)

**I G Tananaev** V I Vernadsky Institute of Geochemistry and Analytical Chemistry, Russian Academy of Sciences, ul. Kosygina 19, 117975 Moscow, Russian Federation. Fax (7-495) 938 20 54, tel. (7-495) 137 86 50, e-mail: tananaev@geokhi.ru (I G Tananaev)

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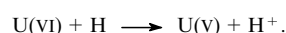
The reduction of U(VI) with hydrogen was carried out in carbonate solutions at 100–150 °C in the presence of a nickel catalyst (3–10 g litre<sup>-1</sup>).<sup>1–3</sup> The U(IV) formed precipitated as  $\text{UO}_2 \cdot x\text{H}_2\text{O}$ . It was found that the reduction rate was proportional to  $p_{\text{H}_2}^{0.5}$  ( $p_{\text{H}_2}$  is partial hydrogen pressure). Thus, one can suggest the following scheme of the process. Hydrogen is dissolved and adsorbed on the nickel surface:



The adsorbed hydrogen undergoes dissociation:



The hydrogen atoms react with U(VI) adsorbed on the adjacent sites on the surface of the nickel catalyst:



The pentavalent uranium disproportionates both on the nickel surface and in the solution:



Considering that equilibria (1)–(3) are attained sufficiently fast, the kinetic equation for this process appears as:

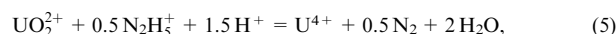
$$\frac{d[\text{U(IV)}]}{dt} = K[\text{H}_2]_{\text{gas}}^{0.5}[\text{U(VI)}] = Kp_{\text{H}_2}^{0.5}[\text{U(VI)}].$$

Large-scale production of U(IV) in acid solutions by reduction with hydrogen under pressure with Pt/SiO<sub>2</sub> as a catalyst was realised at the La Hague nuclear installation (France).<sup>4</sup>

The hydrogen technology was recommended for the production of  $\text{UO}_2$  sols.<sup>3</sup> Treatment of a solution of uranyl nitrate (pH ~ 1) with hydrogen was carried out at 7–35 atm and 30–80 °C in the presence of platinum on charcoal.

The reduction of U(VI) with hydrazine was the subject of several investigations.<sup>5–8</sup> Thus U(VI) was reduced with  $\text{N}_2\text{H}_4 \cdot \text{HNO}_3$  in nitric acid solution in the presence of 0.5% Pt/Al<sub>2</sub>O<sub>3</sub><sup>5</sup> both in a static and a flow regime (on a column) at constant temperature. Analysis of gaseous reaction products revealed that no hydrogen was formed.

With regard to the reaction stoichiometry



it was noted<sup>5</sup> that one mole of U(VI) consumed ~1.5 moles of  $\text{H}^+$ , but the consumption of hydrazine exceeded 0.5 moles. In the author's opinion, decomposition of hydrazine on the catalyst yields  $\text{H}_2$ , and it is hydrogen that reduces U(VI) to U(IV) and hydrazine to ammonium ion. This conclusion seems to be erroneous, since in more recent studies<sup>9</sup> no hydrogen formation was observed upon catalytic decomposition of hydrazine on platinised catalysts in nitric acid solutions.

The kinetics of reaction (5) was studied predominantly in 1.2 M  $\text{HNO}_3$  containing 1.5 and 0.5 mol litre<sup>-1</sup> of U(VI) at 52 °C. The increase in the hydrazine concentration from 0.3 to 0.9 mol litre<sup>-1</sup> caused a pronounced increase in the reaction rate. A decrease in the  $\text{HNO}_3$  concentration from 1.2 to 0.5 mol litre<sup>-1</sup> also increased the accumulation of U(IV). In the temperature range 46–65 °C, the activation energy of this reaction for the solution under study [1.8 mol litre<sup>-1</sup> U(VI) + 1.4 mol litre<sup>-1</sup>  $\text{HNO}_3$  + 1.1 mol litre<sup>-1</sup>  $\text{N}_2\text{H}_5^+$ ] was estimated to be equal to 58 kJ mol<sup>-1</sup>. At 65 °C, the formation rate of U(IV) decreased as its concentration exceeded 0.3 mol litre<sup>-1</sup>. Presumably,<sup>5</sup> these conditions favour the oxidation of U(IV) by nitric acid.

Under conditions of column chromatography, the rate of accumulation of U(IV) diminished nearly twofold on going from 0.6 to 1.2 M  $\text{HNO}_3$ . A twofold reduction in the reaction rate was also observed upon a twofold decrease in the hydrazine concentration.

It was shown that technological solutions of U(VI) poison the catalyst. The search for impurities responsible for the decrease in

the catalytic activity did not give any positive result despite the thorough analysis of cations and compounds present in the uranium(VI) solutions prior to their purification for catalytic experiments.

The stability of the catalyst with respect to prolonged exposure to U(VI) solutions (2 mol litre<sup>-1</sup>) in 1.6 M  $\text{HNO}_3$  at 50 °C has been studied. It was found that the catalytic activity decreased as a result of platinum entrainment. The result obtained can be attributed to the improper choice of the substrate (Al<sub>2</sub>O<sub>3</sub>), which possesses limited resistance to nitric acid-containing media. Platinised SiO<sub>2</sub> was used as a catalyst for the preparation of U(IV) solutions in nitric acid.<sup>6,7</sup> Solutions of 0.42 mol litre<sup>-1</sup> U(VI) and hydrazine in 1.5–4 M  $\text{HNO}_3$  were made to react with 1% Pt/SiO<sub>2</sub> (C : R was 1 : 10<sup>†</sup> at 55–70 °C). The reaction mixture was stirred by passing nitrogen at a controlled rate. The kinetic curves for the accumulation of U(IV) in the coordinates  $\ln[c_0/(c_0 - c)]$  vs. time [where  $c_0$  is the initial concentration of U(VI) and  $c$  is the running concentration of U(IV)] are nearly straight lines, which can formally be interpreted as the first reaction order with respect to uranium(VI). Therefore, the kinetic regularities of this reaction were described by the equation:

$$-\frac{d[\text{U(VI)}]}{dt} = k'[\text{U(VI)}].$$

Here,  $k'$  (in min<sup>-1</sup>) is the frequency factor or the apparent rate constant; its value is proportional to the initial reaction rate. Obviously,  $k'$  is not a true first-order rate constant, since the initial concentrations of uranium and hydrazine in this reaction mixture are commensurable and the decrease in the concentration of the reducing reagent during the reaction cannot be insignificant. The dependence of  $k'$  on the concentration of nitric acid is well approximated by a straight line in the logarithmic coordinates with an angular coefficient of about -0.6, which can be attributed to the apparent reaction order with respect to nitric acid. However, this value does not provide an unambiguous conclusion on the involvement of hydrogen ions in the rate-determining step of the reduction, since the experiments were carried out at various ionic strengths. At the same time, it is expected that higher concentrations of  $\text{HNO}_3$  will increase the yields of nitrate complexes of uranium(VI), which manifest different (in comparison with free uranyl ions) reactivities with respect to hydrazine. Based on the general considerations, it may be assumed that the true order of this reaction with respect to  $\text{H}^+$  will be equal to -1. This conclusion is based on an assumption that only neutral  $\text{N}_2\text{H}_4$  molecules preactivated by adsorption on the surface of platinum are involved in the reaction with uranium(VI). The yield of the molecular form of hydrazine is inversely proportional to  $[\text{H}^+]$ , which should result in the -1 order of this reaction with respect to hydrogen ions. However, the catalytic activation of  $\text{N}_2\text{H}_5^+$  ions and, as a consequence, the zero order of the reaction with respect to  $\text{H}^+$  cannot be ruled out either.

Changes in the concentration of the reducing agent in the range 0.5–2 mol litre<sup>-1</sup> do not influence the reaction rate, *i.e.*, the reaction is of the zero order with respect to hydrazine. The activation energy of the reduction was estimated in the temperature range 55–70 °C and was equal to  $85.4 \pm 3.0$  kJ mol<sup>-1</sup>.

The increase in the platinum content on silica gel from 0.25% to 2% resulted in a monotonic increase in the reaction rate. Increases in the catalyst concentration in the reaction mixture (the C : R ratio) accelerated the reduction.

The reduction of U(VI) (0.75 mol litre<sup>-1</sup>) with hydrazine in  $\text{HNO}_3$  has been studied by Shilov *et al.*<sup>7</sup> The catalyst was prepared by impregnation of silica gel (grain size 0.5–1 mm) with  $\text{H}_2\text{PtCl}_6$  followed by drying and treatment with a hot solution of hydrazine hydrate (2–4 mol litre<sup>-1</sup>). The experiments

<sup>†</sup> C : R is the ratio of the amount of the catalyst (in g) to the volume of the reaction mixture (in ml).

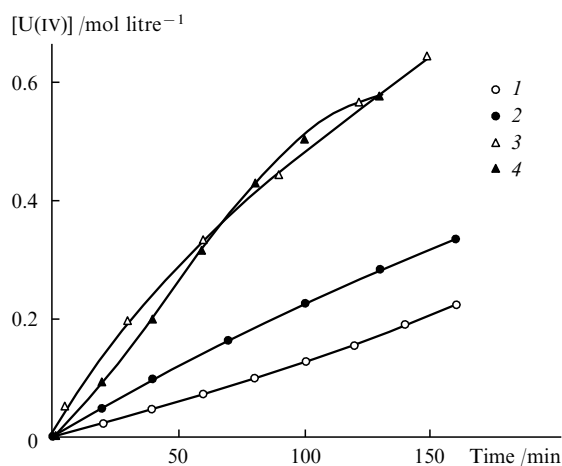


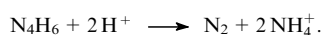
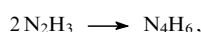
**Figure 1.** Kinetic curves of the reduction of U(VI) with hydrazine in the presence of Pt/SiO<sub>2</sub> containing different concentrations of Pt.<sup>7</sup> [U(VI)]<sub>0</sub> = 0.75 mol litre<sup>-1</sup>, [HNO<sub>3</sub>]<sub>0</sub> = 2.0 mol litre<sup>-1</sup>, [N<sub>2</sub>H<sub>5</sub><sup>+</sup>]<sub>0</sub> = 1.0 mol litre<sup>-1</sup> at 58.5 °C, C: R = 1:10; Pt content (%): (1) 0.76, (2) 0.83, (3) 1.0, (4) 1.0 (another sample).

were carried out in a thermostated cell mounted onto a shaker. The kinetic curves for U(IV) accumulation represent virtually straight lines up to the concentration of 0.5 mol litre<sup>-1</sup>, which testified to a zero order of the reaction with respect to the metal (Fig. 1). For certain catalyst samples, the kinetic curves occupied an intermediate position between those for the zero and first order. In solutions of U(VI) (0.75 mol litre<sup>-1</sup>) containing 2 mol litre<sup>-1</sup> HNO<sub>3</sub> and 1–1.5 mol litre<sup>-1</sup> N<sub>2</sub>H<sub>5</sub><sup>+</sup>, about 0.55 mol litre<sup>-1</sup> of U(IV) was usually formed when the reaction was carried out for 2 h at 58 °C in the presence of 1% Pt/SiO<sub>2</sub> as a catalyst (C: R = 1:10). The reproducibility of the results with the same catalyst sample was satisfactory. The rate of formation of U(IV) decreased with a decrease in the platinum concentration on the support. A decrease in the N<sub>2</sub>H<sub>5</sub><sup>+</sup> concentration to 0.75 mol litre<sup>-1</sup> or an increase in the HNO<sub>3</sub> concentration to 3–4 mol litre<sup>-1</sup> decelerated this process. Altogether, 1.2 mol of U(IV) was formed per mol of hydrazine. Thus, the reaction (5) paralleled catalytic decomposition of hydrazine or its reaction with HNO<sub>3</sub> in this system. It is known that the latter process yields N<sub>2</sub>, N<sub>2</sub>O, NH<sub>4</sub><sup>+</sup> and HN<sub>3</sub> (see Ref. 10). However, it was shown in special experiments that the gas evolved contained no HN<sub>3</sub>. The activation energy of this reaction was measured in the temperature range 23–66 °C and was equal to 84 kJ mol<sup>-1</sup>.

It may be assumed that this reaction proceeds through preliminary sorption of the reactants on the catalyst and is followed by their reaction



In this case, metallic platinum plays the role of a bridge in the electron transfer from hydrazine to uranyl. U(V) disproportionates into U(IV) and U(VI) [reaction (4)], the radicals react with U(VI), NO<sub>3</sub><sup>-</sup> and one another:



In a series of experiments, leaching of silicon from the catalysts was studied. The concentration of silicon in a solution of U(VI) and hydrazine in 1 M HNO<sub>3</sub> in the presence of 1% Pt/SiO<sub>2</sub> (C: R = 1:10; 58 °C) amounted to 13, 36 and 58 mg litre<sup>-1</sup> after 1, 2 and 3 h, respectively. An increase in HNO<sub>3</sub> concentration diminished leaching.

The catalyst 1% Pt/SiO<sub>2</sub> was used for the reduction of U(VI) with hydrazine in H<sub>2</sub>SO<sub>4</sub> solutions.<sup>8</sup> The kinetic curves are well described by the first-order equation with respect to U(VI) over the

whole range of experimental conditions. The reaction rate decreased slightly on going from 0.1 to 1.0 M H<sub>2</sub>SO<sub>4</sub>. The increase in the hydrazine content from 0.1 to 0.4 mol litre<sup>-1</sup> only slightly increased the rate constant. The activation energy in the temperature range 30–60 °C was equal to 69.0 ± 4.0 kJ mol<sup>-1</sup>. The reduction of uranium(VI) in H<sub>2</sub>SO<sub>4</sub> solutions was not complicated by reverse oxidation of uranium(IV) and catalytic decomposition of hydrazine, which became apparent only at the temperatures above 60 °C, whereas the reduction of U(VI) occurred at a much higher rate even at 30 °C. The method described can be used for the preparation of H<sub>2</sub>SO<sub>4</sub> solutions of uranium(IV) with concentrations of up to 0.25 mol litre<sup>-1</sup> with respect to the metal. Further increase in uranium concentration is impossible due to the limited solubility of U(SO<sub>4</sub>)<sub>2</sub>.

The mechanism of U(VI) reduction by hydrazine in H<sub>2</sub>SO<sub>4</sub> solutions is similar to that in HNO<sub>3</sub> solutions in general features.

The applicability of formic acid for the reduction of uranium(VI) in the presence of various catalysts was studied. Thus, 2%–5% Pt on Al<sub>2</sub>O<sub>3</sub> was used as a catalyst in the preparation of U(IV) in HNO<sub>3</sub> solutions containing HCO<sub>2</sub>H and (NH<sub>2</sub>)<sub>2</sub>CO.<sup>11</sup>

The catalyst Pt/Al<sub>2</sub>O<sub>3</sub> was used for the reduction of U(VI) (0.1 mol litre<sup>-1</sup>) in 0.4 M HCO<sub>2</sub>H at 46–59 °C. (NH<sub>2</sub>)<sub>2</sub>CO was added to the solution to remove traces of HNO<sub>2</sub>.<sup>12</sup> The reduction rate was found to be proportional to [U(VI)] and did not depend on [HCO<sub>2</sub>H].

The method for the reduction of U(VI) by formic acid in HNO<sub>3</sub> solutions (0.5 mol litre<sup>-1</sup>) in the presence of a platinum catalyst has been patented in Germany.<sup>13</sup> Virtually complete conversion of UO<sub>2</sub>(NO<sub>3</sub>)<sub>2</sub> (100 g litre<sup>-1</sup> of uranium) into U(NO<sub>3</sub>)<sub>4</sub> served as an example; the residual content of U(VI) was less than 10 mg litre<sup>-1</sup>.

Platinum-group catalysts were used for the preparation of U(IV) in HNO<sub>3</sub> solutions.<sup>7,14,15</sup> It was found that formic acid containing no hydrazine failed to reduce U(VI) in 2 M HNO<sub>3</sub> in the presence of 1% Pt/SiO<sub>2</sub> (58 °C).<sup>7</sup> The addition of N<sub>2</sub>H<sub>5</sub><sup>+</sup> resulted in the formation of U(IV), the threshold concentration of hydrazine being ~0.02 mol litre<sup>-1</sup>. The increase in [N<sub>2</sub>H<sub>5</sub><sup>+</sup>] up to 0.05 mol litre<sup>-1</sup> favoured accelerated accumulation of U(IV). Further increase in the hydrazine concentration up to 0.1 mol litre<sup>-1</sup> had little effect on the reaction rate. The reaction was decelerated with an increase in HNO<sub>3</sub> concentration; higher concentrations of HCO<sub>2</sub>H increased the reduction rate. In the temperature range 17–65 °C, the activation energy was 48 kJ mol<sup>-1</sup>.

The consumption of 1 mole of HCO<sub>2</sub>H (with consideration of hydrazine consumed) was accompanied by formation of 0.83 mole of U(IV), i.e., the catalytic reduction occurred mainly according to the reaction:



This mechanism includes sorption of UO<sub>2</sub><sup>2+</sup> and HCO<sub>2</sub>H on the active sites of the catalyst with subsequent formation of UO<sub>2</sub><sup>+</sup> and the radical ·CO<sub>2</sub>H. This radical reduces UO<sub>2</sub><sup>2+</sup> and UO<sub>2</sub><sup>+</sup>. In addition, disproportionation of UO<sub>2</sub><sup>+</sup> occurs [reaction (4)]. In this reaction, the role of hydrazine is confined to stabilisation of U(IV) and prevention of the reaction of HCO<sub>2</sub>H with HNO<sub>2</sub> by fast reduction of trace amounts of the latter and nitrogen oxides. Primary and secondary amines and (NH<sub>2</sub>)<sub>2</sub>CO also serve as HNO<sub>2</sub> acceptors, however, control experiments have shown that urea does not replace hydrazine in the catalytic reaction of U(VI) with HCO<sub>2</sub>H due to the low binding rate of HNO<sub>2</sub>. The reduction of U(VI) by formic acid in the presence of 1% Pt/VP-1AP anion-exchange resin as a catalyst was studied. Its efficiency was found to be similar to that of 1% Pt/SiO<sub>2</sub>.<sup>7</sup>

In addition to platinum-group catalysts, Re<sub>2</sub>S<sub>7</sub> (see Refs 16 and 17) and PdS were used for the reduction of U(VI).<sup>18</sup> Dirhenium heptasulfide proved to be an efficient catalyst in the reactions of U(VI) with formaldehyde, formic acid and ethanol. These studies were carried out in acidic solutions at temperatures of 20–100 °C with stirring. It was found that U(VI) was com-

pletely reduced by formaldehyde at temperatures above 80 °C. The reduction was complete in 20–30 min in the presence of  $\text{Re}_2\text{S}_7$  (0.2–0.3 g per g of uranium) and a threefold excess of  $\text{HCHO}$ .  $\text{Cl}^-$  ions decelerated, while  $\text{F}^-$  ions accelerated this reaction. The concentration of  $\text{H}^+$  had little effect on the reaction rate. Ethanol and formic acid reacted with  $\text{U(VI)}$  at a slower rate than formaldehyde.

The kinetics of the reaction of  $\text{U(VI)}$  with  $\text{C}_2\text{H}_5\text{OH}$  in  $\text{H}_2\text{SO}_4$  solutions in the presence of  $\text{Re}_2\text{S}_7$  was studied at 50.6–90 °C.<sup>17</sup> The content of  $\text{Re}_2\text{S}_7$  was  $\sim 0.8$  g per g of uranium. Under these conditions, the reaction was of the first order with respect to  $\text{U(VI)}$ . The increase in  $[\text{C}_2\text{H}_5\text{OH}]$  from 0.17 to 2.52 mol litre<sup>-1</sup> favoured a nearly proportional increase in the reaction rate. The increase in  $[\text{H}_2\text{SO}_4]$  from 0.81 to 1.53 mol litre<sup>-1</sup> had no effect on the reaction rate. The activation energy of this reaction was 69.4 kJ mol<sup>-1</sup>.

Palladium sulfide was used as a catalyst in the reduction of  $\text{U(VI)}$  by formaldehyde in solutions of sulfuric, nitric or hydrochloric acids.<sup>18</sup> The concentration of uranium in the starting solutions was 50 g litre<sup>-1</sup> (0.2 mol litre<sup>-1</sup>). As the specific surface of powdered  $\text{PdS}$  was  $\sim 3.5$  m<sup>2</sup> g<sup>-1</sup>, more than 0.8 g  $\text{PdS}$  per g of uranium was required for efficient reduction. The efficiency of uranyl reduction depended on the anion present in the solution and increased in the series chloride < nitrate < sulfate. Fluoride ions increased the reduction rate. At a concentration of  $\text{HF}$  up to 1.5 mole per mole of uranium, all the  $\text{U(IV)}$  was present in the solution. Further increase in the  $\text{HF}$  concentration resulted in partial precipitation of  $\text{U(IV)}$  in the form of  $\text{UF}_4 \cdot x\text{H}_2\text{O}$ .

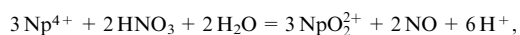
The catalytic reduction of uranyl by formaldehyde occurred at temperatures above 50 °C. In  $\text{H}_2\text{SO}_4$  solutions, the concentration of formaldehyde should be in the range from 2 to 3 moles per mole of uranium. The change in  $\text{H}_2\text{SO}_4$  concentration from 0.3 to 1 mol litre<sup>-1</sup> had virtually no effect on the yield of  $\text{U(IV)}$ .

The oxidation of formaldehyde by uranyl ions in solutions yields formic acid. Under similar conditions,  $\text{HCO}_2\text{H}$  competed favourably as a reducing agent with formaldehyde. Uranyl is not reduced by methanol. Repeated use of the catalyst demonstrated that  $\text{PdS}$  was not poisoned in the aqueous solutions under study and it could be employed many times without recourse to regeneration.

## 2. Neptunium

The known heterogeneous catalytic reactions of neptunium occur in acidic and alkaline media. Nitric acid plays the role of an oxidant, while hydrogen, hydrazine, hydroxylamine, formic acid and formaldehyde are reducing agents. Platinum-on-platinum, platinum-on-silica gel, platinum black and support-free palladium are used as catalysts.

Nitric and nitrous acids oxidise neptunium(IV) to a hexavalent state according to the reactions:<sup>19</sup>



However, these thermodynamically allowed reactions are extremely slow for kinetic reasons and the fact that the accumulation of  $\text{Np(V,VI)}$  over tens of hours in  $\text{HNO}_3$  solutions is insignificant can be associated with radiolytic rather than chemical processes.<sup>20,21</sup> Being quite stable in 0.5–3 M  $\text{HNO}_3$ , neptunium(IV) undergoes fast oxidation in the presence of 1%  $\text{Pt/SiO}_2$  as a solid-phase catalyst.<sup>22</sup> The catalytic oxidation of neptunium(IV) in  $\text{HNO}_3$  solutions takes place even in the presence of antinitrite reagents, such as  $\text{NH}_2\text{SO}_3\text{H}$ , although in this case the reaction rate is somewhat smaller. The kinetics of heterogeneous catalytic oxidation of  $\text{Np(IV)}$  in  $\text{HNO}_3$  solutions has been studied.<sup>22</sup> This reaction yields  $\text{Np(V)}$  with admixture of  $\text{Np(VI)}$  (up to 5%); the content of the latter depends on the concentrations of nitric and nitrous acids. The oxidation of neptunium(IV) by nitric acid follows first-order kinetics with respect to  $\text{Np(IV)}$  over the whole range of experimental conditions. An increase in the

catalyst concentration results in a monotonic increase in the reduction rate. The linear dependence  $k'$  vs.  $(\text{C}:\text{R})$  in logarithmic coordinates allows the estimation of the apparent reaction order with respect to the active sites of the catalyst. For the reaction under consideration, it is equal to  $0.97 \pm 0.07$  in the  $\text{C}:\text{R}$  range under study (0.025–0.1). The oxidation rate of  $\text{Np(IV)}$  by nitric acid decreases with an increase in the solution acidity from 0.5 to 4.0 mol litre<sup>-1</sup>  $[\text{H}^+]$  at a constant concentration of nitrate ions ( $[\text{NO}_3^-] = 0.5$  mol litre<sup>-1</sup>). The linear dependence of the rate constants on the  $\text{H}^+$  concentration in the logarithmic coordinates has an angular coefficient corresponding to the apparent reaction order of  $0.7 \pm 0.1$  with respect to  $\text{H}^+$ . The increase in the total concentration of nitrate ions in the concentration range 0.5–4.0 mol litre<sup>-1</sup> at constant acidity ( $[\text{H}^+] = 0.5$  mol litre<sup>-1</sup>) causes a slight increase in the reaction rate which corresponds to the apparent reaction order of  $0.25 \pm 0.07$  for  $\text{NO}_3^-$ . The increment in  $[\text{HNO}_3]$  in the range 0.5–4.0 mol litre<sup>-1</sup> slows down the reaction up to its complete cessation, which occurs at  $[\text{HNO}_3] > 4.0$  mol litre<sup>-1</sup>. The apparent reaction order for nitric acid varies from  $-0.3$  at low  $[\text{HNO}_3]$  to  $-3.3$  at a concentration of  $\text{HNO}_3 > 3$  mol litre<sup>-1</sup>, which suggests a complex type of heterogeneous catalytic interaction in the  $\text{Np(IV)}-\text{HNO}_3-\text{Pt/SiO}_2$  system. The deceleration of the catalytic oxidation of  $\text{Np(IV)}$  in the presence of sulfamic acid can be attributed to the effect of nitrous acid formed in one of the reaction steps, which increases the rate of the catalytic oxidation of neptunium(IV).

The dependence of the apparent activation energy ( $E^*$ ) on the concentration of nitric acid has a complex form.

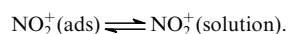
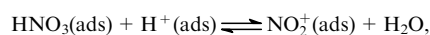
| $[\text{HNO}_3]$<br>/mol litre <sup>-1</sup> | $E^*$<br>/kJ mol <sup>-1</sup> | $[\text{HNO}_3]$<br>/mol litre <sup>-1</sup> | $E^*$<br>/kJ mol <sup>-1</sup> |
|----------------------------------------------|--------------------------------|----------------------------------------------|--------------------------------|
| 0.5                                          | 60.1                           | 2.0                                          | 83.3                           |
| 1.0                                          | 61.0                           | 3.0                                          | 85.1                           |

These data show that an abrupt increase in  $E^*$  (by more than 20 kJ mol<sup>-1</sup>) occurs in the concentration range of  $\text{HNO}_3$  of 1.0–2.0 mol litre<sup>-1</sup> where the change in the reaction mechanism apparently occurs.

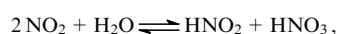
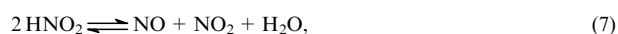
The oxidative properties of nitric acid are usually considered in relation to the oxidising effect of nitroyl cations ( $\text{NO}_2^+$ ) present in nitric acid solutions in a certain equilibrium concentration.<sup>10,23,24</sup> The  $\text{NO}_2^+$  species are formed in the solution as a result of a fast equilibrium reaction:



One should not rule out the possibility of the formation of nitroyl ions in the system under consideration as a result of fast heterogeneous reactions.



The fact that the catalytic oxidation of  $\text{Np(IV)}$  is decelerated in the presence of antinitrite reagents suggests that  $\text{HNO}_2$  or one of its transformation products is involved in the formation of an activated complex on the surface of the catalyst. Taking into account the disproportionation equilibrium of  $\text{HNO}_2$  and  $\text{NO}_2$ ,



the following scheme for heterogeneous catalytic conversions in the  $\text{Np(IV)}-\text{HNO}_3-\text{Pt/SiO}_2$  system can be proposed:

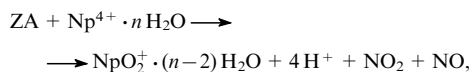


Here, Z is the active site of the catalyst;



ZA is the intermediate oxidising species (quite probably, the oxidising species are formed from  $\text{NO}_3^-$  and  $\text{HNO}_2$  and are then adsorbed on the active catalytic sites).

In dilute solutions ( $[\text{HNO}_3] < 1 \text{ mol litre}^{-1}$ ), the catalytic oxidation of neptunium(IV) can result from the following rate-limiting step:



Nitrous acid is formed in the reaction:



In the presence of antinitrite reagents,  $\text{HNO}_2$  and nitrogen oxides that are in equilibrium with it are absent from the solution. Such conditions apparently favour the direct oxidation of  $\text{Np(IV)}$  by  $\text{NO}_2^+(\text{ads})$  species, although the rate of this is much lower.

As mentioned above, the mechanism of this reaction markedly changes in the  $[\text{HNO}_3]$  range  $1-2 \text{ mol litre}^{-1}$ . Here, the concentration of  $\text{Np}^{4+} \cdot n\text{H}_2\text{O}$  becomes negligibly small as a result of complexation with nitrate ions.<sup>25,26</sup> Under these conditions, it is nitrate complexes of neptunium(IV) that are the only oxidisable species. The formation of neptunium(V) dioxo cation from the aqua-ions  $\text{Np}^{4+} \cdot n\text{H}_2\text{O}$  should occur more easily than from the nitrate  $\text{Np(IV)}$  complex where the  $\text{H}_2\text{O}$  molecules are partly displaced from the coordination sphere of Np by nitrate ions. Therefore, the increase in  $[\text{HNO}_3]$  above  $1 \text{ mol litre}^{-1}$  is accompanied by a significant decrease in the oxidation rate and an increase in the activation energy.

The effect of neptunium(IV) concentrations on the yield of neptunium(III) in  $\text{HClO}_4$  solutions under the action of hydrogen in the presence of a platinum-on-platinum catalyst using  $^{237}\text{Np}$  and  $^{239}\text{Np}$  was studied.<sup>27</sup> The degree of neptunium oxidation was established using extraction with tenoyltrifluoroacetone (TTA) in xylene:  $\text{Np(IV)}$  was extracted into the organic phase and  $\text{Np(III)}$  remained in the aqueous solution. The concentration of neptunium was determined from  $\alpha$ - ( $^{237}\text{Np}$ ) and  $\gamma$ - ( $^{239}\text{Np}$ ) activities. It was shown that at neptunium concentrations above  $10^{-3} \text{ mol litre}^{-1}$  in  $1 \text{ M HClO}_4$  its reduction to  $\text{Np(III)}$  was virtually complete. The contribution of  $\text{Np(III)}$  diminished with a decrease in the total neptunium concentration; no reduction of  $\text{Np(IV)}$  took place when its concentration dropped below  $10^{-8} \text{ mol litre}^{-1}$ . Neither purification of hydrogen by activated copper and pyrogallol, nor the prolongation of the reaction time with hydrogen to 3 h favoured this process. It was first suggested that if reoxidation of  $\text{Np(III)}$  that had been generated on the catalyst surface occurred in the bulk of the solution, the proportion of reduced neptunium depended on the surface area of the catalyst. However, even a 10-fold increase in the surface area of the catalyst did not affect the proportion of reduced neptunium. It was therefore suggested that the solution contained oxidising admixtures. Their effect could be neutralised where the oxidised forms of cations with redox potentials below the  $\text{Np}^{4+}/\text{Np}^{3+}$  pair [0.155 V relative to the normal hydrogen electrode (NHE)] were added to a support-free solution of  $^{239}\text{Np}$ . The following pairs,  $\text{Zn}^{2+}/\text{Zn}$  (−0.763 V),  $\text{U}^{4+}/\text{U}^{3+}$  (−0.631 V),  $\text{Cr}^{3+}/\text{Cr}^{2+}$  (−0.41 V),  $\text{Cd}^{2+}/\text{Cd}$  (−0.403 V) and  $\text{Ti}^{4+}/\text{Ti}^{3+}$  (−0.055 V), with potentials lower than the hydrogen potential could not enhance  $^{239}\text{Np(IV)}$  reduction. However support-free  $^{239}\text{Np(IV)}$  was quantitatively reduced to a trivalent state when  $\text{H}_2$  was passed for 2 h in the presence of  $\text{Sn(IV)}$  ( $10^{-2} \text{ mol litre}^{-1}$ ). At a concentration of tin(IV) of  $10^{-3} \text{ mol litre}^{-1}$ , its effect began to fade away and at concentrations  $< 10^{-4} \text{ mol litre}^{-1}$  no  $\text{Np(III)}$  could be detected. It should be noted that the results of these experiments are rather obscure, since oxidised forms of the added cations reacted with neither  $\text{Np(III)}$  nor hydrogen. In our opinion, it is adsorption of  $\text{H}_2$  and its dissociation into hydrogen atoms that occur on the platinum surface [reactions (1)–(3)] and part of the H atoms are desorbed and pass into the solution. Pulse radiolysis of  $\text{Np(III)}$  in  $1 \text{ M HClO}_4$  revealed<sup>28</sup> that  $\text{Np(III)}$  is oxidised by

hydrogen atoms at a rate of  $6 \times 10^7 \text{ litre mol}^{-1} \text{ s}^{-1}$ . Thus, the hydrogen atoms leaving the platinum surface convert  $\text{Np(III)}$  into  $\text{Np(IV)}$ . The oxidation of  $\text{Np(III)}$  by perchloric acid should not be ruled out either.

The effect of  $[\text{HClO}_4]$  on the reduction of  $\text{Np(IV)}$  has been studied.<sup>27</sup> It was found that the fraction of  $\text{Np(III)}$  decreased with a decrease in  $[\text{HClO}_4]$  and no reduction of  $5 \times 10^{-7}$  or  $4 \times 10^{-3} \text{ mol litre}^{-1}$  solutions of  $^{237}\text{Np(IV)}$  occurred in  $2 \times 10^{-3} \text{ M HClO}_4$ . The absorption spectrum of the latter solution was similar to that of  $\text{Np(IV)}$  hydroxide. A decrease in yields of  $\text{Np(III)}$  seems to be due to hydrolysis of  $\text{Np(IV)}$ , which brings about a shift of the potential of  $\text{Np(IV)}/\text{Np(III)}$  to a more negative region. This argument seems tenable. Thus calculations performed with consideration of  $\text{Np(IV)}$  hydrolysis constants (see Ref. 29) gave a more negative potential of the  $\text{Np(IV)}/\text{Np(III)}$  pair at  $[\text{H}^+] = 2 \times 10^{-3} \text{ mol litre}^{-1}$  than that of the  $\text{H}_2/\text{H}^+$  pair.

Hydrazine in the presence of  $\text{Pt/SiO}_2$  was also used for the reduction of  $\text{Np(VI)}$  and  $\text{Np(V)}$  in nitric acid.<sup>30</sup> Upon exposure to a catalyst (0.25%  $\text{Pt/SiO}_2$  or 2%  $\text{Pt/SiO}_2$ ) (C : R = 1 : 40 at  $15^\circ\text{C}$ ), the rate of reduction of  $\text{Np(VI)}$  ( $2.5 \times 10^{-4} \text{ mol litre}^{-1}$ ) in  $2 \text{ M HNO}_3$  containing  $\text{N}_2\text{H}_5\text{NO}_3$  ( $1 \times 10^{-3} \text{ mol litre}^{-1}$ ) depended on the intensity of stirring, and the reaction occurred under diffusion control. An increase in the rate of mechanical stirring in order to attain the kinetic regime failed because of attrition wear of the catalyst. The kinetic curves were rectified in semilogarithmic coordinates. The values of the first-order rate constants calculated from the slopes of the straight lines prompted the following conclusions. The increase in the platinum content on silica gel from 0.25 to 1% caused an increase in the reduction rate, while further increases in the platinum concentration had virtually no effect on the reaction rate. The rate constant changed in a virtually linear manner with a change in the C : R ratio as could be expected for the reaction occurring on a surface. The increase in  $[\text{HNO}_3]$  from 1 to  $2 \text{ mol litre}^{-1}$  slightly inhibited this process, while the increase in hydrazine concentration in the range  $(0.1-100) \times 10^{-3} \text{ mol litre}^{-1}$  accelerated it. At  $15-40^\circ\text{C}$ , the activation energy was about  $19 \text{ kJ mol}^{-1}$ , i.e., typical of reactions whose rates are diffusion-controlled.<sup>31</sup>

Upon addition of a catalyst ( $\text{Pt/SiO}_2$ ) to solutions of  $\text{Np(V)}$  and hydrazine in  $\text{HNO}_3$  at  $30-40^\circ\text{C}$ , the formation of  $\text{Np(IV)}$  occurred. The rate of the reduction was virtually independent of the intensity of stirring of the solution with the catalyst, therefore it was easy to select the stirring regime allowing the experiments to be carried out under kinetic control. The reaction rate is described by a first-order equation with respect to  $\text{Np(V)}$ . The first-order rate constants obtained under different conditions characterised the reduction process and made it possible to estimate the contribution of each factor. First, the rate constant increased linearly with the platinum concentration on the support and the C : R ratio. Second, the rate constant increased with the acid concentration (from 0.2 to  $7 \text{ mol litre}^{-1}$ ). Third, in the range  $30-60^\circ\text{C}$  the activation energy is nearly  $32 \text{ kJ mol}^{-1}$ , which is much smaller than in the homogeneous catalytic reduction of  $\text{Np(V)}$  by hydrazine in the presence of  $\text{Mo(VI)}$  [ $100 \text{ kJ mol}^{-1}$  at  $60-88^\circ\text{C}$  (see Ref. 32)].

If the concentration of  $\text{HNO}_3$  in solution is lower than  $2 \text{ mol litre}^{-1}$ , the reduction of  $\text{Np(V)}$  is incomplete with 2% to 4% of  $\text{Np(V)}$  remaining. Complete conversion of  $\text{Np(V)}$  into  $\text{Np(IV)}$  occurred in  $4 \text{ M HNO}_3$  where the catalytic reduction of  $\text{Np(V)}$  is accompanied by simultaneous oxidation of  $\text{Np(IV)}$ . The higher extent of reduction in  $4-6 \text{ M HNO}_3$  is due to complexation with nitrate ions and the resistance of the complexes to oxidation. The rates of oxidation and reduction increase with temperature, but the degree of passage of neptunium into a hexavalent state at  $30-60^\circ\text{C}$  changes only insignificantly. However, at temperatures above  $70^\circ\text{C}$  the yields of  $\text{Np(IV)}$  decrease as a result of rapid decomposition of hydrazine in the presence of a catalyst, especially in  $0.5-2 \text{ M HNO}_3$ . The mechanism of this process is similar to that of  $\text{U(VI)}$  reduction.

In alkaline hydrazine solutions, the concentration of Np(V) did not change in the temperature range from 40 to 80 °C. Finely dispersed metallic palladium formed from palladium salts under these conditions plays the role of a catalyst in the reduction of Np(V). The Np(IV) formed precipitates as the hydroxide.<sup>33</sup> The amount of Np(V) reduced is proportional to the concentration of Pd(II). The increase in the alkali (LiOH) concentration inhibits this process. The increase in the hydrazine concentration from 0.02 to 0.2 mol litre<sup>-1</sup> in 2 M NaOH slightly increases the reduction rate. The activation energy was estimated to be equal to ~88 kJ mol<sup>-1</sup> (40–80 °C).

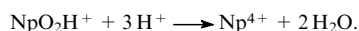
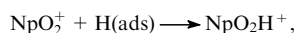
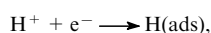
The kinetics and mechanism of the Np(V) to Np(IV) reduction by hydroxylamine in nitric acid solutions in the presence of platinum black have been studied,<sup>34</sup> although no information on the procedure of the preparation of platinum black and the grain size and the catalyst surface was provided. No reaction occurred at room temperature in the absence of the catalyst. The solutions were magnetically stirred at 22.4 °C. The reaction rate did not depend on [NH<sub>3</sub>OH<sup>+</sup>] in the range 0.25–1.87 mol litre<sup>-1</sup> and was described by the kinetic equation:

$$-\frac{d[\text{Np(V)}]}{d\tau} = k_0[\text{Np(V)}]^{0.54}[\text{H}^+]^{1.52}[\text{Pt}_{\text{black}}]^{1.01}$$

at [Np(V)] = (0.83–5.82) × 10<sup>-3</sup> mol litre<sup>-1</sup>; [H<sup>+</sup>] = 0.5–3.0 mol litre<sup>-1</sup>; [Pt<sub>black</sub>] = 2.04–10.16 g litre<sup>-1</sup>. Based on the data obtained, the following mechanism was proposed:



(this reaction is probably preceded by sorption of NH<sub>3</sub>OH<sup>+</sup> on the surface of platinum black):



Formic acid plays the role of a reducing agent; the redox potential of the pair CO<sub>2</sub>H<sup>+</sup>/HCO<sub>2</sub>H is equal to 0.199 V (NHE).<sup>35</sup> The redox potentials of the pairs Np(VI)/Np(V) and Pu(VI)/Pu(V) (1.24 and 1.02 V, respectively<sup>36</sup>) are much larger than that of formic acid. However, Np(VI) and Pu(VI) are not reduced in formate solutions.<sup>37</sup> A possible reason for the kinetic stability of hexavalent neptunium and plutonium ions in formate solutions is that formic acid, being a two-electron reducing agent, reacts with one-electron oxidants *via* formation of a radical.<sup>38</sup>



For the first step, ΔG° = 157.2 kJ mol<sup>-1</sup> (see Ref. 39), which is equivalent to the potential of 1.63 V, thus preventing the reduction of Np(VI) and Pu(VI). The above-said holds for Np(V), Pu(IV) and U(VI), since the redox potentials of the Np(V)/Np(IV), Pu(IV)/Pu(III) and U(VI)/U(IV) pairs are below 1 V.<sup>36</sup> It might be expected that the catalytic reduction of Np(VI) occurs at noticeable rates. This was demonstrated<sup>40</sup> in a study of kinetic regularities of the reaction of Np(VI,V) with HCO<sub>2</sub>H in HClO<sub>4</sub> solutions in the presence of 1% Pt/SiO<sub>2</sub>, the reaction mixture being stirred by a flow of argon.

The analysis of the kinetic curves revealed that the catalytic reduction of Np(VI) to Np(V) is a first-order reaction with respect to Np(VI) over the whole range of experimental conditions. The contributions of different factors to Np(VI) reduction were estimated based on the analysis of apparent rate constants *k*<sub>1</sub>. The increase in *k*<sub>1</sub> with an increase in the stirring intensity points to the diffusion-controlled mechanism of this reaction.

An increase in the catalyst content in the reaction mixture results in a monotonic increase in *k*<sub>1</sub>. The reaction rate increases with the concentration of formic acid in the range from 0.2 to

1.5 mol litre<sup>-1</sup>. The apparent order of the reaction with respect to HCO<sub>2</sub>H is 0.43 ± 0.01. The increase in the concentration of perchloric acid in the range from 0.2 to 4.0 mol litre<sup>-1</sup> results in a slight decrease in the reaction rate. The apparent order of this reaction with respect to HClO<sub>4</sub> is -0.26 ± 0.02. The activation energy in the temperature interval from 30 to 60 °C is 18.3 ± 0.9 kJ mol<sup>-1</sup>, which is consistent with the corresponding values for the diffusion-controlled processes.

The catalytic reduction of Np(VI) with formic acid is not stopped at the formation of Np(V), the concomitant accumulation of Np(IV) occurs in parallel (Fig. 2). The reduction rate of Np(V) does not depend on the stirring intensity, hence the reaction is kinetically controlled.

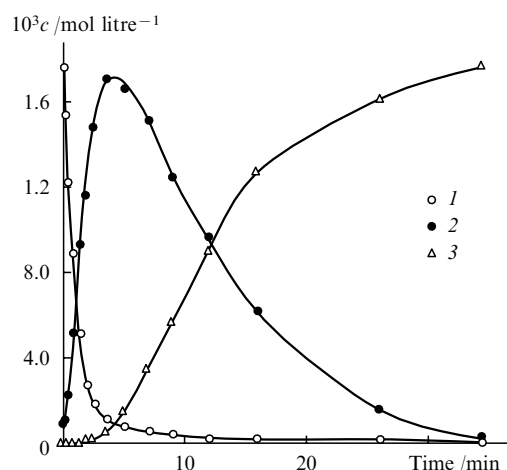


**Figure 2.** Time-dependent changes in the concentrations of valence forms of neptunium in the presence of 0.1 g ml<sup>-1</sup> 1% Pt/SiO<sub>2</sub> at 60 °C (see Ref. 40). [HClO<sub>4</sub>] = 1.0 mol litre<sup>-1</sup>, [HCO<sub>2</sub>H] = 0.1 mol litre<sup>-1</sup>. (1) Np(VI), (2) Np(V), (3) Np(IV).

The stoichiometry of the catalytic reduction of Np(V) with formic acid was studied in solutions with [Np] = 6.20 × 10<sup>-3</sup> mol litre<sup>-1</sup> and [HCO<sub>2</sub>H] = 1.01 × 10<sup>-3</sup> mol litre<sup>-1</sup>. The stoichiometric coefficient, *i.e.*, Δ[Np(V)]/Δ[HCO<sub>2</sub>H], was equal to 2.15 ± 0.08.

The S-shaped curves of the Np(V) reduction, *i.e.*, the presence of an induction period is characteristic of reactions in solutions with [HClO<sub>4</sub>] = 2 mol litre<sup>-1</sup>. At [HClO<sub>4</sub>] > 2 mol litre<sup>-1</sup>, the reaction rate obeys the first-order law. The appearance of the induction period depends also on the concentration of HCO<sub>2</sub>H. If the concentration of HCO<sub>2</sub>H in 1 M HClO<sub>4</sub> is < 0.05 mol litre<sup>-1</sup>, the induction period is absent and the reaction kinetics follows the first order with respect to Np(V). Using different initial concentrations of Np(V), it was possible to determine the orders of reactions described by kinetic curves with induction periods. The reaction rates were determined by the slopes of the tangents in the points corresponding to 50% conversion. The dependence of the reaction rate on [Np(V)]<sub>0</sub> was a straight line with the angular coefficient 1.05 in logarithmic coordinates. This suggests that the catalytic reduction of neptunium(V) with formic acid is a first-order reaction with respect to Np(V) for any composition of the reaction mixture. The duration of the induction period depends on the order of the reactants. If Np(V) is added last, the induction period is much longer than if it was formic acid or the catalyst (Fig. 3).

In solutions of HClO<sub>4</sub> with the concentration ≥ 2 mol litre<sup>-1</sup>, the reaction rate was characterised by an apparent first-order rate constant *k*'. If [HClO<sub>4</sub>] was smaller than 2 mol litre<sup>-1</sup>, induction periods were observed in the kinetic curves and the reaction rates were measured in the points corresponding to the 50% conversion of Np(V).

An increase in the catalyst concentration in the reaction mixture resulted in a monotonic increase in the reduction rate.



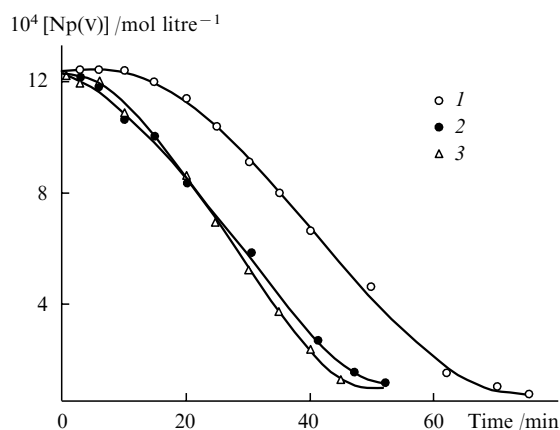


**Figure 3.** Effect of the mode of initiation of the reaction on the shapes of the kinetic curves in the catalytic reduction of neptunium(V) with formic acid in the presence of 0.1 g ml<sup>-1</sup> of 1% Pt/SiO<sub>2</sub>.<sup>40</sup> [HClO<sub>4</sub>] = 1.0 mol litre<sup>-1</sup>; [HCO<sub>2</sub>H] = 0.5 mol litre<sup>-1</sup>; 59 °C. The reaction was initiated by the addition of Np(V) (1), the catalyst (2) and HCO<sub>2</sub>H (3).

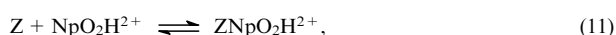
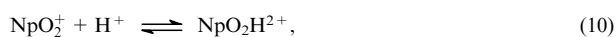
The linear type of the logarithmic dependence  $k'$  vs. (C : R) allowed the estimation of the apparent reaction order with respect to the active sites of the catalyst. For the reaction under consideration, it is equal to  $1.11 \pm 0.04$  in the C : R range from 1 : 100 to 1 : 10.

The rate of the catalytic reduction of neptunium(V) increases with the increase in acid concentration in the solution. At low concentrations of HClO<sub>4</sub> (0.1–1.5 mol litre<sup>-1</sup>) where the reaction occurs with an induction period, the apparent reaction order with respect to perchloric acid changes from 0 to ~0.25, while at 2–4 M HClO<sub>4</sub> it is constant and is equal to  $1.38 \pm 0.06$ . Taking into account the changes in the activity coefficients  $\gamma$  (1.055 and 2.08 for 2 M and 4 M HClO<sub>4</sub>, respectively<sup>41</sup>) the reaction order with respect to hydrogen ions is less than unity.

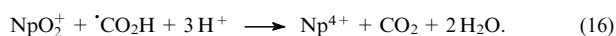
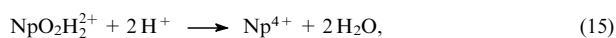
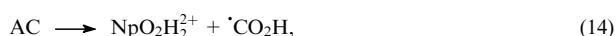
The rate of the catalytic reduction of Np(V) is independent of [HCO<sub>2</sub>H] in the concentration range 0.04–1.0 mol litre<sup>-1</sup>, but a certain statistically significant increase in the reaction rate with a decrease in [HCO<sub>2</sub>H] from 0.04 to 0.002 mol litre<sup>-1</sup> is observed.

From the temperature dependences of the rate constants measured for 0.1 and 0.005 mol litre<sup>-1</sup> HCO<sub>2</sub>H in 2 M HClO<sub>4</sub>, the apparent activation energy values of  $60 \pm 2$  and  $28.4 \pm 0.8$  kJ mol<sup>-1</sup>, respectively, were determined.

Considering that in 2–4 M HClO<sub>4</sub> the reduction rate is proportional to the activities of the hydrogen ions, the reaction begins with the adsorption of protonated Np(V) ions and HCO<sub>2</sub>H molecules in the active sites Z:



The adsorbed reactants form an activated complex (AC) which is then slowly decomposed:



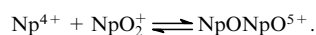
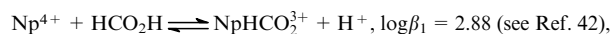
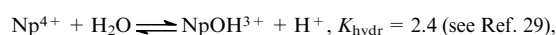
The independence of  $k'$  of [HCO<sub>2</sub>H] concentration above 0.04 mol litre<sup>-1</sup> is characteristic of catalytic reactions where the surface of the catalyst is saturated with one of the reactants. A decrease in [HCO<sub>2</sub>H] below the adsorption threshold level favours the adsorption of Np(V) ions, which increases the reaction rate

with a decrease in the concentration of the reducing agent. Significant difference in the activation energies obtained at the reducing agent concentrations of 0.1 and 0.005 mol litre<sup>-1</sup> seems to be due to the same reasons. The change in  $E^*$  reflects the fact that the experimental values of the activation energy of a heterogeneous catalytic reaction are in fact apparent, they are related to the true activation energy of a heterogeneous process by an equation:

$$E^* = E_{\text{true}} - \lambda,$$

where  $\lambda$  is the integral heat of adsorption. In the general case,  $\lambda$  depends on the heats of adsorption of the reactants and their molar ratios. The heat of adsorption is the function of the degree of occupation of the active sites, which in turn is determined by the energetic nonuniformity of the catalyst surface. An increase in the concentration of formic acid favours its adsorption on the surface of a platinum catalyst. Since formic acid is used in a large excess, its molecules occupy the most energetically favourable active sites, thus diminishing the heat of adsorption of neptunoyl ions and, as a consequence, increasing the apparent activation energies.

The presence of an induction period in solutions with [HClO<sub>4</sub>] < 2 mol litre<sup>-1</sup> suggests the acceleration of the reaction by one of the reaction products. The fast disappearance of the radical  $\cdot\text{CO}_2\text{H}$  is accompanied by accumulation of Np(IV) (which is probably responsible for the catalytic effect). This ion takes part in several reactions:



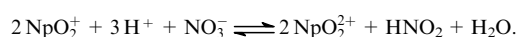
The formation of the  $\text{Np}^{4+} \cdot \text{NpO}_2^+$  complex is very likely, since the formation of the  $\text{Th}^{4+} \cdot \text{NpO}_2^+$  complex is now well established (see Ref. 43). The cation–cation complex is adsorbed on the active site. A decrease in the HCO<sub>2</sub>H concentration results in a decrease in the concentration of the formate complex of Np(IV) and in an increase in the yield of the cation–cation complex Np(IV)·Np(V).

After introduction of a catalyst into a solution of Np(V) and HCO<sub>2</sub>H in 1 M HClO<sub>4</sub>, Np(V) ions and HCO<sub>2</sub>H molecules simultaneously attack the surface, which is occupied in proportion to their concentrations and free energies of adsorption. Neptunium(V) occupies only a very small part of the active sites. As the reaction proceeds, Np(IV) is accumulated, the cation–cation complex occupies more active sites than  $\text{NpO}_2^+$ , the reaction is accelerated and the induction period is over.

If HCO<sub>2</sub>H is added last to the reaction mixture, its molecules occupy free active sites and partly displace  $\text{NpO}_2^+$  ions from the occupied positions. Then the reaction follows the scenario described above.

If Np(V) ions are added last, they have to displace HCO<sub>2</sub>H molecules from the occupied active site. As this step is usually very slow, the induction period becomes longer (see Fig. 3).

The catalytic reduction of neptunium(VI) to neptunium(V) with formic acid on Pt/SiO<sub>2</sub> in HNO<sub>3</sub> solutions does not go to completion.<sup>44</sup> Neptunium(VI) remains in the solution at a certain steady-state concentration determined by the fast equilibrium reaction:<sup>19</sup>



In the presence of antinitrite reagents (urea, 0.05–0.5 mol litre<sup>-1</sup>), the reduction of neptunium(VI) to neptunium(IV) proceeds *via* neptunium(V). In this case, the reduction of Np(VI) to Np(V) follows the same kinetic regularities as in HClO<sub>4</sub>. At the same time, the reduction of Np(V) to Np(IV) in HNO<sub>3</sub> in the presence of urea has a number of features that make it different from the reduction in HClO<sub>4</sub>. Thus the absence of an induction period in the catalytic curves of neptunium(V) reduction may be due to complexation, since in HNO<sub>3</sub> the cation–cation interaction  $\text{Np}^{4+} - \text{NpO}_2^+$  is impossible because of the substitution of nitrate ions for water molecules in the hydrate shell of  $\text{Np}^{4+}$ .

Processing of the kinetic curves has shown that the best fit of the experimental results is achieved with the kinetic equation:

$$-\frac{d[\text{Np(V)}]}{d\tau} = k_{0.5}[\text{Np(V)}]^{0.5}.$$

In other words, in this case the order of the reaction is 0.5 with respect to neptunium(V). This is not changed with the increase in neptunium concentration from  $10^{-3}$  to  $10^{-2}$  mol litre $^{-1}$ , which allows one to consider it as a true order [with respect to Np(V)] of the reaction occurring according to a redox mechanism rather than an apparent order of a heterogeneous process. Kinetic measurements performed at different concentrations of formic acid showed that the decrease in  $[\text{HCO}_2\text{H}]$  from 1.0 to 0.01 mol litre $^{-1}$  caused a significant increase in the rate of neptunium(V) reduction. It is of note that in the  $\text{HCO}_2\text{H}$  concentration range from  $\sim 0.1$  to 0.05 mol litre $^{-1}$  the reaction order changes from 0.5 to 1 with respect to Np(V). The rate of the catalytic reduction of neptunium(V) with formic acid increased with the concentration of nitric acid. The reaction orders with respect to  $\text{HNO}_3$  are the same and constitute  $0.71 \pm 0.02$  and  $0.71 \pm 0.01$  for the reaction orders 0.5 and 1, respectively. The temperature dependences  $k_{0.5}$  and  $k_1$  in the range from 40 to 70 °C correspond to the values of apparent activation energies ( $43.6 \pm 1.5$  and  $30 \pm 2$  kJ mol $^{-1}$ , respectively).

It was suggested<sup>44</sup> that the mechanism of the catalytic reduction of Np(V) with formic acid in  $\text{HNO}_3$  in the presence of urea is generally similar to that in  $\text{HClO}_4$  and can be described by reactions (10)–(16). However, this reaction scheme cannot be regarded as a comprehensive presentation of events that take place in the catalytic reduction of Np(V) with formic acid in  $\text{HNO}_3$ . This covers a relatively narrow range of experimental conditions ( $[\text{HCO}_2\text{H}] < 0.1$  mol litre $^{-1}$ ) where the reaction follows the first order with respect to neptunium(V). The reason for the order of 0.5 with respect to Np(V) at  $[\text{HCO}_2\text{H}] < 0.1$  mol litre $^{-1}$  is still obscure. In the general case, the reaction order 0.5 with respect to a reagent in heterogeneous catalytic processes is associated with its chemisorption on two adjacent sites of the catalyst, as follows from the Langmuir equation of the chemisorption isotherm.<sup>45</sup> Thus, it may be assumed that at a high degree of occupation of the catalyst with formic acid, secondary adsorption of  $\text{NpO}_2^+$  ions occurs on two adjacent catalytic sites formed by the adsorbed  $\text{HCO}_2\text{H}$  molecules. The composition of the activated complex formed is conventionally described by the formula  $\{\text{ads}\cdot\text{HO}_2\text{C}-\text{H}\cdots\text{O}=\text{Np}^+=\text{O}\cdots\text{H}-\text{CO}_2\text{H}_{\text{ads}}\}^*$ , while decomposition of this charge-transfer complex is accompanied by the generation of the species ( $\text{O}=\text{Np}^+-\text{OH}$ ,  $\text{CO}_2\text{H}$ ) and a molecule of formic acid followed by the fast reactions (15) and (16).

The catalytic reduction of neptunium with formic acid using 1% Pt/ $\gamma$ - $\text{Al}_2\text{O}_3$  (grain size = 3–5 mm) as a catalyst for the preparation of neptunium(IV) sols has been studied.<sup>46</sup> The most complete reduction of Np(V) occurred where the initial concentrations of Np(V) and  $\text{HCO}_2\text{H}$  were 0.5 mol litre $^{-1}$ . Higher concentrations of  $\text{HCO}_2\text{H}$  resulted in a higher percentage of Np(V) in the sols. At a concentration of Np(V)  $\leq 0.1$  mol litre $^{-1}$ , the reduction was incomplete.

The concentration of Np(V) did not change over 5 h at 50–60 °C in 1–5 M NaOH solutions containing formate. The addition of  $\text{PdCl}_2$  ( $2 \times 10^{-3}$  mol litre $^{-1}$ ) resulted in formation of metallic palladium where Np(IV) hydroxide sedimented.<sup>47</sup> This process includes the reaction of hydrolysed Pd(II) ions with formate ions and formation of Pd(0). Palladium ions aggregate to form particles with a well-developed surface. Adsorption of formate and Np(V) ions on the active sites of the catalyst results in the reduction of Np(V). Platinum derivatives appeared to be less efficient in the reduction of Np(V) with formate.

The reduction of Np(V) with formate in alkaline solutions was studied in the presence of palladium or platinum on anion-exchange resins.<sup>47</sup>

### 3. Plutonium

The heterogeneous catalytic reactions of plutonium ions reported so far include reduction with hydrogen, hydrazine and formic acid in acidic media and reduction of plutonium(VII) with water in alkaline media.

In the presence of platinised platinum, Pu(VI) was reduced to Pu(V) with gaseous hydrogen. Hydrogen was passed through a solution of Pu(VI) ( $3.1 \times 10^{-3}$  mol litre $^{-1}$ ) in 0.5 M HCl for 15 min at room temperature. Forty minutes later, the composition of the solution was as follows: 10% Pu(VI), 14% Pu(V), 6% Pu(IV) and 70% Pu(III). In 0.5–4 M HCl, the reduction of Pu(IV) (0.02 mol litre $^{-1}$ ) with hydrogen (40 min, room temperature) reaches 99% provided that 2 cm $^2$  of platinised platinum per ml of the solution was used and hydrogen was passed at a rate of 5 ml min $^{-1}$  per ml of the solution.<sup>48</sup>

A mixture of  $\text{H}_2$  (4%) and Ar (96%) was used for the reduction of Pu(IV) to Pu(III) in tributyl phosphate (TBP) with simultaneous reextraction of Pu(III) into the aqueous phase.<sup>49</sup> This was carried out on a column. Equal volumes of 0.5 M  $\text{HNO}_3$  and 30% TBP containing U(VI) (95 g litre $^{-1}$ ), Pu(IV) (1 g litre $^{-1}$ ) and  $\text{HNO}_3$  (0.1 mol litre $^{-1}$ ) were passed through a column filled with  $\text{Al}_2\text{O}_3$  beads coated with 0.5% Pt; the elution time was  $\sim 10$  min. The extent of the Pu reduction was 99% and that of U, 1%. The reduction of U reached  $\sim 3\%$  if pure hydrogen was used.

A 0.5% Pt/ $\text{Al}_2\text{O}_3$  catalyst was used<sup>5</sup> to increase the reaction rate of Pu(IV) with hydrazine in argon at 25 °C. The results obtained in the presence and in the absence of U(VI) are summarised in Table 1.

**Table 1.** Catalytic reduction of plutonium(IV) in 2 M  $\text{HNO}_3$  containing 0.1 mol litre $^{-1}$  of  $\text{N}_2\text{H}_5\text{NO}_3$  at 25 °C.<sup>5</sup>

| [Pu(IV)] $\times 10^3$<br>/mol litre $^{-1}$ | Exposure time<br>/min | [Pu(III)] $\times 10^3$ /mol litre $^{-1}$            |                            |
|----------------------------------------------|-----------------------|-------------------------------------------------------|----------------------------|
|                                              |                       | in the presence of<br>0.12 mol litre $^{-1}$<br>U(VI) | in the absence<br>of U(VI) |
| 1.9                                          | 1                     | 0.7                                                   | 0.5                        |
|                                              | 3                     | 1.7                                                   | 1.2                        |
|                                              | 5                     | —                                                     | 1.6                        |
| 4.7                                          | 1                     | 1.6                                                   | 1.4                        |
|                                              | 3                     | 3.3                                                   | 2.8                        |
|                                              | 5                     | 4.3                                                   | 3.8                        |
|                                              | 7                     | —                                                     | 4.4                        |

These data suggest that the reduction of Pu(IV) occurs according to two routes, *viz.*, as the catalytic reduction of Pu(IV) itself with hydrazine and as the catalytic reduction of U(VI) to U(IV), which then quickly reduces Pu(IV). The kinetic dependences for U(IV)-free Pu(IV) solutions appear as straight lines, *i.e.*, the reaction rate does not depend on the concentration of Pu(IV).

The catalytic reduction of Pu(IV) with hydrazine on platinum-on-silica gel (grain size = 0.5–1 mm) as a catalyst was studied in more detail.<sup>50</sup> The reaction rates of Pu(IV) [ $(0.7-1) \times 10^{-2}$  mol litre $^{-1}$ ] with hydrazine (0.025–0.2 mol litre $^{-1}$ ) in 1.5–4 M  $\text{HNO}_3$  (C : R = 1 : 100) depended only slightly on the stirring intensity.

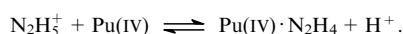
The kinetic curves for the loss of [Pu(IV)] were rectified in the semilogarithmic coordinates, *i.e.*, the reduction virtually followed the first-order law. The rate constant of the first-order reaction  $k'$  increased linearly with the catalyst concentration. An increase in the platinum content on the support resulted in a linear increase in the rate constant. The reaction order with respect to hydrazine was 0.5. In 1.5–4 M  $\text{HNO}_3$ , hydrogen ions had no effect on the reaction rate. The activation energy in the temperature range 30–60 °C was equal to 23 kJ mol $^{-1}$ . This is somewhat higher than the corresponding values for the mass transfer-controlled

reactions. It may thus be concluded that the catalytic reaction occurred in a virtually kinetic regime.

The reduction process can schematically be presented as follows. Its first step includes adsorption of  $\text{N}_2\text{H}_3^+$  and  $\text{Pu(IV)}$  ions [ $\text{Pu}^{4+}$  forms nitrate complexes  $\text{PuNO}_3^{3+}$ ,  $\text{Pu(NO}_3)_2^{2+}$ , etc.]. Adsorbed hydrazine reacts with  $\text{Pu(IV)}$  either in an electron-transfer mode (from hydrazine to plutonium) through Pt–Pt bridges or by preliminary formation of an activated complex, which is further decomposed to  $\text{Pu(III)}$ ,  $\text{N}_2\text{H}_3$  and  $\text{H}^+$ . Part of the radicals reduce  $\text{NO}_3^-$  and  $\text{Pu(IV)}$ , while the other part undergoes dimerisation to give  $\text{NH}_4^+$  and  $\text{N}_2$ .

Catalysts based on ruthenium,<sup>51</sup> activated charcoal<sup>52</sup> and heteropoly compounds were also used for the reduction of  $\text{Pu(IV)}$  with hydrazine.<sup>53</sup> The ruthenium catalysts were prepared by treatment of silica gel (grain size = 0.5–1 mm) with ruthenium nitronitrate with subsequent drying and reduction with hydrogen at 350–500 °C. Studies of the catalytic reduction of  $\text{Pu(IV)}$  solutions ( $1 \times 10^{-2}$  mol litre<sup>-1</sup>) with hydrazine revealed that the reaction rate depended on the stirring intensity. Therefore, the rate of stirring was selected so as to ensure the kinetic regime. The concentration of  $\text{Pu(IV)}$  decreased with time according to the first-order reaction, and the reaction rate increased linearly with the amount of the catalyst (the C:R ratio varied from 1:100 to 1:10) and the Ru content (the latter varied from 0.5% to 5%). The orders of the reactions with respect to hydrazine (0.1–0.5 mol litre<sup>-1</sup>) and hydrogen ions (0.5–4.8 mol litre<sup>-1</sup> of  $\text{HNO}_3$ ) were ~1 and –1, respectively. The activation energy was 78 kJ mol<sup>-1</sup> at 30–60 °C.

It was suggested that  $\text{N}_2\text{H}_3^+$  and  $\text{Pu(IV)}$  ions adsorbed on the catalyst formed an activated complex with simultaneous elimination of a hydrogen ion:



The activated complex was slowly converted into  $\text{Pu(III)}$ ,  $\text{N}_2\text{H}_3$  and  $\text{H}^+$ .

Ruthenium catalysts are less effective than their platinum analogues, but their advantage over the latter is very slow decomposition of hydrazine.

It was recommended to use activated charcoal for the reduction of  $\text{Pu(IV)}$  (1–20 g litre<sup>-1</sup>) in  $\text{HNO}_3$  solutions (0.1–1 mol litre<sup>-1</sup>) containing  $>0.2$  mol litre<sup>-1</sup>  $\text{N}_2\text{H}_5\text{NO}_3$ .<sup>52</sup> Activated charcoal (50–100 g litre<sup>-1</sup>) effected 99.5% reduction of  $\text{Pu(IV)}$  (1.2 g litre<sup>-1</sup>) in 30 min.

It was found<sup>53</sup> that support of  $\text{Cs}_5\text{PV}_2\text{Mo}_{10}\text{O}_{40}$  onto silica gel increased the rate of  $\text{Pu(IV)}$  reduction with hydrazine in  $\text{HNO}_3$ . The catalyst was prepared by impregnating silica gel (grain size = 0.5–1 mm) with a solution of a heteropolyacid or its sodium salt and subsequent treatment with a solution of a caesium salt. This resulted in formation of a poorly soluble heteropoly compound (HPC) on the surface of  $\text{SiO}_2$ . The concentration of HPC on  $\text{SiO}_2$  was 1 mol.%–10 mol.%. The reduction of  $\text{Pu(IV)}$  depended only slightly on the stirring intensity, *i.e.*, it occurred in a nearly kinetically-controlled mode. The reaction rate was described by a first-order equation with respect to  $\text{Pu(IV)}$ . In the presence of 10% HPC/ $\text{SiO}_2$ , the first-order rate constant increased linearly with a change in C:R from 1:100 to 1:20, while the decrease in the HPC content on the support decreased the rate constant. The calculated value of the activation energy was 80 kJ mol<sup>-1</sup> at 25–80 °C.

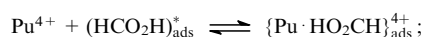
In contrast to platinum catalysts, HPC/ $\text{SiO}_2$  did not increase the rate of  $\text{U(VI)}$  reduction with hydrazine in  $\text{HNO}_3$  solutions. It was suggested<sup>53</sup> that hydrazine caused the reduction of the heteropolyanion (HPA)  $\text{PV}_2\text{Mo}_{10}\text{O}_{40}^{5-}$  to the so-called 'heteropolyblue' which had a heteropolyanionic structure. For  $\text{PV}_2\text{Mo}_{10}\text{O}_{40}^{5-}$ , the first half-wave of reduction  $E_{1/2}$  was about 0.65 V;<sup>54</sup> therefore, the 'heteropolyblue' was able to convert  $\text{Pu(IV)}$  into  $\text{Pu(III)}$  through oxidation to the original HPC.

As mentioned above, finely dispersed platinum accelerates the reduction of  $\text{Np(VI)}$ ,  $\text{Np(V)}$  and  $\text{Pu(IV)}$  with hydrazine in  $\text{HNO}_3$  solutions to give  $\text{Np(IV)}$  and  $\text{Pu(III)}$ . In 6–8 M  $\text{HNO}_3$ , the former

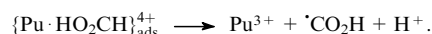
yields anionic complexes with the composition  $\text{Np(NO}_3)_n^{4-n-}$ , which can be adsorbed on anion-exchange resins. This is not inherent in  $\text{Pu(III)}$  nitrate complexes. Therefore, 1% Pt/VP-1Ap was used as a catalyst for the reduction and separation of neptunium and plutonium.<sup>55</sup> Passage of a solution of a neptunium–plutonium mixture of any valence state in 6–7 M  $\text{HNO}_3$  containing hydrazine through a layer of the anion-exchange resin with supported platinum resulted in sorption of  $\text{Np(IV)}$ , while  $\text{Pu(III)}$  remained in the eluate. The effects of various factors (*e.g.*, the mode of preparation of the catalyst, temperature variation from 30 to 50 °C, hydrazine concentration [0.1–0.2 mol litre<sup>-1</sup>]) on the separation of the neptunium–plutonium mixture have been studied.<sup>55</sup> Under optimum conditions, neptunium contained no more than  $2 \times 10^{-3}\%$  of plutonium. In addition to platinum-based catalysts, the separation of neptunium and plutonium was carried out on anion-exchange resins with a supported heteropolyanion in  $\text{HNO}_3$  containing hydrazine.<sup>56</sup> The catalysts were prepared by sorption of  $\text{PV}_2\text{Mo}_{10}\text{O}_{40}^{5-}$  on various anion-exchange resins (VP-1Ap, VPBs, PX-1, AV-17), the former being catalysts of choice (the grain size was 0.18–0.63 mm). The effects of the catalyst preparation procedure, the content of HPA on the resin, the concentration of hydrazine in the solution as well as of temperature on the degree of separation of neptunium and plutonium were investigated.

The catalytic reduction of  $\text{Pu(IV)}$  in the process of denitration with excess of formic acid in highly radioactive solutions containing palladium and ruthenium was studied.<sup>57</sup> Partial reduction of  $\text{Pu}$  to the trivalent state was also observed<sup>58</sup> in the final step of the catalytic denitration of plutonium-containing solutions in the presence of 1% Pt/ $\text{SiO}_2$ . It was suggested<sup>57</sup> that  $\text{Pu(IV)}$  was reduced with atomic hydrogen formed upon catalytic decomposition of  $\text{HCO}_2\text{H}$  on the surface of reduced blacks of noble metals. No hydrogen formation was observed upon catalytic denitration on Pt/ $\text{SiO}_2$ ,<sup>58</sup> therefore, it was concluded that the reduction of  $\text{Pu(IV)}$  under these conditions results from direct catalytic reaction of  $\text{Pu(IV)}$  with  $\text{HCO}_2\text{H}$ . More recent investigations (including kinetic studies)<sup>59</sup> have shown that  $\text{Pu(IV)}$  was completely and irreversibly reduced to the trivalent state in 0.27–2.0 M  $\text{HNO}_3$  containing formic acid and urea in the presence of 1% Pt/ $\text{SiO}_2$ . In the presence of urea, the catalytic reduction of  $\text{Pu(IV)}$  with formic acid proceeded at a noticeable rate even at room temperature. If the reaction was carried out at 60 °C, the reduction of  $\text{Pu(IV)}$  (0.01 mol litre<sup>-1</sup>) with formic acid (0.5 mol litre<sup>-1</sup>) in 1 M  $\text{HNO}_3$  was complete within less than 10 min. The rate of catalytic reduction of plutonium(IV) did not depend on the intensity of stirring of the reaction mixture with nitrogen, *i.e.*, in this case we deal with a kinetically controlled first-order reaction with respect to  $\text{Pu(IV)}$ . The fact that the reaction rate did not depend on the urea concentration in the range 0.05–1.0 mol litre<sup>-1</sup> places additional emphasis on the role of  $(\text{NH}_2)_2\text{CO}$  as an antinitrite agent. Virtually no effect of the concentration of formic acid (from 0.2 to 1.0 mol litre<sup>-1</sup>) on the rate constant  $k'$  was observed. The rate of plutonium(IV) reduction depended only slightly on the concentration of  $\text{HNO}_3$  in the range from 0.3 to 2.0 mol litre<sup>-1</sup>. Further increase in nitric acid concentration resulted in rapid decomposition of urea accompanied by abundant gas evolution and denitration of the solution. Under these conditions, plutonium(IV) was first partly reduced to the trivalent state and then oxidised as urea decomposed. The activation energy of this process at 30–60 °C was  $29.6 \pm 1.8$  kJ mol<sup>-1</sup>.

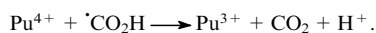
In the authors' opinion, the reduction of  $\text{Pu(IV)}$  on the catalyst surface proceeds *via* an activated complex:



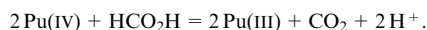
its slow decomposition yields  $\text{Pu(III)}$  and the radical  $^*\text{CO}_2\text{H}$



The radical  $^*\text{CO}_2\text{H}$  formed reacts with  $\text{Pu(IV)}$  ions:



The overall stoichiometry of this reaction appears as:



A possibility of adsorption of Pu(IV) ions on the active sites vicinal to  $(\text{HCO}_2\text{H})_{\text{ads}}^*$  with subsequent charge transfer through the catalytic bridge Pt–Pt and decay of the radical  $(\cdot\text{HCO}_2\text{H})_{\text{ads}}^*$  into  $\cdot\text{CO}_2\text{H}$  and the hydrogen ion was also considered. However, these two processes were found to be kinetically indistinguishable.

It was also found<sup>58</sup> that formic acid derivatives, *viz.*, formaldehyde and formamide, also efficiently reduce plutonium(IV) in the presence of a catalyst (1% Pt/SiO<sub>2</sub>).

The effect of immersion of platinum, graphite and lead dioxide electrochemically deposited on a platinum support on the stability of Pu(VII) solutions in 0.5 M NaOH was studied.<sup>60</sup> It was found that these conductive non-reducing materials decreased markedly the stability of Pu(VII) as could be judged from the formation of oxygen bubbles on the surface of the submerged materials. However, no visible changes occurred with the materials themselves. Thus, they exerted a purely catalytic effect on the Pu(VII) reduction. The reduction of Pu(VII) with water in the presence of the assayed electrode materials proceeded as a first-order reaction with respect to Pu(VII). The rate constants  $k'$  increased linearly with the increase in the visible surface area of the electrode materials, which is in good accord with the concepts of heterogeneous kinetics. Under comparable conditions, the rates of catalytic reduction of Pu(VII) being in contact with these electrode materials decreased in the following order: Pt > PbO<sub>2</sub>/Pt > graphite. In the authors' opinion, the catalytic effect of the conductive materials on the Pu(VII) reduction with water is electrochemical in its character. Plutonium(VII) created a high potential on the surface (0.98 V), which exceeded the sum of the equilibrium potential for H<sub>2</sub>O oxidation in alkaline solutions and the overvoltage of liberation of oxygen on this material. Hence, the electrode material becomes an anode where oxygen evolves owing to the catalytic reduction of Pu(VII).

Presumably, the molecular mechanism of the catalytic reduction of Pu(VII) with water in the presence of platinum, graphite and PbO<sub>2</sub> on platinum consists merely of electron transfer from hydroxyl ions and water molecules adsorbed on the surface to Pu(VII) ions.

#### 4. Americium

Americium(V) is rather stable in weakly acidic aqueous solutions. Many reducing agents including multielectron agents, *e.g.*, hydrazine, hydroxylamine, formic acid and other organic acids, virtually do not react with Am(V). The chemical stability of Am(V) is determined by kinetic rather than thermodynamic factors [the potential of the Am(V)/Am(III) pair is 1.72 V (see Ref. 36)]. However, the low potential of the Am(V)/Am(IV) pair and high first potentials of the reducing agents should be taken into consideration. Therefore, catalysts should accelerate the reduction.

Some reduction reactions of americium(V) in the presence of 1% Pt/SiO<sub>2</sub> as a catalyst have been studied.<sup>61</sup> The reduction pattern depended on the intensity of an air flow through the reaction mixture. However, in the majority of cases where the air passed through a 20 ml solution at 5 litre h<sup>−1</sup> and higher rates, the reaction rate only slightly depended on the stirring efficiency. Thus, these reactions are predominantly kinetically controlled. The results of the experiments carried out at 25 °C (C : R = 1 : 20) and an air flow of 6 litre h<sup>−1</sup> are summarised in Table 2. It can be seen that finely dispersed platinum increased the reaction rate not only in the presence of conventional reducing agents (N<sub>2</sub>H<sub>5</sub><sup>+</sup>, H<sub>2</sub>O<sub>2</sub>), but also in the presence of nitrilotriacetic acid (NTA), EDTA and even ethylene glycol.

The change in pH from 1 to 4 had little effect on the reduction. This was accelerated with an increase in temperature and decreased almost linearly with a drop of C : R ratio from 1 : 5 to

**Table 2.** Reduction of Am(V) [(0.6–1.5) × 10<sup>−3</sup> mol litre<sup>−1</sup>] in the presence of 1% Pt/SiO<sub>2</sub> (0.05 g litre<sup>−1</sup>) at 25 °C.<sup>61</sup>

| Reducing agent (X)                         | [X] / mol litre <sup>−1</sup> | pH  | Reduction time (50%) / min |
|--------------------------------------------|-------------------------------|-----|----------------------------|
| N <sub>2</sub> H <sub>5</sub> <sup>+</sup> | 0.05                          | 1   | 6.5                        |
| H <sub>2</sub> O <sub>2</sub>              | 0.0075                        | 1   | 120                        |
|                                            | 0.18                          | 1   | 50                         |
| HCO <sub>2</sub> H                         | 0.5                           | 1   | 6                          |
| Tartaric acid                              | 0.5                           | 4   | < 5                        |
| Nitrilotriacetic acid (NTA)                | 0.4                           | 3   | ~ 50                       |
| EDTA                                       | 0.01                          | 1   | 150                        |
| Acetoxime                                  | 0.25                          | 2.3 | ~ 50                       |
| Formaldehyde                               | 0.5                           | 1   | ~ 60                       |
| Ethylene glycol                            | 0.5                           | 1   | 50                         |

1 : 50. The reduction rate increased with the increase in the Pt content on the silica gel surface from 0.1% to 4%, however, to a lesser degree than the increase in the platinum content.

These data prompt several conclusions about the mechanisms of this reduction. Presumably, transfer of an electron or a hydrogen atom from the adsorbed reducing agent to the Am(V) ion also adsorbed on the platinum surface is the limiting step. The Am(IV) ions formed either undergo disproportionation or react with the reducing agent. Higher local concentration of Am(IV) favours disproportionation due to adsorption on the catalyst. Moreover, by virtue of its high oxidation potential Am(IV) is highly reactive with respect to the reducing agents mentioned above.

It was found<sup>62</sup> that trace amounts of metallic platinum accelerated dramatically the reduction of Am(VI) with formic acid, especially at pH > 4.

### III. Catalytic decomposition of organic and inorganic components of liquid radioactive wastes

The reprocessing of radioactive wastes (including those of the nuclear fuel cycle) is often complicated without preliminary removal of certain organic and inorganic impurities, such as complexones, oxalic acid, hydrazine, hydrazoic acid, urea, excess nitric acid, nitrates, *etc.* This problem is successfully overcome by heterogeneous catalytic decomposition of these compounds in HNO<sub>3</sub> solutions or the use of strong oxidants, *e.g.*, ozone, bichromate, permanganate.<sup>63,64</sup> Catalytic reactions are preferable, since no additional reactants are needed.

#### 1. Decomposition of complexones

It was found<sup>65</sup> that polyaminopolycarboxylic complexones are decomposed at moderate rates upon heating of their solutions in HNO<sub>3</sub> in the presence of heterogeneous catalysts, such as Pt/SiO<sub>2</sub>, Pt/anion-exchange resin AV-17, activated charcoals AG-3, BAU, SKT, *etc.*

The decomposition of diethylenetriaminopentaacetic acid (DTPA) (0.05 mol litre<sup>−1</sup>) in HNO<sub>3</sub> in the presence of 1% Pt/SiO<sub>2</sub> (C : R = 1 : 10) at 40–80 °C proceeded as a first-order reaction with respect to DTPA. The quantitative characteristics of this reaction were calculated from the half-time  $\tau_{1/2}$ , *i.e.*, the time required for a twofold decrease in the complexone concentration.

The decomposition rate of DTPA increased with the increase in the HNO<sub>3</sub> concentration from 0.5 to 2.0 mol litre<sup>−1</sup>. Further increase in [HNO<sub>3</sub>] inhibited the reaction. The reaction rate increased as the content of Pt on SiO<sub>2</sub> changed from 0.5% to 2%. The activation energy was 67 kJ mol<sup>−1</sup>. The use of the anion-exchange resin AV-17 instead of silica gel as a support for platinum decreased the decomposition rate of DTPA 20-fold. This suggests direct involvement of the support in the formation of active sites of the catalyst.

Organic and inorganic impurities can be removed from all known brands of activated charcoals by washing. Their concen-

tration was the lowest in BAU, therefore, this was selected for kinetic studies. The rate of DTPA decomposition in the presence of BAU charcoal (C : R = 1 : 10) increased with the HNO<sub>3</sub> concentration, although to a far lesser degree than in the presence of Pt/SiO<sub>2</sub>. The activation energy at 50–80 °C was equal to ~61 kJ mol<sup>-1</sup>.

In contrast to DTPA, the decomposition of EDTA (0.05 mol litre<sup>-1</sup>) in 0.3–0.5 M HNO<sub>3</sub> in the presence of BAU charcoal (C : R = 1 : 10) was described by a zero- or a close to zero-order rate constant with respect to the complexone. In 1–2 M HNO<sub>3</sub> solutions, the decomposition rate increased nearly twofold.

A series of experiments were devoted to the elucidation of the role of the anion in the decomposition of DTPA and EDTA in the presence of BAU (C : R = 1 : 10, 80 °C). Hydrochloric, perchloric and sulfuric acids (0.5–2.0 M) had similar effects on the catalytic decomposition of complexones and were nearly 100 times less efficient than HNO<sub>3</sub>. Similar results were obtained in the presence of Pt/SiO<sub>2</sub>.

The following scheme for the process was suggested. The first step included sorption of the complexone molecule on the active site of the catalyst. The adsorbed molecule underwent thermal decomposition in HCl, HClO<sub>4</sub> and H<sub>2</sub>SO<sub>4</sub>. In HNO<sub>3</sub> solutions, the adsorbed species were subject to an attack by NO<sub>3</sub><sup>-</sup> (or NO<sub>2</sub><sup>+</sup>) ions and were oxidised. No complexone decomposition products were identified, therefore, it is difficult to specify the details of the reaction mechanism.

## 2. Decomposition of oxalic acid

Decomposition on solid-phase catalysts is the most convenient and reliable method for removal of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> from nitric acid solutions.<sup>66</sup> Different brands of activated charcoals, platinum on silica gel and on anion-exchange resins AV-17 and VP-3Ap were assayed as such catalysts.

In semilogarithmic coordinates, the kinetic curves for H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> decomposition in the presence of 1% Pt/SiO<sub>2</sub> appeared as straight lines up to the degree of conversion of 85%–90%. Then the reaction rate showed a further increase. In the authors' opinion, the gaseous products generated in the first steps of the reaction prevent penetration of the solution into the pores. Gas evolution slowed down to the end of the process, which results in an increase in the effective surface area of the catalyst and a parallel increase in the reaction rate. The decomposition of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> to the degree of conversion of 90% is characterised by a first-order equation with respect to H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> and a first-order rate constant.

An increase in the rate of air flow through the solution (10 ml) from 50 to 400 ml min<sup>-1</sup> caused only a small (1.4-fold) increase in *k*. This suggests that the decomposition of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> is predominantly under kinetic control.

The rate of the catalytic decomposition increased threefold with an increase in the HNO<sub>3</sub> concentration from 1 to 3 mol litre<sup>-1</sup>. No catalytic decomposition of oxalic acid took place in HCl, HClO<sub>4</sub> and H<sub>2</sub>SO<sub>4</sub>. An increase in the amount of the catalyst resulted in an increase in the reaction rate. The activation energy of decomposition of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> (0.3 mol litre<sup>-1</sup>) in 2.5 M HNO<sub>3</sub> in the presence of 1% Pt/SiO<sub>2</sub> (C : R = 1 : 10) was 54.8 kJ mol<sup>-1</sup> at 40–70 °C. The decomposition rate of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> increased ~ fourfold with an increase in the Pt content on silica gel from 0.25% to 4%.

The catalysts prepared by reduction of H<sub>2</sub>PtCl<sub>6</sub> with hydrogen or boiling hydrazine hydrate possessed similar efficiencies.

The effect of impurities on the catalytic decomposition of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> in 2.5 M HNO<sub>3</sub> at 60 °C in the presence of 1% Pt/SiO<sub>2</sub> (C : R = 1 : 10) has also been studied. The presence of Ni(II) (0.1 g litre<sup>-1</sup>) and U(VI) (5 g litre<sup>-1</sup>) had little effect on the reaction rate. At the same time, the decomposition rate decreased in the presence of Cr(III) (2 g litre<sup>-1</sup>), Fe(III) (5 g litre<sup>-1</sup>) and Pu(IV) (0.3 g litre<sup>-1</sup>), apparently as a result of formation of oxalate complexes.

Stirring of solutions with catalysts results in attrition wear and crushing of silica gel. The concentration of silicon during H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> decomposition at 60 °C reached 20–30 mg litre<sup>-1</sup>. This drawback is absent from the catalysts prepared by absorption of PtCl<sub>6</sub><sup>-</sup> on the anion-exchange resins AV-17 and VP-3Ap and subsequent reduction of platinum with hydrazine. The catalysts thus prepared were activated by refluxing in 2–4 M HCO<sub>2</sub>H for 15–30 min and were only slightly inferior to catalysts based on silica gel in the ability to decompose H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>.

The decomposition of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> in HNO<sub>3</sub> solutions in the presence of seven different brands of activated charcoals without additional stirring has been studied. Stirring was effected by the gas evolved during the reaction. Upon heating to 80–100 °C, the decomposition of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> in the presence of activated charcoals proceeded at moderate rates. The reaction rate increased with the increase in the C : R ratio. With BAU charcoal, the maximum value of C : R did not exceed 1 : 3.5.

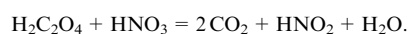
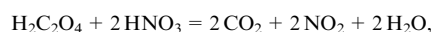
In addition to static experiments, the decomposition of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> was studied upon continuous passage of the solution through a column filled with the catalyst. The solution was fed into the thermostated column from the bottom. The degree of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> decomposition depended on the flow rate of the solution.

In the presence of hydrazine, the mode of decomposition of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> changed considerably.<sup>67</sup> The concentration of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> remained constant until the decomposition of N<sub>2</sub>H<sub>5</sub><sup>+</sup> was nearly complete and diminished only thereafter. This suggests that hydrazine inhibits the catalytic decomposition of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> in HNO<sub>3</sub> solutions and that its effect is related to removal of HNO<sub>2</sub> from the solution.

The stoichiometry and the mechanism of heterogeneous catalytic decomposition of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> in nitric acid solutions have been studied.<sup>68</sup> Under the conditions specified (1% Pt/SiO<sub>2</sub>, 80 °C, [H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>] = 0.3 mol litre<sup>-1</sup>, exposure time 30 min), the ratio  $n = \Delta[\text{HNO}_3]/\Delta[\text{H}_2\text{C}_2\text{O}_4]$  was 0.4–0.5; it changed only slightly in 0.2–0.5 M HNO<sub>3</sub> and increased to 1.01 and 1.74 in 5 and 7 M HNO<sub>3</sub>, respectively. In 7 M HNO<sub>3</sub>, the value of *n* dropped to 1.1 with an increase in the exposure time. A decrease in temperature had no effect on this parameter (at 50 °C in 7 M HNO<sub>3</sub>, *n* was equal to 0.9). In an argon atmosphere, the value of *n* exceeded those in aerated solutions.

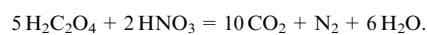
In the presence of Pt/anion-exchange resins, the decomposition of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> proceeded with virtually the same stoichiometry as with 1% Pt/SiO<sub>2</sub>.

Nitric acid at a concentration ≥ 7 mol litre<sup>-1</sup> behaves as a one- or two-electron oxidant of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>.

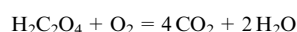


This was concomitant with more profound partial reduction of nitric acid.

In dilute solutions, the reaction of HNO<sub>3</sub> with H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> is described by the equation:



The reaction:



also takes place.

Thus, the increase in HNO<sub>3</sub> concentration prevents its more complete reduction with oxalic acid.

The IR spectra of gaseous products obtained under different conditions of catalytic oxidation of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> contained the bands corresponding to NO<sub>2</sub>, N<sub>2</sub>O<sub>4</sub>, CO<sub>2</sub> and H<sub>2</sub>O. No bands corresponding to NO or N<sub>2</sub>O were detected.

The decomposition of H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> in solutions containing HNO<sub>3</sub> (0.2 mol litre<sup>-1</sup>) and variable amounts of HClO<sub>4</sub> in the presence of 1% Pt/SiO<sub>2</sub> (C : R = 1 : 2, 60 °C) reached 6%, 31% and 68% after 60 min, [H<sup>+</sup>] being 0.2, 1.2 and 2.2 mol litre<sup>-1</sup>, respectively.

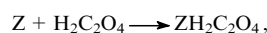
This suggests that  $H^+$  ions are involved in the rate-determining step or in a preceding step.

The dependence of the decomposition rate of  $H_2C_2O_4$  ( $0.33 \text{ mol litre}^{-1}$ ) on the reaction conditions (1% Pt/SiO<sub>2</sub>, C:R = 1:2, 60 °C, 90 min) in the presence of  $HNO_2$  ( $0.17 \text{ mol litre}^{-1}$ ) can be seen from the following data (no decomposition occurred in the absence of  $HClO_4$  and  $HNO_3$ ):

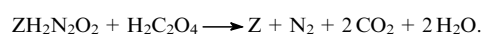
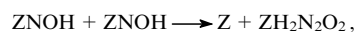
| $[HClO_4]/\text{mol litre}^{-1}$ | $[HNO_3]/\text{mol litre}^{-1}$ | Degree of decomposition (%) |
|----------------------------------|---------------------------------|-----------------------------|
| 2                                | —                               | 5                           |
| —                                | 0.2                             | 80                          |

The decomposition of  $H_2C_2O_4$  depends on  $[HNO_2]$ : the loss of  $H_2C_2O_4$  in a solution containing  $0.2 \text{ mol litre}^{-1}$   $HNO_3$  and  $0.17 \text{ mol litre}^{-1}$   $HNO_2$  was 80% (*cf.* 6% in  $0.2 \text{ M}$   $HNO_3$  containing minor amounts of  $HNO_2$ ). The reaction does not go further after removal of trace amounts of  $HNO_2$  with hydrazine. In the absence of  $HNO_3$  no reaction occurred either. It is the simultaneous presence of nitric and nitrous acids that brings about the catalytic decomposition of  $H_2C_2O_4$ .

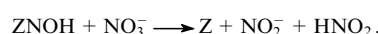
The catalytic reaction occurs through sorption of the reducing agent ( $H_2C_2O_4$ ) and the oxidant. In the authors' opinion,<sup>68</sup> the role of the oxidant is played by  $NO_2^+$  ions and NO molecules formed in the equilibrium reactions (6) and (7). The formation of the intermediate oxidising species ZA in the active catalytic site Z proceeds in conformity with reactions (8) and (9). Subsequent conversions include the following reactions:



If the concentration of  $HNO_3$  (and, correspondingly, of  $NO_2^+$ ) is small, the reaction probably follows another pathway:



High concentrations of  $NO_3^-$  ions trigger the reaction:

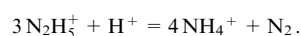


In addition, molecular oxygen oxidises intermediate reducing species.

### 3. Decomposition of hydrazine

The kinetics and mechanisms of catalytic decomposition of hydrazine in the presence of various catalysts were studied in detail. The results of these investigations are generalised in a monograph.<sup>69</sup> The studies cited therein are devoted to the catalytic decomposition of anhydrous  $N_2H_4$  or the hydrate  $N_2H_4 \cdot H_2O$  in the gaseous or liquid state. Therefore, the available data do not provide an adequate explanation for the behaviour of hydrazine in the presence of heterogeneous catalysts in acidic solutions where it exists in the form of the hydrazinium ion,  $N_2H_5^+$ .

The stoichiometry, kinetics and mechanism of the catalytic decomposition of hydrazine were studied in solutions of perchloric and sulfuric acids in the presence of 1% Pt/SiO<sub>2</sub> as a catalyst.<sup>70</sup> It was found that the catalytic decomposition of hydrazine was accompanied by the formation of ammonium ions and nitrogen. It is noteworthy that the stoichiometric ratio  $[N_2H_5^+]:[NH_4^+]$  was  $0.746 \pm 0.08$  and did not depend on the nature of the acid ( $HClO_4$  or  $H_2SO_4$ ) or the concentration of hydrogen ions in the range from  $0.3$  to  $3 \text{ mol litre}^{-1}$ , *i.e.*, the decomposition of hydrazine occurred according to the equation:



Kinetic studies revealed that the reaction order with respect to hydrazine was variable and changed from 0.2 to 1 with the decrease in  $[N_2H_5^+]_0$  from  $0.2$  to  $0.01 \text{ mol litre}^{-1}$ . The fractional order of the reaction with respect to hydrazine was probably

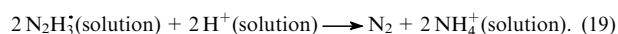
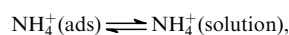
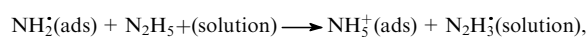
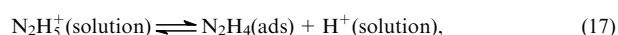
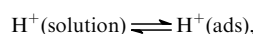
apparent and reflected the adsorption-type character of heterogeneous catalytic decomposition of hydrazine. Actually, this reaction was of zero and first orders with respect to  $N_2H_5^+$  and the contribution of each of them to the overall process depended on the concentrations of hydrazine and the amount of the catalyst in the reaction system. At low initial hydrazine concentrations ( $0.01 \text{ mol litre}^{-1}$ ) where the catalytic decomposition strictly followed first-order kinetics with respect to  $N_2H_5^+$ , the reaction rate decreased monotonically with an increase in the concentration of hydrogen ions. The reaction order with respect to  $H^+$  was  $-0.24 \pm 0.1$ . The negative fractional order of the reaction with respect to  $H^+$  suggests that hydrogen ions are not directly involved in the chemical reaction leading to the decomposition of hydrazine. Apparently, the inhibitory effect is due to competitive adsorption on the active sites of the catalyst.

The experimental values of the activation energies for the catalytic decomposition of hydrazine increased monotonically with the acid concentration.

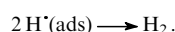
| $[H^+]$<br>/mol litre <sup>-1</sup> | $E^*$<br>/kJ mol <sup>-1</sup> | $[H^+]$<br>/mol litre <sup>-1</sup> | $E^*$<br>/kJ mol <sup>-1</sup> |
|-------------------------------------|--------------------------------|-------------------------------------|--------------------------------|
| $\sim 10^{-5}$                      | $31.6 \pm 1.6$                 | 1.2                                 | $59.2 \pm 2.2$                 |
| 0.1                                 | $36.1 \pm 2.4$                 | 3.4                                 | $79.9 \pm 1.4$                 |
| 0.2                                 | $36.4 \pm 2.1$                 |                                     |                                |

The monotonic increase in  $E^*$  with an increase in the acid concentration reflects the fact that the experimental values of activation energies of the heterogeneous catalytic reactions are apparent. The true activation energy of any chemical conversion always exceeds that determined experimentally by a value of the heat of adsorption. The latter depends on the degree of occupation of the active sites of the catalyst, which in turn reflects the non-uniformity of the catalyst surface with respect to energy. Adsorption of hydrogen ions on the surface of a platinum catalyst increases with the increase in acid concentration in the solution. Being present in large excess,  $H^+$  ions occupy the most energetically favourable active sites, which results in a decrease in the heats of adsorption of interacting species and hence in an increase in apparent activation energy of a heterogeneous catalytic reaction.

The mechanism of catalytic decomposition of hydrazine in  $HClO_4$  and  $H_2SO_4$  postulated on the basis of stoichiometric and kinetic data can be described by the following scheme:



The dissociation of adsorbed hydrazine molecules seems to be the rate-limiting step of the overall process (reaction 18). The first order of the reaction with respect to hydrazine is determined by the adsorption equilibrium (17). The reaction of the adsorbed radical  $NH_2^+(\text{ads})$  with the hydrazinium ion must be fast, otherwise further dissociation of the amino radical would result in the production of hydrogen:



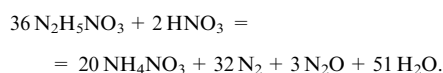
The disproportionation of  $N_2H_3^+$  radicals into nitrogen and ammonium ions [reaction (19)] is yet another example of a very fast reaction: ( $k > 3 \cdot 10^{12} \text{ litre mol}^{-1} \text{ s}^{-1}$ ).<sup>71</sup>

The catalytic decomposition of hydrazine ( $0.20$ – $0.23 \text{ mol litre}^{-1}$ ) in  $HNO_3$  was studied in a thermostated cell mounted onto a shaker.<sup>67</sup> The loss of  $[N_2H_5^+]$  in  $1.25 \text{ M}$   $HNO_3$  in

the presence of 0.7% Pt/SiO<sub>2</sub> (50–80 °C) was described by kinetic curves; their initial segments correspond to the first-order reaction, which changes to the zero order in the terminal steps of the process. The decomposition of N<sub>2</sub>H<sub>5</sub><sup>+</sup> in the presence of activated charcoal occurred at a slower rate than on Pt/SiO<sub>2</sub> and strictly obeyed the zero-order kinetics. When BAU and Pt/SiO<sub>2</sub> containing up to 1% platinum were used as catalysts in 0.2–7 M HNO<sub>3</sub> at 50–80 °C, the reaction rate did not depend on the stirring intensity, *i.e.*, the reaction was kinetically controlled.

With an increase in [HNO<sub>3</sub>], the kinetic parameters of the N<sub>2</sub>H<sub>5</sub><sup>+</sup> decomposition on Pt/SiO<sub>2</sub> changed: the zero-order rate constant, *k*<sub>0</sub>, was invariable, whereas the first-order rate constant *k*<sub>1</sub> manifested a peak around 1–2 M HNO<sub>3</sub>. The overall effect of [HNO<sub>3</sub>]-dependent changes in *k*<sub>0</sub> + *k*<sub>1</sub> led to a situation where the maximum decomposition rate of hydrazine was observed in 1–2 M HNO<sub>3</sub>. The activation energies of first- and zero-order reactions in the presence of Pt/SiO<sub>2</sub> (50–80 °C) were equal to 61 and 50.6 kJ mol<sup>−1</sup>, respectively. For BAU, the activation energy was 68.6 kJ mol<sup>−1</sup> at 70–95 °C. With an increase in the Pt content on SiO<sub>2</sub> from 0.5% to 4%, *k*<sub>0</sub> and *k*<sub>1</sub> showed a tendency to increase, this increase being more pronounced for *k*<sub>1</sub>.

The stoichiometry, kinetics and mechanism of the catalytic decomposition of hydrazine in HNO<sub>3</sub> in the presence of 1% Pt/SiO<sub>2</sub> were studied in detail.<sup>9</sup> The results obtained by chemical and mass spectrometric methods suggest that N<sub>2</sub>, N<sub>2</sub>O and ammonium nitrate are the main decomposition products of hydrazine in HNO<sub>3</sub>. The formation of trace amounts of NO and NO<sub>2</sub> was also noted. The reaction products contained no hydrazoic acid (HN<sub>3</sub>), which made this reaction totally different from homogeneous oxidation of hydrazine with nitric acid.<sup>10</sup> The stoichiometric ratios [NH<sub>4</sub><sup>+</sup>]<sub>∞</sub>: [N<sub>2</sub>H<sub>5</sub><sup>+</sup>]<sub>0</sub> and ([NO<sub>3</sub><sup>−</sup>]<sub>0</sub> − [NO<sub>3</sub><sup>−</sup>]<sub>∞</sub>): [N<sub>2</sub>H<sub>5</sub><sup>+</sup>]<sub>0</sub> reflecting accumulation of ammonium ions and decrease in the total nitrate content vary depending on the concentration of nitric acid. Thus the increase in [HNO<sub>3</sub>] in the range 0.075–9.34 mol litre<sup>−1</sup> results in a decrease in [NH<sub>4</sub><sup>+</sup>]<sub>∞</sub>: [N<sub>2</sub>H<sub>5</sub><sup>+</sup>]<sub>0</sub> from 0.65 ± 0.01 to 0.36 ± 0.03, whereas ([NO<sub>3</sub><sup>−</sup>]<sub>0</sub> − [NO<sub>3</sub><sup>−</sup>]<sub>∞</sub>): [N<sub>2</sub>H<sub>5</sub><sup>+</sup>]<sub>0</sub> increased from 0.40 ± 0.01 to 0.97 ± 0.04. These data suggest a complex mechanism of catalytic decomposition of hydrazine in nitric acid-containing media. Presumably, the overall process is a superposition of two or more reactions where the contribution of each component is determined by the concentration of nitric acid. In 0.5–5 M HNO<sub>3</sub>, changes in these ratios are insignificant, which suggests that in the given range of [HNO<sub>3</sub>] the catalytic decomposition of hydrazinium nitrate occurs according to the stoichiometric equation:



The kinetics of the catalytic decomposition of hydrazine was studied in a thermostated glass reactor equipped with a reflux condenser. Stirring of the reaction mixture was carried out by a flow of argon at a controlled rate. Kinetic studies were performed at low initial concentrations of hydrazine (0.01 mol litre<sup>−1</sup>) in order to avoid problems in determining the reaction order with respect to N<sub>2</sub>H<sub>5</sub><sup>+</sup> due to adsorption saturation of active catalytic sites. The rate of catalytic decomposition of hydrazine increased with the intensity of the argon flow, which suggests that either this reaction proceeded in the diffusion regime or one of the volatile decomposition products decelerated the primary reaction by blocking the catalyst active sites.

The reaction order with respect to N<sub>2</sub>H<sub>5</sub><sup>+</sup> is not a constant value and varies from 0 to 1 with a change in [HNO<sub>3</sub>]. The dependence of the rate of the catalytic decomposition of hydrazine on the concentration of nitric acid is complex and has a minimum around [HNO<sub>3</sub>] 3.0–3.7 mol litre<sup>−1</sup>. The kinetic curves for this reaction are well described by the equation

$$-\frac{dc}{dt} = k_1c + k_0$$

over the whole range of experimental conditions.

The nature of the changes in the rate constants of the first- and zero-order reactions reflects the complex nature of heterogeneous catalytic reactions in the N<sub>2</sub>H<sub>5</sub><sup>+</sup>–HNO<sub>3</sub>–Pt system with an increase in [HNO<sub>3</sub>] (Fig. 4). At low concentrations of HNO<sub>3</sub> (0.25–2.0 mol litre<sup>−1</sup>), the changes in the first-order rate constant correspond with the negative fractional order (−0.24 ± 0.01) with respect to nitric acid. At higher concentrations of HNO<sub>3</sub> (4.0–8.0 mol litre<sup>−1</sup>), the value of the constant *k*<sub>1</sub> increases according to the apparent reaction order with respect to HNO<sub>3</sub> equal to 2.6 ± 0.2. The changes in the zero-order rate constants are consistent with the apparent reaction orders (1.96 ± 0.3 at 1.0–4.0 mol litre<sup>−1</sup> HNO<sub>3</sub> and −3.07 ± 0.3 at 4.0–7.0 mol litre<sup>−1</sup> HNO<sub>3</sub>). It is noteworthy that in 3 M nitric acid the catalytic decomposition of hydrazine strictly follows zero-order kinetics with respect to N<sub>2</sub>H<sub>5</sub><sup>+</sup>.

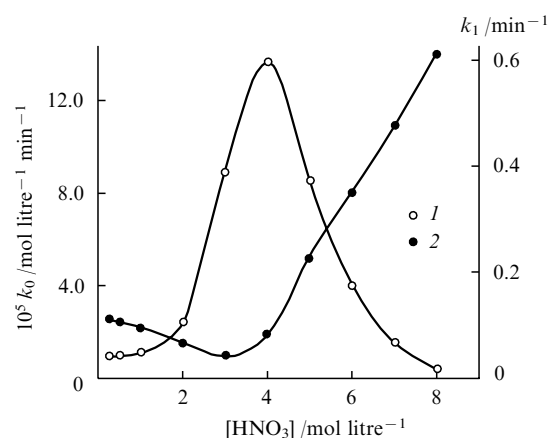


**Figure 4.** Changes in the zero- (1) and first- (2) order rate constants in the catalytic decomposition of hydrazine at 42 °C in the presence of 0.06 g ml<sup>−1</sup> of 1% Pt/SiO<sub>2</sub> with an increase in the concentration of nitric acid.<sup>6</sup>

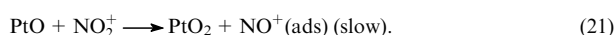
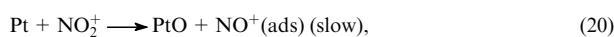
The temperature dependences of these rate constants were studied at three different concentrations of nitric acid (0.25, 3.1 and 6.2 mol litre<sup>−1</sup>).

In 0.25 M HNO<sub>3</sub>, the catalytic decomposition of hydrazine occurred predominantly as a first-order reaction with respect to N<sub>2</sub>H<sub>5</sub><sup>+</sup>. Therefore, only the *k*<sub>1</sub> values were used for the calculation of apparent activation energies. The value of *E*<sup>\*</sup> = 34.2 ± 0.5 kJ mol<sup>−1</sup> measured at 30.5–69 °C agreed, within the limits of experimental error, with that previously established for the catalytic decomposition of hydrazine in 0.2 M HClO<sub>4</sub> (36.4 ± 2.1 kJ mol<sup>−1</sup>) (see Ref. 70).

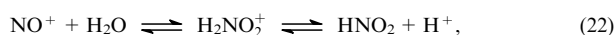
In 3.1 M HNO<sub>3</sub>, the values of apparent activation energies determined from the temperature dependences *k*<sub>0</sub> and *k*<sub>1</sub> were equal to 114.6 ± 4 kJ mol<sup>−1</sup> (22–52 °C) and 33.7 ± 2 kJ mol<sup>−1</sup> (22–41 °C) for zero- and first-order reactions with respect to N<sub>2</sub>H<sub>5</sub><sup>+</sup>, respectively. In 6.2 M HNO<sub>3</sub>, the apparent activation energy of the first-order reaction with respect to [N<sub>2</sub>H<sub>5</sub><sup>+</sup>] was 44.73 kJ mol<sup>−1</sup> in the temperature range 28–50 °C. The zero-order component was not taken into consideration, since its contribution to the overall process was extremely small under the given conditions. It is of note that the increase in temperature increased the contribution of the zero-order (with respect to N<sub>2</sub>H<sub>5</sub><sup>+</sup>) reaction to the overall process in 3.1 M HNO<sub>3</sub>, whereas in 6.2 M HNO<sub>3</sub> an opposite regularity was observed. The experimental apparent activation energies markedly exceeded those of diffusion-controlled processes [~19 kJ mol<sup>−1</sup> (see Ref. 31)], thus suggesting that all reactions involved in the heterogeneous cata-

lytic decomposition of hydrazine in  $\text{HNO}_3$  solutions are under kinetic control.

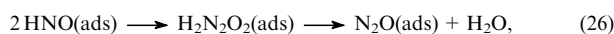
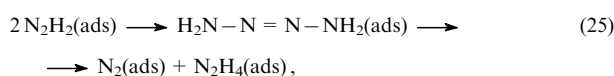
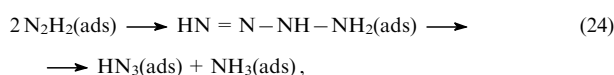
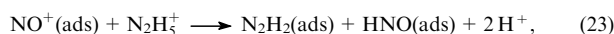
The analysis of kinetic curves revealed that the catalytic decomposition of hydrazine in nitric acid in the presence of  $\text{Pt}/\text{SiO}_2$  is a superposition of three independent first- and zero-order processes with respect to  $\text{N}_2\text{H}_5^+$ . These reactions occur in parallel and their contributions to the overall process are determined by the concentration of nitric acid. At low concentrations of  $\text{HNO}_3$  ( $0.25\text{--}2.0\text{ mol litre}^{-1}$ ), the first-order reaction with respect to  $\text{N}_2\text{H}_5^+$  and the negative fractional order with respect to the concentration of nitric acid are determined by heterogeneous decomposition of hydrazine on the platinum surface; the mechanism of this process was described previously for non-nitric acid solutions.<sup>70</sup> This conclusion is derived from the formal coincidence of reaction orders with respect to acid and apparent activation energies for solutions in perchloric and nitric acids. With an increase in the nitric acid concentration up to  $1\text{ mol litre}^{-1}$ , the contribution of the zero-order reaction with respect to  $\text{N}_2\text{H}_5^+$  becomes more apparent. In  $3\text{ M HNO}_3$ , the reaction rate is of the zero order with respect to hydrazine. At low concentrations of hydrazine ( $0.01\text{ mol litre}^{-1}$ ) in the C : R range from 1 : 100 to 1 : 10, no saturation of the catalyst surface with hydrazine occurs<sup>70</sup> and the appearance of a zero-order component with respect to  $\text{N}_2\text{H}_5^+$  cannot be attributed to the adsorption nature of this process. Most probably, the zero order of the reaction with respect to hydrazine is determined by its fast reaction with hydrazoic acid or one of its derivatives generated on the catalyst surface upon contact with  $\text{HNO}_3$ . The rate of hydrazine loss depends on the rate of formation of  $\text{HNO}_2$ . The possibility of oxidation of the surface of the platinum catalyst with nitric acid was substantiated<sup>9</sup> by thermodynamic calculations of equilibrium electrochemical potentials of platinum and nitric acid. It was shown that the equilibrium potential of the  $\text{HNO}_3/\text{HNO}_2$  pair in  $3\text{ M}$  nitric acid at nitrous acid concentrations of  $10^{-6}\text{--}10^{-4}\text{ mol litre}^{-1}$  (where  $\gamma_{\text{HNO}_2}$  was taken equal to unity) varied from 1.14 to 1.08 V relative to NHE. At the same time, assuming arbitrarily that  $[\text{Pt}^{2+}] = 10^{-6}\text{ mol litre}^{-1}$  and  $\gamma_{\text{Pt}^{2+}} = 1$ , the equilibrium potential values for the  $\text{Pt}^{2+}/\text{Pt}$  and  $\text{PtO}_2/\text{Pt}^{2+}$  pairs in  $3\text{ M HNO}_3$  are 1.011 and 1.077 V (NHE), respectively. A comparison of experimental values of equilibrium oxidation potentials suggests that metallic platinum is oxidised in  $\text{HNO}_3$  solutions to a tetravalent state ( $\text{PtO}_2$ ). This process is accompanied by the reduction of nitric acid to  $\text{HNO}_2$ . The following reaction scheme can be proposed:



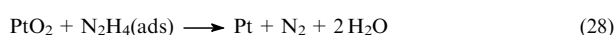
The adsorbed nitrosyl cations derived from nitrous acid according to the equilibrium



react with hydrazine by a cascade of fast reactions on the catalyst surface, which determines the zero order of the overall process with respect to  $\text{N}_2\text{H}_5^+$ :



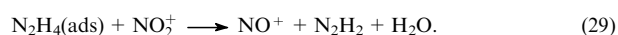
The oxidised active sites of the catalyst are regenerated as a result of their reaction with hydrazine



and thus become accessible for the next catalytic act.

From the above scheme, it can be seen that  $\text{HN}_3$  is a product of reaction (24). However, as mentioned above, no hydrazoic acid was detected either in the solution or in the effluent gases. Presumably, the  $\text{HN}_3$  molecules adsorbed on the catalyst were not desorbed into the solution, but underwent catalytic decomposition directly on the platinum surface.

The rate of the catalytic decomposition of hydrazine increases with an increase in the concentration of nitric acid in the range  $4\text{--}8\text{ mol litre}^{-1}$  simultaneously with a rapid change in the reaction order from zero to first with respect to  $\text{N}_2\text{H}_5^+$ . Presumably, in the region of high concentrations of  $\text{HNO}_3$  the crucial role should be ascribed to the catalytic oxidation of hydrazine with nitric acid. The rate-determining step of this reaction is the reaction of hydrazine molecules adsorbed on the catalyst surface with nitroyl cations generated in the equilibrium reaction (6):

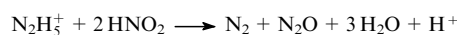


The concentration of adsorbed hydrazine is directly proportional to its solution concentration, which determines the first order of the reaction with respect to  $\text{N}_2\text{H}_5^+$ . The diimide and the nitrosyl cation generated in the reaction (29) undergo a series of fast transformations (23)–(27) both on the catalyst and in the solution.

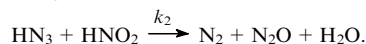
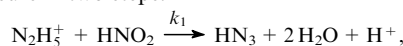
A comparative analysis of experimental results<sup>9,67</sup> of the catalytic decomposition of hydrazine in nitric acid suggests that the kinetic characteristics of this process depend critically on the mode of stirring of the reaction components. Thus the decomposition rate of hydrazine showed virtually no dependence on the shaking intensity<sup>67</sup> and passed through a maximum with an increase in  $[\text{HNO}_3]$  from 0.2 to  $7\text{ mol litre}^{-1}$ , whereas more intense stirring by a flow of argon caused a monotonic increase in the reaction rate. With an increase in the nitric acid concentration from 0.25 to  $8\text{ mol litre}^{-1}$ , the decomposition rate first slowed down and then showed an increase passing through a minimum around  $3.0\text{--}3.7\text{ mol litre}^{-1}$ . The reason for such a difference is that shaking of the reaction components in a closed volume results in accumulation of the gaseous decomposition products in the solution and on the catalyst surface, which inhibits the catalytic process by blocking the active sites. At the same time, passage of argon favours degassing of the solution and faster regeneration of the active surface of the catalyst.

#### 4. Decomposition of hydrazoic acid

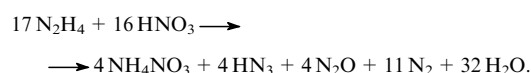
The use of hydrazine together with nitric acid in reprocessing of the used nuclear fuel results in the formation of hydrazoic acid as an undesirable intermediate.  $\text{HN}_3$  is formed in the reaction of hydrazine with nitrous acid. The overall oxidation reaction



occurs in two steps:



In solutions of moderate acidity,  $k_1 \approx 5k_2$  (see Ref. 72). From the above scheme it follows that the oxidation of excess hydrazine results in the accumulation of hydrazoic acid in the solution. At elevated temperatures,  $\text{HN}_3$  is formed by direct oxidation of hydrazine with nitric acid.<sup>31</sup>



The pertechnetate ions present in technological solutions catalyse hydrazine oxidation to give  $\text{HN}_3$ .<sup>73</sup>

Hydrazoic acid is related to the class of potentially hazardous chemical compounds due to its toxicity and explosive risk under certain conditions.<sup>74</sup> Therefore, its uncontrolled accumulation in technological solutions is inadmissible from the standpoint of



environmental and technological safety. The problem of elimination of hydrazoic acid from solutions can successfully be solved by using heterogeneous catalysis due to its ability to undergo catalytic decomposition in the presence of platinum black.<sup>75</sup> The kinetics and the decomposition mechanism of hydrazoic acid in solutions of nitric and perchloric acids in the presence of a catalyst (1% Pt/SiO<sub>2</sub>) have been studied.<sup>76</sup> The rate of the catalytic decomposition of HN<sub>3</sub> did not depend on the intensity of stirring of the reaction mixture. The reaction rate followed first-order kinetics with respect to HN<sub>3</sub> over the whole range of experimental conditions. An increase in the amount of the catalyst resulted in a proportional increase in the rate constant. The catalytic decomposition of HN<sub>3</sub> in nitric acid solutions first slowed down with an increase in the nitric acid concentration followed by its acceleration after passage through a minimum at [HNO<sub>3</sub>] 6 mol litre<sup>-1</sup>. In perchlorate solutions, the reaction rate decreased monotonically over the whole range of HClO<sub>4</sub> concentrations (0.5–8 mol litre<sup>-1</sup>) (Fig. 5). The apparent reaction orders with respect to nitric acid determined in 0.5–6 M HNO<sub>3</sub> and in 0.5–8.0 M HClO<sub>4</sub> were equal to -0.37 and -0.47, respectively. The negative fractional order of the reaction with respect to the acid in the concentration range specified suggests that neither hydrogen ions nor HNO<sub>3</sub> molecules directly participate in the chemical reaction resulting in the catalytic decomposition of hydrazoic acid. The inhibitory effect of H<sup>+</sup> ions may be due to competitive adsorption on the active catalytic sites.

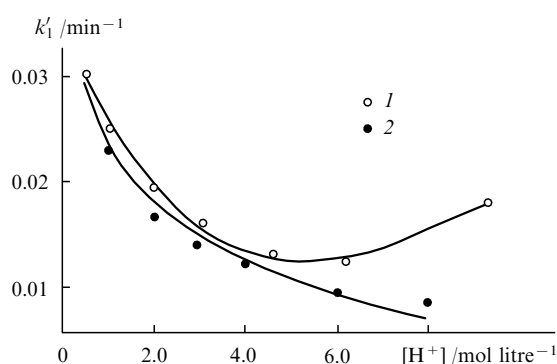
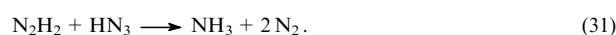
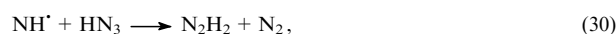
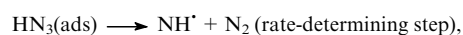
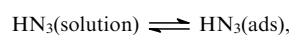


**Figure 5.** Effect of acid concentration on the decomposition rate of hydrazoic acid at [HN<sub>3</sub>]<sub>0</sub> = 0.025 mol litre<sup>-1</sup> and 64 °C in the presence of 0.1 g ml<sup>-1</sup> of 1% Pt/SiO<sub>2</sub>.<sup>76</sup> (1) HNO<sub>3</sub>, (2) HClO<sub>4</sub>.

The effect of temperature on the decomposition rate of HN<sub>3</sub> was studied in solutions of various compositions. The values of apparent activation energies are listed in the table below:

| Acid                   | <i>E</i> <sup>*</sup> / kJ mol <sup>-1</sup> | Acid                    | <i>E</i> <sup>*</sup> / kJ mol <sup>-1</sup> |
|------------------------|----------------------------------------------|-------------------------|----------------------------------------------|
| 1.0 M HNO <sub>3</sub> | 63.5 ± 1.8                                   | 6.2 M HNO <sub>3</sub>  | 74.6 ± 2.3                                   |
| 3.1 M HNO <sub>3</sub> | 69.0 ± 2.0                                   | 3.0 M HClO <sub>4</sub> | 67.2 ± 1.6                                   |

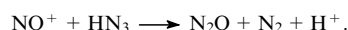
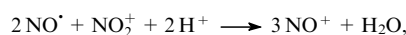
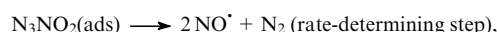
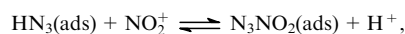
The increase in *E*<sup>\*</sup> with an increase in the acid concentration is due to the same reasons as in the catalytic decomposition of hydrazine in non-nitric acid media.<sup>70</sup> The mechanisms of the catalytic decomposition of hydrazoic acid in 0.5–8 M HClO<sub>4</sub> and in 0.5–6 M HNO<sub>3</sub> are virtually identical and based on heterogeneous catalytic decomposition of HN<sub>3</sub> adsorbed on the active sites of the catalyst.



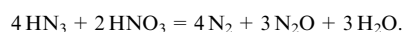
The fast reactions (30) and (31) may occur both on the catalyst surface and in solution. The general stoichiometric equation for both reactions is as follows:



The rate of the catalytic decomposition of HN<sub>3</sub> in solutions with [HNO<sub>3</sub>] > 6 mol litre<sup>-1</sup> increases considerably due to an increase in the contribution of oxidation reactions involving nitric acid.<sup>76</sup> The catalytic oxidation of hydrazoic acid consists of heterogeneous reactions of adsorbed HN<sub>3</sub> molecules with nitroyl ions in nitric acid media according to the equilibrium (6) followed by a series of fast homogeneous transformations *via* intermediate radicals.



In general, the oxidation process can be presented as follows:



It is noteworthy that the kinetic regularities and catalytic decomposition mechanisms of hydrazoic acid and hydrazine in nitric acid are roughly similar. In both cases, in solutions of low or medium acidities, the heterogeneous catalytic disproportionation of these compounds due to increase in [HNO<sub>3</sub>] is followed by heterogeneous catalytic oxidation, which involves nitroyl cations. It may thus be assumed that the catalytic decomposition of HN<sub>3</sub> in nitric acid, as of hydrazine, occurs through a catalytic redox cycle on the surface of platinum, which is similar to reactions (20), (21) and (28). However, in the case of HN<sub>3</sub> this process is kinetically indistinguishable, since its rate is considerably lower than the rates of catalytic disproportionation and oxidation of HN<sub>3</sub>, which occur in parallel.

The catalytic decomposition of hydrazoic acid in nitric acid was studied in the dynamic regime<sup>77</sup> using 1% Pt/SiO<sub>2</sub> as a catalyst. It was shown that the main characteristics of the continuous process, *viz.*, the effects of nitric acid concentration and temperature on the decomposition rate of HN<sub>3</sub>, were in good agreement with the kinetic data obtained in the static regime. The presence of sodium nitrate (20 g litre<sup>-1</sup>) and uranium (0.1 g litre<sup>-1</sup>) in the solution had no effect on the efficiency of the catalytic decomposition of hydrazoic acid. The decomposition rate of HN<sub>3</sub> decreased slightly when 0.5 M nitric acid saturated with spent TBP was used. However, such an effect was not related to the progressive poisoning of the catalyst, since the effects of TBP and its decomposition products on the reaction rate were of a steady and therefore reversible character. The decrease in the decomposition rate of HN<sub>3</sub> in the presence of TBP might be attributed to the equilibrium adsorption of organic molecules on the catalyst surface, as a result of which part of the active sites appeared to be occupied and did not take part in the catalytic process. The decrease in the reaction rate can be compensated for by mere elevation of temperature or by reduction of the flow rate of the working solution.

The catalytic decomposition of hydrazoic acid in the dynamic regime is a technologically efficient process and can be recommended for removal of HN<sub>3</sub> from radioactive wastes before their final processing.

## 5. Catalytic denitration of nitric acid solutions

Modern wet technologies for processing waste nuclear fuels starting from the dissolution of fuel elements and ending with separation and purification of isolated radioactive components are based on the use of nitric acid solutions. However, the problem of processing of water-tail fractions by their further vitrification cannot successfully be solved without removal of excess nitric acid and nitrates. This is usually accomplished by chemical denitration

of solutions with formic acid or formaldehyde.<sup>78–82</sup> The main problem in this procedure consists of the autocatalytic mode of the reaction of nitric acid with  $\text{HCO}_2\text{H}$  and  $\text{HCHO}$ . Such reactions are usually characterised by induction periods where accumulation of threshold concentrations of nitrous acid in the solution occurs and subsequent fast propagation of the process. Under certain conditions, the denitration assumes the form of an explosive process that is difficult to control. This circumstance makes chemical denitration a potentially dangerous process. Numerous cases of grave accidents upon denitration at pilot-plant and industrial installations for processing used materials are documented in the literature.<sup>83,84</sup>

It has been established<sup>58</sup> that the reaction of nitric acid with formic acids in the presence of a catalyst ( $\text{Pt}/\text{SiO}_2$ ) begins without any induction period and proceeds without any pressure surge in the reaction system (Fig. 6). The kinetics and stoichiometry of the catalytic reaction of  $\text{HNO}_3$  with  $\text{HCO}_2\text{H}$  were studied in a broad range of experimental conditions ( $[\text{HNO}_3]_0 = 0.7\text{--}8.0\text{ mol litre}^{-1}$ ;  $[\text{HCO}_2\text{H}]_0 = 0.5\text{--}4.3\text{ mol litre}^{-1}$ ; temperature  $55\text{--}85\text{ }^\circ\text{C}$ ;  $\text{C}:\text{R} = 1:10\text{--}1:50$ , 1%  $\text{Pt}/\text{SiO}_2$ ). In all cases, the reaction began without any induction period. If such a period did exist, its duration would be no longer than the time required for the mixing of the reactants. In dilute ( $2\text{ mol litre}^{-1}$ )  $\text{HNO}_3$  solutions, the kinetic curves were described by a first-order equation with respect to  $\text{HCO}_2\text{H}$ . In more concentrated  $\text{HNO}_3$  solutions, the reaction was of the first order with respect to formic acid until the extent of decomposition reached 40%–50%; at higher degrees of conversion, the reaction rate decreased. In these cases, the first-order equation was used for the estimation of the initial rate of the reaction. The increase in the stirring intensity on passing an inert gas through the reaction mixture resulted in deceleration of the reaction, which points to the involvement of intermediate gaseous products in the oxidation of  $\text{HCO}_2\text{H}$ . A similar phenomenon was observed where the reaction was carried out in the absence of the catalyst.<sup>78</sup> The rate of the reaction of  $\text{HCO}_2\text{H}$  with  $\text{HNO}_3$  increased linearly with the increase in the  $\text{C}:\text{R}$  ratio, which points to the catalytic nature of the process. The reaction rate increased rapidly with the concentration of nitric acid. The dependence of the rate constant on  $[\text{HNO}_3]$  had a complex form, which did not permit an unambiguous estimation of the reaction order with respect to nitric acid. It may be concluded, however, that the apparent order of the reaction with respect to nitric acid approximated 3 with an increase in  $[\text{HNO}_3]$  above  $2\text{ mol litre}^{-1}$ , which is characteristic of reactions occurring in the absence of a catalyst.<sup>78,80</sup> The apparent reaction order with respect to hydrogen ions at a constant concentration of nitrate ions changed monotonically from 0 to 4 with an increase in  $[\text{H}^+]$  from 0.7 to  $5\text{ mol litre}^{-1}$ . The activation energy of the reaction of

$\text{HNO}_3$  with  $\text{HCO}_2\text{H}$  in the presence of a platinum catalyst was determined at different concentrations of nitric acid:

| $[\text{HNO}_3]/\text{mol litre}^{-1}$ | $E^*/\text{kJ mol}^{-1}$ |
|----------------------------------------|--------------------------|
| 0.94                                   | $84.2 \pm 2.2$           |
| 3.14                                   | $105.0 \pm 4.0$          |
| 4.92                                   | $113.2 \pm 3.1$          |

It can be seen that the increase in the concentration of nitric acid results in a considerable increase in the apparent activation energy, which gradually approximates that for a denitration process occurring in the absence of a catalyst [ $126\text{ kJ mol}^{-1}$  (see Ref. 80)].

This fact and the effects of acidity and total concentration of nitric acid on the reaction rate suggest that two parallel processes, viz., catalytic reaction of nitric acid with  $\text{HCO}_2\text{H}$  and homogeneous denitration, occur in the system under study, the contribution of the latter to the overall process being increased with  $[\text{HNO}_3]$ . Earlier studies<sup>38</sup> have demonstrated the absence of autocatalytic accumulation of nitrous acid at low ( $1\text{ mol litre}^{-1}$ ) concentrations of  $\text{HNO}_3$ . If  $\text{HNO}_2$  was present in the solution from the very first steps, its concentration diminished gradually during its reaction with  $\text{HCO}_2\text{H}$ . Here, the denitration occurred only in the presence of a catalyst according to a heterogeneous catalytic mechanism. Therefore, the value of  $E^* = 84.2\text{ kJ mol}^{-1}$  obtained at  $[\text{HNO}_3] = 0.94\text{ mol litre}^{-1}$  can be regarded as an apparent activation energy of the catalytic process. At higher concentrations of nitric acid that favour the accumulation of  $\text{HNO}_2$ , the contribution of the autocatalytic reaction increased and at  $[\text{HNO}_3] > 4\text{ mol litre}^{-1}$  the process occurred mainly according to the kinetic regularities of homogeneous denitration.

The catalytic denitration gaseous products are represented by  $\text{CO}_2$ ,  $\text{NO}_2$ ,  $\text{NO}$  and  $\text{N}_2\text{O}$ ; the evolution of  $\text{N}_2\text{O}$  was suppressed upon increase in the concentration of nitric acid. The fact that no hydrogen was found in the gaseous reaction products suggests the absence of catalytic self-decomposition of formic acid under the given experimental conditions. Calculations of the gas balance of  $\text{HCO}_2\text{H}$  based on the results of gas analysis and kinetic measurements show the formation of 1 mole of  $\text{CO}_2$  per mole of the consumed formic acid. Stoichiometric measurements demonstrated that the consumption of formic acid in the catalytic denitration was 1.1–1.5 moles of  $\text{HCO}_2\text{H}$  per mole of the consumed  $\text{HNO}_3$  (Table 3), which is virtually the same as in a non-catalysed reaction, all other experimental conditions being the same.

**Table 3.** Stoichiometry of the denitration reaction in the presence of a catalyst (1%  $\text{Pt}/\text{SiO}_2$ ) at  $60\text{ }^\circ\text{C}$ .<sup>58</sup>

| $[\text{HNO}_3]_0$<br>/mol litre <sup>-1</sup> | $[\text{HCO}_2\text{H}]_0$<br>/mol litre <sup>-1</sup> | $\text{C}:\text{R}$<br>/g ml <sup>-1</sup> | Time<br>/min | Degree of<br>conversion of<br>$\text{HCO}_2\text{H}$ (%) | $\frac{\Delta[\text{HCO}_2\text{H}]}{\Delta[\text{HNO}_3]}$<br>(see <sup>a</sup> ) |
|------------------------------------------------|--------------------------------------------------------|--------------------------------------------|--------------|----------------------------------------------------------|------------------------------------------------------------------------------------|
| 4.72                                           | 1                                                      | 0.04                                       | 30           | 50                                                       | $1.19 \pm 0.04$                                                                    |
| 4.75                                           | 1                                                      | 0.04                                       | 30           | 50                                                       | $1.18 \pm 0.03$                                                                    |
| 4.75                                           | 1                                                      | 0.04                                       | 60           | 80                                                       | $1.25 \pm 0.01$                                                                    |
| 4.75                                           | 1                                                      | 0.04                                       | 120          | 92                                                       | $1.26 \pm 0.02$                                                                    |
| 4.08                                           | 4.3                                                    | 0.03                                       | 70           | 82                                                       | $1.49 \pm 0.02$                                                                    |
| 4.08                                           | 4.3                                                    | 0.03                                       | 120          | 92                                                       | $1.50 \pm 0.01$                                                                    |
| 4.08 <sup>b</sup>                              | 4.3                                                    | 0.07                                       | 120          | 96                                                       | $1.49 \pm 0.02$                                                                    |
| 4.08                                           | 4.3                                                    | see <sup>c</sup>                           | 70           | 85                                                       | $1.44 \pm 0.01$                                                                    |
| 6.37                                           | 1                                                      | 0.04                                       | 16           | 47                                                       | $1.06 \pm 0.01$                                                                    |
| 6.37                                           | 1                                                      | 0.04                                       | 25           | 73                                                       | $1.09 \pm 0.01$                                                                    |
| 6.37                                           | 1                                                      | 0.04                                       | 45           | 85                                                       | $1.11 \pm 0.01$                                                                    |
| 6.37                                           | 1                                                      | 0.04                                       | 60           | 90                                                       | $1.2 \pm 0.1$                                                                      |
| 5.52                                           | 4.17                                                   | 0.04                                       | 120          | 98                                                       | $1.36 \pm 0.01$                                                                    |

<sup>a</sup> Average values from five measurements. <sup>b</sup> In this case, the temperature was  $70\text{ }^\circ\text{C}$ . <sup>c</sup> Without catalyst.

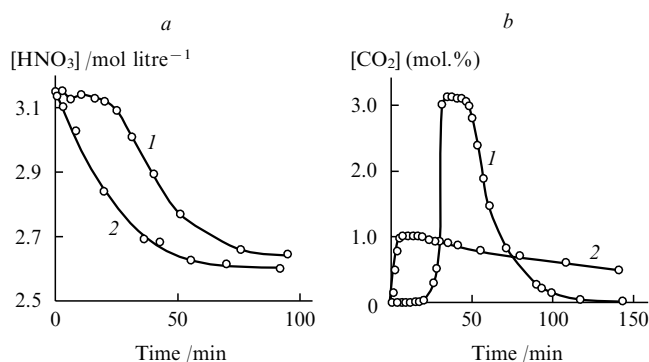


**Figure 6.** Effect of a platinum catalyst on the decomposition kinetics of nitric acid (a) and  $\text{CO}_2$  formation (b) in the denitration.<sup>58</sup>  
 $[\text{HNO}_3]_0 = 3.14\text{ mol litre}^{-1}$ ;  $[\text{HCO}_2\text{H}]_0 = 1.1\text{ mol litre}^{-1}$  at  $70\text{ }^\circ\text{C}$ .  
 (1) without catalyst, (2) with catalyst (1%  $\text{Pt}/\text{SiO}_2$ ); (a)  $0.04\text{ g ml}^{-1}$ , (b)  $0.1\text{ g ml}^{-1}$ .

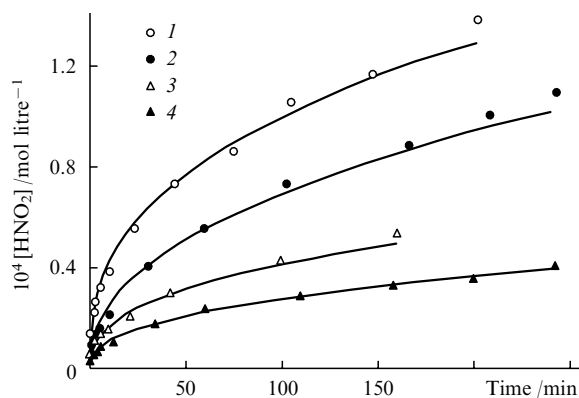
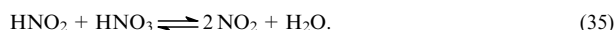
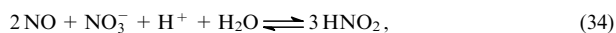
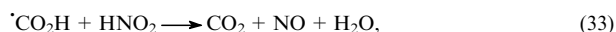
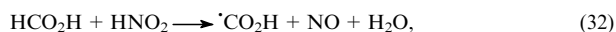


**Figure 7.** Effect of the catalyst (1% Pt/SiO<sub>2</sub>) on the accumulation of nitrous acid in 1.1 M HNO<sub>3</sub> at 60 °C.<sup>58</sup>

C : R / g ml<sup>-1</sup>: 0.20 (1), 0.15 (2), 0.10 (3), 0.05 (4).

The mechanism of catalytic denitration and the role of a platinum catalyst in the initiation of the reaction and suppression of the induction period have been reviewed.<sup>58, 85</sup> It was found<sup>58</sup> that the addition of a catalyst (Pt/SiO<sub>2</sub>) to 0.5–4 M solutions of HNO<sub>3</sub> resulted in rapid accumulation of nitrous acid (Fig. 7), which reacts with HCO<sub>2</sub>H to initiate the denitration.



Accelerated formation of HNO<sub>2</sub> in nitric acid solutions upon a contact with a platinum catalyst results from oxidation of surface platinum atoms with nitroyl cations [see reactions (20)–(22)], as is the case with catalytic decomposition of hydrazine in HNO<sub>3</sub> solutions.<sup>9</sup> In the absence of a reducing agent, the catalyst surface is passivated and the formation of hydrazoic acid is discontinued.<sup>85</sup> After addition of formic acid to the reaction system, the oxidised platinum atoms react with HCO<sub>2</sub>H molecules and thus become accessible to a new attack by nitric acid resulting in the formation of HNO<sub>2</sub>. Thus, the surface catalytic redox cycle is implemented in the system, which favours fast initial accumulation of the threshold concentration of nitrous acid [ $\sim 10^{-2}$  mol litre<sup>-1</sup> (see Ref. 79)] required for triggering the denitration reaction. The mechanism of the catalytic denitration is schematically depicted in Fig. 8.

A significant advantage of catalytic denitration over the homogeneous process is that it occurs even in the presence of the

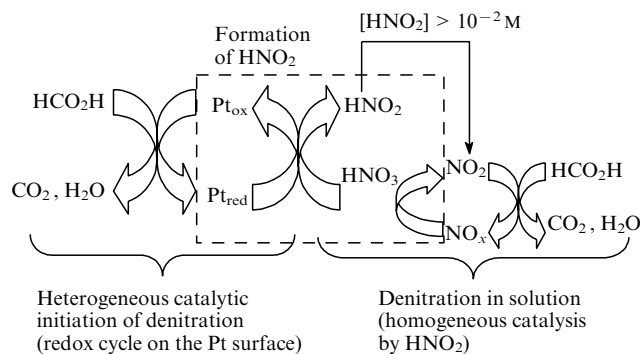


**Figure 8.** A schematic representation of a catalytic denitration mechanism.

antinitrite reagent (urea), although the reaction is slowed down.<sup>58</sup> However, the reaction rate increases after complete decomposition of (NH<sub>2</sub>)<sub>2</sub>CO. The same is true for hydrazine. Studies on catalytic decomposition of excess nitric acid in plutonium-containing solutions have shown that in the presence of Pt(IV) (2–25 g litre<sup>-1</sup>) the denitration proceeds without any induction period and complications in a broad range of initial concentrations of nitric and formic acids. In the presence of excess of HCO<sub>2</sub>H, partial (up to 30%) reduction of Pu(IV) to Pu(III) is observed at the end of the process.<sup>58</sup> The catalytic denitration in the presence of excess of HCO<sub>2</sub>H enables virtually complete decomposition of nitric acid. Thus no nitric acid could be detected by potentiometry in a solution containing  $\sim 1$  mol litre<sup>-1</sup> of formate following denitration. Long-term use of catalysts for denitration does not result in their poisoning. After more than 100 cycles, not a single case of a decrease in the catalytic activity of the catalyst (1% Pt/SiO<sub>2</sub>) taken from the same batch was noted.<sup>58</sup>

## 6. Decomposition of urea and ammonium nitrate in the catalytic denitration

Urea (carbamide) is widely employed in radiochemical processes as an antinitrite reagent, *e.g.*, for electrochemical reduction of uranium(VI) in nitric acid solutions.<sup>19</sup> Like any other antinitrite reagent, urea is decomposed by an addition of sodium nitrite to nitric acid solutions<sup>72</sup> or by passage of gaseous nitrogen oxides NO and NO<sub>2</sub> (NO<sub>x</sub>-gases) through a solution.<sup>86</sup> However, despite the obvious simplicity and efficiency of these procedures, the addition of NaNO<sub>2</sub> to the solution is not always desirable, since it is accompanied by an increase in the total salt content, whereas the latter method requires an additional source of NO<sub>x</sub> gases.

As shown above, the platinum-catalysed reaction of nitric acid with formic acids (catalytic denitration) occurs successfully in the presence of urea and is accompanied by its efficient decomposition.<sup>58</sup> At the same time, this reaction is impossible in the absence of a catalyst and carbamide-containing HNO<sub>3</sub>–HCO<sub>2</sub>H mixtures remain stable over indefinitely long periods of time even at elevated temperatures. The specific behaviour of urea in the catalytic denitration in the presence of a catalyst (1% Pt/SiO<sub>2</sub>) has been studied.<sup>87, 88</sup> It was shown that in the absence of formic acid carbamide was not subject to catalytic decomposition in 0–8 M HNO<sub>3</sub> even at temperatures close to the boiling point of the solution. However, the addition of 0.1–2 mol litre<sup>-1</sup> of HCO<sub>2</sub>H to 2 M HNO<sub>3</sub> containing 0.5 mol litre<sup>-1</sup> of carbamide and 0.02–0.2 g ml<sup>-1</sup> of 1% Pt/SiO<sub>2</sub> induced the decomposition of (NH<sub>2</sub>)<sub>2</sub>CO at 60 °C resulting in the denitration of the solution. The catalytic decomposition of urea in the presence of 0.2–1.3 mol litre<sup>-1</sup> of HCO<sub>2</sub>H and at C : R = 1 : 50 began at 60 °C at a concentration of nitric acid equal or higher than 2 mol litre<sup>-1</sup> (see Ref. 87). The kinetic curves of the consumption of (NH<sub>2</sub>)<sub>2</sub>CO changed significantly with an increase in [HNO<sub>3</sub>] (Fig. 9). In the HNO<sub>3</sub> range 2–2.5 M, the reaction occurred with an induction period followed by accelerated decomposition of urea. At higher concentrations of nitric acid, the decomposition of urea occurred without the induction period and is zero order with respect to (NH<sub>2</sub>)<sub>2</sub>CO. The rate of this zero-order process did not depend on the intensity of stirring of the solution, *i.e.*, the reaction proceeded under kinetic control. The increase in C : R in the range 1 : 50–1 : 10 resulted in a proportional increase in the reaction rate, which is characteristic of heterogeneous catalytic processes in solutions. The reaction rate increases with the concentration of formic acid; the reaction order with respect to HCO<sub>2</sub>H was close to unity. With an increase in the initial concentration of nitric acid from 2.3 to 7.0 mol litre<sup>-1</sup>, the decomposition rate of urea decreased considerably. The dependence of *k*<sub>0</sub> on [HNO<sub>3</sub>] in logarithmic coordinates was not approximated by a straight line, which excluded the unambiguous interpretation of the reaction order with respect to nitric acid. The apparent activation energy of this reaction determined at [HNO<sub>3</sub>]<sub>0</sub> = 2.9 mol litre<sup>-1</sup>, [HCO<sub>2</sub>H]<sub>0</sub> = 1.0 mol litre<sup>-1</sup> and [(NH<sub>2</sub>)<sub>2</sub>CO]<sub>0</sub> = 0.2 mol litre<sup>-1</sup> was 58.7 ± 1.6 kJ mol<sup>-1</sup>.

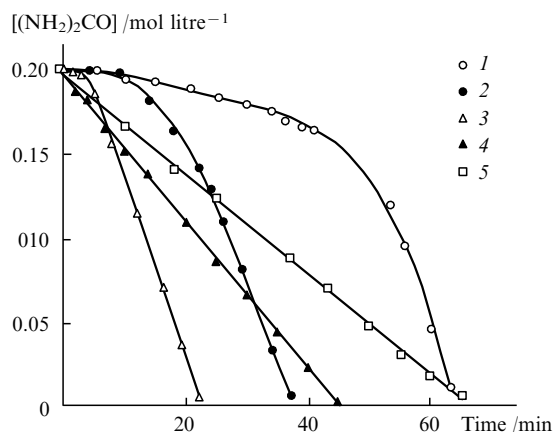


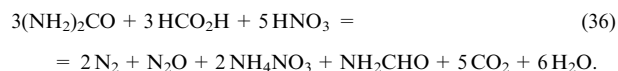
**Figure 9.** Kinetic curves for the decomposition of urea ( $0.2 \text{ mol litre}^{-1}$ ) in nitric acid solutions of variable concentrations in the presence of  $0.1 \text{ g ml}^{-1}$  of 1% Pt/SiO<sub>2</sub> at  $[\text{HCO}_2\text{H}]_0 = 1.0 \text{ mol litre}^{-1}$  and at  $60^\circ\text{C}$ .<sup>87</sup>  $[\text{HNO}_3] / \text{mol litre}^{-1}$ : 2.0 (1), 2.1 (2), 2.3 (3), 2.6 (4), 5.6 (5).

The kinetic data altogether, namely, the threshold type of the reaction with respect to  $[\text{HNO}_3]$ , the induction period, the zero reaction order with respect to  $(\text{NH}_2)_2\text{CO}$ , the impossibility of performing the catalytic decomposition of carbamide in the absence of  $\text{HCO}_2\text{H}$ , prompt a conclusion that the decomposition of urea is a result of its reaction with nitrous acid generated in the reaction system upon catalytic denitration according to the equations (32)–(34). The rate of decomposition of carbamide is determined by the rate of formation of  $\text{HNO}_2$  generated upon catalytic reaction of nitric acid with  $\text{HCO}_2\text{H}$  according to a mechanism presented in Fig. 8.

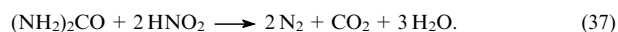
As mentioned above, the kinetics of decomposition of urea manifests a rather complex dependence on the concentration of nitric acid. The threshold type of this reaction with respect to  $[\text{HNO}_3]$  and the induction period in the range  $2.0\text{--}2.3 \text{ M HNO}_3$  are determined by the autocatalytic type of the reaction of nitric acid with formic acid. The concentration of nitrous acid in the  $\text{HNO}_3\text{--HCO}_2\text{H}$  mixture increases in an autocatalytic manner at  $[\text{HNO}_3] = 1\text{--}3.8 \text{ mol litre}^{-1}$  and decreases at  $[\text{HNO}_3] < 1 \text{ mol litre}^{-1}$ .<sup>38</sup> This is associated with a strong effect of  $[\text{HNO}_3]$  on the rate and the equilibrium of the reaction (34).<sup>89</sup> In a system containing  $\text{HCO}_2\text{H}$ ,  $\text{HNO}_3$  and carbamide, a positive balance of  $\text{HNO}_2$  generated by reaction (34) with respect to  $\text{HNO}_2$  consumed in reactions (37) and (38) (see below) in the presence of Pt/SiO<sub>2</sub> is established at  $[\text{HNO}_3] > 2 \text{ mol litre}^{-1}$ . Reaction of excess nitrous acid with urea leads to the decomposition of the latter. At  $[\text{HNO}_3] = 2\text{--}2.3 \text{ mol litre}^{-1}$ , the formation of nitrous acid occurs with acceleration, which results in the appearance of an induction period. Urea is related to the class of ‘mild antinitrite reagents’. The rate of its reaction with nitrous acid is relatively low, but shows a rapid increase with an increase in the solution acidity.<sup>73</sup> It is this fact that is responsible for the decrease in the rate of the catalytic decomposition of urea with an increase in the concentration of nitric acid. Indeed, the formation of nitrous acid in the solution (the reaction system) results from two different processes, *viz.*, the catalytic redox cycle involving nitric acid and  $\text{HCO}_2\text{H}$  on the platinum surface and autocatalytic generation of  $\text{HNO}_2$  in the solution [see reactions (32)–(34)]. The rapid acceleration of the rate of the reaction of nitrous acid with carbamide at increasing  $[\text{HNO}_3]$  leads to the inhibition of autocatalytic formation of  $\text{HNO}_2$ . As a result, the rate of formation of nitrous acid in the solution decreases with a concomitant decrease in the decomposition rate of urea with an increase in  $[\text{HNO}_3]$ .

The composition of the reaction products and the stoichiometry of the catalytic decomposition of urea in the  $\text{HNO}_3\text{--HCO}_2\text{H}\text{--Pt/SiO}_2$  system have been studied in detail.<sup>88</sup> Gaseous decomposition products of urea include  $\text{CO}_2$ ,  $\text{N}_2\text{O}$  and

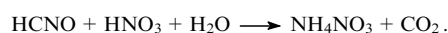
$\text{N}_2$ . A small amount of  $\text{NO}_2$  and trace amounts of  $\text{H}_2$  are also formed. Ammonium nitrate and formamide are formed in the solution. In general, the decomposition of urea under catalytic denitration conditions can be described in terms of the stoichiometric equation:



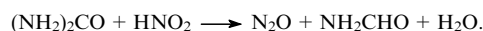
Although this process is based on the reaction of  $(\text{NH}_2)_2\text{CO}$  with nitrous acid formed, the compositions of gaseous and soluble decomposition products of urea in the  $\text{HNO}_3\text{--HCO}_2\text{H}\text{--Pt/SiO}_2$  system differ essentially from that expected for the generally accepted scheme of the reaction of carbamide with  $\text{HNO}_2$ .<sup>72, 86, 90</sup>



The reason for this discrepancy is that carbamide, being in excess under catalytic denitration conditions, reacts with  $\text{HNO}_2$  formed. In this case, the following reaction sequence leading to ammonium nitrate as a result of acid hydrolysis of the intermediate product, *viz.*, cyanic acid, is implemented:<sup>91</sup>

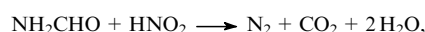


Formamide and nitrogen(I) oxide also seem to be partial oxidation products of urea with nitrous acid in the presence of excess of  $(\text{NH}_2)_2\text{CO}$ .



Formamide is less subject to acid hydrolysis in comparison with cyanic acid<sup>92</sup> and is therefore accumulated in the solution until the decomposition of carbamide is complete.

The rate of catalytic denitration increases after urea decomposition is over. This is accompanied by a jump-like increase in  $[\text{HNO}_2]$  in the solution with subsequent rapid return to the quasi-steady state;  $[\text{HNO}_2]$  remains at this level up to the end of the denitration (Fig. 10). Under these conditions, soluble decomposition products of urea, *viz.*, formamide and ammonium nitrate, are unstable and undergo further degradation.<sup>88</sup> Apparently, these reactions can be described by the following equations:



It was suggested<sup>88</sup> that the decomposition of formamide and ammonium nitrate is accelerated in the presence of catalysts. The regularities of decomposition reactions of nitrogen-containing compounds present substantial scientific and practical interest.

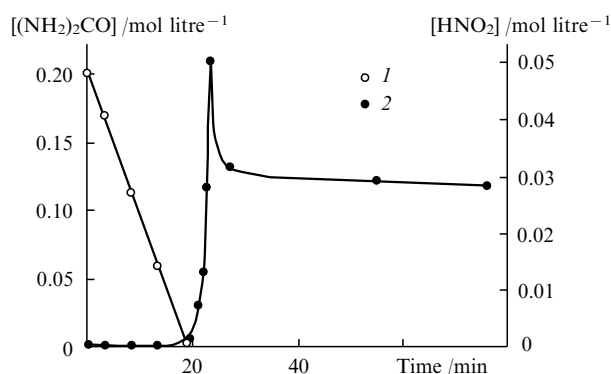


**Figure 10.** Dynamics of changes in the concentrations of urea (1) and nitrous acid (2) in the decomposition of urea in the presence of  $0.1 \text{ g ml}^{-1}$  of 1% Pt/SiO<sub>2</sub> at  $70^\circ\text{C}$ .<sup>87</sup>  $[\text{HNO}_3]_0 = 3.3 \text{ mol litre}^{-1}$ ,  $[\text{HCO}_2\text{H}]_0 = 1.0 \text{ mol litre}^{-1}$

In the first place, this concerns ammonium nitrate. The search for approaches to its removal from water-tail fractions of radiochemical plants presents a serious problem for the technology of the nuclear fuel cycle. The decomposition of ammonium nitrate under conditions of denitration was considered in detail.<sup>93</sup> A series of experiments on the denitration of nitric acid solutions containing ammonium nitrate under static conditions have been carried out recently in order to elucidate the role of platinum catalysts in the homogeneous and catalytic decomposition of ammonium nitrate formed in the reaction of  $\text{HNO}_3$  with  $\text{HCO}_2\text{H}$ . As expected, in the absence of catalysts the denitration was preceded by an induction period of 3–60 min, which varied depending on the initial concentration of nitric acid, and followed by a fast reaction characteristic of homogeneous denitration. In all cases, in the presence of a platinum catalyst this reaction proceeded without an induction period. The results obtained suggest that the presence of  $\text{Pt}/\text{SiO}_2$  in the reaction system has virtually no effect on the degree of decomposition of ammonium nitrate in the course of denitration. From the kinetic point of view, the role of the catalyst is only reduced to the elimination of the induction period, *i.e.*, to the initiation of the reaction of nitric acid with  $\text{HCO}_2\text{H}$ . As a consequence, the chemical reaction resulting in the oxidation of the ammonium ion takes place in the solution rather than on the catalyst surface, *i.e.*, is homogeneous. It was found that the degree of decomposition of ammonium nitrate increases with an increase in the initial concentration of nitric acid in the range 0.5–4 mol  $\text{litre}^{-1}$ . Further increase in  $[\text{HNO}_3]$  slightly reduces the reaction yield. The increase in the concentration of formic acid in the presence of an excess of  $\text{HNO}_3$  enhances the decomposition of  $\text{NH}_4\text{NO}_3$ . However, the efficiency of this reaction diminishes at the molar ratios  $[\text{HCO}_2\text{H}]:[\text{HNO}_3] > 0.8\text{--}1.0$ . The increase in temperature from 80 to 100 °C increases the reaction yields by 12%. These regularities were interpreted under the assumption that the disappearance of ammonium nitrate is due to the homogeneous oxidation of ammonium ions with nitrous acid [reaction (39)]. In this case, the role of a nitrous acid precursor is played by the  $\text{HNO}_3\text{--HCO}_2\text{H}$  system where  $\text{HNO}_2$  is accumulated by an autocatalytic mechanism [reactions (32)–(34)] underlying chemical denitration of nitric acid solutions. Obviously, the oxidation rate of the ammonium ion with nitrous acid is lower than its formation rate, otherwise the presence of ammonium nitrate in the solution will prevent denitration in the absence of a platinum catalyst due to inhibition of the autocatalytic formation of  $\text{HNO}_2$ . The efficiency of ammonium nitrate decomposition should be determined by the steady-state concentration of nitrous acid rather than its formation rate. The equilibrium concentrations of  $\text{HNO}_2$  in nitric acid solutions in the absence of other oxidants and reducing agents are largely determined by the interrelated reversible reactions (34) and (35). A comparison of these equilibria shows that an increase in the concentration of nitric acid in the reaction system results, on the one hand, in an increase in the yield of  $\text{HNO}_2$  and, on the other hand, in its decomposition due to oxidation to nitrogen dioxide. If reactions are carried out in open systems, the yields of  $\text{NH}_4\text{NO}_3$  decomposition products are lower as a result of removal of gaseous  $\text{NO}_2$  from the reactor. It is this factor that accounts for the decrease in the reaction rate and prevents further increases in the yields of decomposition of ammonium nitrate at  $[\text{HNO}_3] > 4$  mol  $\text{litre}^{-1}$ . The non-monotonic changes in the degree of decomposition of ammonium nitrate with an increase in the ratio  $[\text{HCO}_2\text{H}]:[\text{HNO}_3]$  can be attributed to the changes in the stoichiometry of the denitration reaction, which in turn is determined by the ratio of concentrations of nitric and formic acids.<sup>57</sup> The maximum yield of  $\text{NO}$  involved in the formation of nitrous acid is observed at the  $[\text{HCO}_2\text{H}]:[\text{HNO}_3]$  molar ratio  $\approx 0.8\text{--}1.0$ , which accounts for the observed pattern of changes in the degree of decomposition of  $\text{NH}_4\text{NO}_3$ . The maximum (close to 100%) degree of decomposition of ammonium nitrate is reached upon continuous addition of formic acid to solutions of ammonium nitrate in nitric acid in the presence of a catalyst ( $\text{Pt}/\text{SiO}_2$ ). This

method can be used for the decomposition of ammonium nitrate in solutions with complex compositions. Thus it was shown<sup>93</sup> that the presence of caesium or uranyl nitrates (10 g  $\text{litre}^{-1}$  with respect to the metal) in the solution has no effect on the reaction efficiency. If compounds containing  $\text{NH}_2$  groups (*e.g.*, hydrazine, urea or acetamide) are added, their catalytic degradation precedes the decomposition of ammonium nitrate. In this case, the process occurs only in the presence of a catalyst.

#### IV. Conclusion

Analysis of the literature data on the kinetics of heterogeneous catalytic redox reactions of actinide ions in aqueous media revealed that the majority of publications on the subject are devoted to studies of reduction of actinide ions with molecular reducing agents to the lowest oxidation states. The array of catalysts assayed is confined to activated charcoal and finely dispersed metals of the platinum group (as a rule, Pt) on inert supports. Despite the fact that catalytic properties of palladium and rhenium sulfides are now well established, these materials have not found wide application because of poorly developed surfaces. It seemed therefore tempting to prepare  $\text{PdS}$  or  $\text{Re}_2\text{S}_7$  immobilised on supports with a more developed surface and to examine their activities in reactions with  $\text{U(VI)}$ ,  $\text{Np(V)}$  and  $\text{Pu(IV)}$ . It would also be interesting to broaden the range of non-platinum catalysts and to study catalytic properties of  $\text{Tc}_2\text{S}_7$  or a  $\text{Re}_2\text{S}_7 + \text{Tc}_2\text{S}_7$  mixture.

The choice of a support for active catalytic components is a task of no less importance due to demands from radiochemical technology. Aggressive nitric acid media and high-intensity radiation pose serious restrictions on the choice of supports. They should possess high chemical stability and radiation resistance, high mechanical strength and ease of application of the active component. Catalysts with finely dispersed platinum supported on spherical silica gel beads ( $\text{Pt}/\text{SiO}_2$ ) were chosen for the totality of properties. Silica gel is most often used as a support; it possesses high chemical stability in nitric acid media, however, it is not a support of choice due to low mechanical strength and low abrasion resistance, which inevitably leads to mechanical degradation of the catalyst grains upon long-term utilisation. Moreover, the use of  $\text{SiO}_2$  is restricted to acidic media. The use of silica gel as a support in alkaline and carbonate solutions is impossible due to its low chemical stability in these media. Therefore, a search for novel supports is a topical task in heterogeneous catalysis in aqueous media. In this respect, composite materials based on titanium, zirconium and thorium dioxides are promising. By virtue of their high chemical stability in acidic and alkaline media, sintered porous microgranules prepared by the sol-gel procedure should manifest sufficiently high mechanical strengths and high durability. Of special interest are studies of the effect of the nature of the support on the catalytic properties of the active component.

As regards the mechanisms of heterogeneous catalytic reactions of actinide ions, many of their aspects remain obscure. The ionic–molecular schemes of heterogeneous catalytic processes are largely based on the formal kinetics and the generally accepted concepts on the existence of different actinide species in the media under study. As a rule, there are three possible mechanisms of adsorption-type reactions that are discussed. These include: (1) activated adsorption and dissociation (atomisation) of molecular reagents on the active sites of the catalyst followed by reactions of reactive radicals with metal ions in solution, as in the case of reduction of actinide molecules with molecular hydrogen and, probably, hydrazine; (2) complexation of reactants in solution and its activated adsorption on the catalyst surface followed by decomposition due to charge transfer within the complex; (3) adsorption of reactants on the adjacent catalytic sites and charge transfer through the  $\text{Pt}\text{--Pt}$  bridge with subsequent desorption of the reaction products. As a rule, these

mechanisms are kinetically indistinguishable and the choice of a reaction relies on indirect data and is purely arbitrary.

The role of active catalytic components in the initiation of heterogeneous redox reactions in aqueous solutions remains to be elucidated. All the substances previously described in the literature that manifest catalytic activities in redox reactions of actinide ions in aqueous media are conductive or electrode materials. In electrolyte solutions, to which category all the above-mentioned systems belong, these materials acquire a surface charge the magnitude of which is determined by the potential-forming components of the aqueous medium. Catalysts play the role of electrodes on which electrochemical processes occur at rates that obey the laws for the electrode kinetics. Such a mechanism is realised in the catalytic reduction of Pu(VII) with water [the potential-forming pair is Pu(VII)/Pu(VI)] and probably in the catalytic oxidation of Np(IV) with nitric acid (the potential-forming pair is  $\text{HNO}_3/\text{HNO}_2$ ). Here, the platinum catalyst plays the role of an anode on which electrochemical decomposition of water or oxidation of Np(IV) takes place. A similar approach can be applied, in principle, to any other catalytic reaction of actinide ions. In the general case, the analysis of mechanisms of heterogeneous catalytic reactions in aqueous solutions should take into consideration both the adsorption-type and electrochemical constituents of the process.

Catalytic decomposition of organic compounds in nitric acid media largely occurs as redox reactions of organic molecules adsorbed on the surface of a catalyst with oxidising species generated in homogeneous equilibrium reactions ( $\text{NO}_2^+$ ) or in a heterogeneous catalytic redox cycle involving nitric acid and reducing agents on the catalyst surface ( $\text{HNO}_2$ ). In the latter case, the reaction occurs first as a heterogeneous process, but can further be extended to the bulk of the solution owing to the autocatalytic formation of nitrous acid (catalytic denitration with formic acid). Here, the platinum catalyst does not accelerate the process but only initiates it by 'triggering' the reaction of  $\text{HCO}_2\text{H}$  with  $\text{HNO}_3$ . In acidic solutions devoid of nitrate ions, molecular inorganic nitrogen-containing compounds (hydrazine, hydrazoic acid, etc.) decompose in the presence of platinum catalysts through an adsorption–dissociation mechanism. This consists of cleavage of the N–N bond as a result of chemisorption. Taking into account the oxidation states of nitrogen in the starting compounds and reaction products, the overall process can be defined as heterogeneous catalytic disproportionation. In nitric acid media, the contribution of this reaction to the decomposition of nitrogen-containing compounds decreases with an increase in  $[\text{HNO}_3]$ . Under these conditions, the catalytic redox cycle involving surface platinum atoms and direct heterogeneous catalytic oxidation of adsorbed molecules with nitroyl cations are the main processes determining the decomposition.

The behaviour of catalysts themselves in the reaction systems under study is among the main problems of heterogeneous catalysis in aqueous media that still await solution. Indeed, the published data are devoted to chemical conversions of reaction components in aqueous media. At the same time, studies on hydrazine decomposition and catalytic denitration have shown that the catalytic redox reactions involve surface atoms of the active component of the catalyst, i.e., platinum (the surface catalytic redox cycle). Therefore, elucidation of the role of catalysts in the initiation of heterogeneous catalytic redox reactions in aqueous media demands a deeper insight into the mechanisms of their action and in-depth studies of the catalyst surface, determination of the forms of atoms of active components existing on the surface and studies of the effects of chemical environment on their changes.

Despite the obvious progress in the application of catalysts based on platinum-group metals in radiochemical practice, the use of heterogeneous catalytic processes in the technology of the nuclear fuel cycle opens up broad opportunities for their more extensive application. This is explained by obvious advantages

and high competitiveness of catalytic methods in comparison with electrochemical and chemical technologies.

The main disadvantage of the recently developed catalytic methods is the use of expensive and scarce platinum as an active component of catalysts, which are materials subject to strict control. At the same time, due to naturally occurring attrition wear and corrosion of the catalysts, it inevitably falls into the radioactive wastes and its recovery is impossible due to specific features of the radiochemical technology. It is this fact that often restricts the use of catalytic processes in large-scale technologies of the nuclear fuel cycle. From this standpoint, a search for novel catalysts able to initiate redox reactions in aqueous media and their in-depth studies still remain an important scientific and practical problem.

Once such problems have been solved, heterogeneous catalysis will occupy a worthy place in the chemistry and technology of wet processes relevant to the nuclear fuel cycle.

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<sup>a</sup> — *Radiochemistry (Engl. Transl.)*

<sup>b</sup> — *Kinet. Catal. (Engl. Transl.)*

<sup>c</sup> — *Russ. J. Appl. Chem. (Engl. Transl.)*

<sup>d</sup> — *Dokl. Chem. (Engl. Transl.)*

# Nanomaterials based on high-melting carbides, nitrides and borides

R A Andrievski

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**Abstract.** Methods for preparation of high-melting carbides, nitrides and borides in the form of ultradisperse powders, nanotubes, nanowires, and nanoporous and compact nanostructured materials are considered. Information concerning the structure, physicochemical and physicomechanical properties and application fields of these objects are presented. Prospects for the use of nanomaterials based on high-melting compounds are discussed. The bibliography includes 161 references.

## I. Introduction

Carbides, nitrides and borides of various elements are characterised by high values of melting temperatures, hardness, strength, elasticity, chemical passivity and a broad spectrum of electrical properties. This predetermines the use of these compounds in mechanical engineering, electronics, power engineering, chemical industry and other fields of technology. Recently, interest in high-melting compounds has increased in connection with the design of nanostructured materials (from this point on they are called nanomaterials). Nanostructuring is responsible for significant changes in the physicomechanical, physicochemical and biological properties and, correspondingly, for unique operating characteristics of nanomaterials. A characteristic feature of the structure of nanomaterials is the presence of grains (or phase inclusions and pores) of size less than 100 nm. This limit is not a strong physicochemical or physicomechanical criterion and was chosen conditionally.

The state-of-the-art in the field of research on nanocrystalline high-melting compounds was first analysed<sup>1,2</sup> by the author of this review a decade ago. It is of interest to revise the situation now. More than thirty review articles reported in the last decade (see, *e.g.*, Refs 3–36) indicate that research in the field is topical. They are more or less concerned with problems in nanocrystalline high-melting compounds. However, additional analysis of the data available is required. In this review the emphasis is placed on recent information on the synthesis and properties of nanopowders, compacts and nanofilms based on metal and non-metal

carbides, nitrides and borides and their composites; novel species, namely, nanotubes and nanowires are also characterised.

The total number of high-melting carbides, borides and nitrides approaches a hundred (see Ref. 37); however, only a few of them have been well studied. Meeting the condition of nanocrystallinity decreases this number to a total of 15 to 20 binary phases (TiC, ZrC, NbC, WC, VC, TiN, ZrN, NbN, TiB<sub>2</sub>, ZrB<sub>2</sub>, SiC, B<sub>4</sub>C, BN, AlN, Si<sub>3</sub>N<sub>4</sub>, *etc.*), which will be analysed below. In this review, we left the oxide and intermetallic nanocrystalline high-melting compounds out of consideration. Indeed, a wide variety of compounds in the former group require a separate consideration, while the compounds belonging to the latter group have almost not been studied as yet.

## II. Nanopowders.† Nanotubes. Nanowires

### 1. Silicon carbide and silicon nitride, aluminium nitride, boron carbide and boron nitride

Covalent high-melting materials, such as SiC, Si<sub>3</sub>N<sub>4</sub>, AlN, B<sub>4</sub>C and BN are most often obtained by carbothermal reduction (in particular, in the presence of magnesium),<sup>36,38,39</sup> plasma chemical synthesis,<sup>40,41</sup> pyrolysis of organosilicon and inorganic precursors,<sup>42–44</sup> nitridation (including explosion of wires),<sup>45–47</sup> sol–gel techniques,<sup>48</sup> self-propagating high-temperature synthesis<sup>36,49,50</sup> and laser-assisted synthesis.<sup>51</sup> At present, particular attention is focussed on preparation of complex composite nanopowders of the types Si<sub>3</sub>N<sub>4</sub>/SiC,<sup>43</sup> TiN/Si<sub>3</sub>N<sub>4</sub>,<sup>47</sup> AlN/BN (see Ref. 42), *etc.*, and nanopowders with narrow fraction composition (see, *e.g.*, Ref. 51). Various starting compounds for the synthesis of carbides, borides and nitrides and possible strategies of fabrication of silicon carbonitrides and boron nitride have been analysed.<sup>43,50,52</sup>

For instance, a Si<sub>3</sub>N<sub>4</sub>/SiC composite was synthesised from mixtures of the individual compounds necessary for the preparation of SiC and Si<sub>3</sub>N<sub>4</sub>, from a mixture of polysilane with silicon powder or from a complex compound containing reactive groups, SiH, NH and CH<sub>2</sub>CH.<sup>43</sup> Pyrolysis in a nitrogen atmosphere was followed by an X-ray phase analysis (XPA) study, which revealed the formation of composites of desired compositions in all three cases. Monodisperse Si<sub>3</sub>N<sub>4</sub>/SiC nanopowder was obtained after the Si<sub>3</sub>N<sub>4</sub> and carbon (in the form of spherical particles) powders synthesised by heating organosilicon precursors in nitrogen were annealed in argon at 1450 °C.<sup>53</sup> A comparison of different methods of synthesis of BN nanopowder showed that the most

R A Andrievski Institute of Problems of Chemical Physics, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation. Fax (7-496) 515 54 20, tel. (7-496) 522 35 77, e-mail: ara@icp.ac.ru

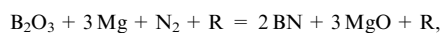
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† Nanopowders (or ultradisperse powders) are powders whose particles are less than 100 nm in size.



efficient method consists of the reduction of  $B_2O_3$  with magnesium in nitrogen atmosphere.<sup>50</sup> MgO particles thus formed play an important role in prevention of the BN [and SiC (see Ref. 39)] particles from further growth; however, the mechanism of the process is still poorly understood. In a general form, combustion in the  $B_2O_3$ –Mg– $N_2$  system can be described by the following reaction



where R is the additive precluding the formation of magnesium borides. The semiproduct, BN + MgO, sintered in the course of self-propagating high-temperature synthesis is then chemically dispersed in sulfuric or hydrochloric acid solutions.<sup>50</sup>

$\beta$ -SiC nanopowder characterised by narrow particle size distribution (15–20 nm) is obtained by laser-assisted synthesis from a silane–acetylene mixture containing diborane (this additive is introduced to form a small amount of boron (~1 mass %), which activates the subsequent sintering of particles).<sup>22, 51</sup> For comparison, mention may be made that a conventional SiC nanopowder prepared using this procedure has a much wider particle size distribution (*e.g.*,  $50 \pm 25$  nm).<sup>22</sup>

Vapour-phase self-propagating high-temperature synthesis with controllable formation of condensed phases is considered promising for the preparation of nanopowders. However, these reactions, as applied to the synthesis of ultradisperse powders comprising particles of preset size, are still poorly understood.<sup>36</sup>

Often, the synthesis of nanopowders results in X-ray amorphous phases. Analysis of the data listed in Table 1 shows that the temperature affects the phase composition and particle size in the  $Si_3N_4$  powders synthesised from a  $SiCl_4$  +  $NH_3$  gaseous mixture in high-frequency plasma. The amorphous phase is quite stable and exists up to ~1500 °C. The particle size increases as a result of grain-coarsening. The results cited<sup>54</sup> can be considered reliable because the grain size was measured using two independent methods, X-ray analysis and transmission electron microscopy (TEM).

**Table 1.** Change in the phase composition [*c* (vol. %)] and  $Si_3N_4$  particle size (*d*/nm) after annealing.<sup>54</sup>

| Phase composition | Before annealing |          | $T = 1350$ °C |          | $T = 1500$ °C |          |
|-------------------|------------------|----------|---------------|----------|---------------|----------|
|                   | <i>c</i>         | <i>d</i> | <i>c</i>      | <i>d</i> | <i>c</i>      | <i>d</i> |
| Amorphous phase   | 80               | 30       | 65            | 50       | 20            | —        |
| $\alpha$ -Phase   | 17               | 35–75    | 32            | 50–60    | 67            | 95       |
| $\beta$ -Phase    | 3                | —        | 3             | —        | 13            | 95       |

More complex amorphous high-melting systems such as Si–N–C and Si–N–C–B can be synthesised using organometallic polymers and monomers based on polysilazanes (*e.g.*,  $[(Si(Me)R-NH)_n-C(O)NH]_m$ , a polyborazole (of the  $[B_3N_3H_4]_n$  type), an oligomer of boron-modified vinylsilazane, *etc.*<sup>55, 56</sup> as precursors. Products of thermolysis of these compounds are used for both the preparation of nanopowders (after additional ball milling) and subsequent high-temperature pressure treatment in order to obtain amorphous or nanocrystalline materials.

Information on the synthesis of nanotubes and nanowires of high-melting compounds is scarce at the moment, but the number of studies on the subject is increasing. For instance, the following methods of synthesis of boron nitride nanotubes have been reported: laser ablation (a 1 kW  $CO_2$  laser focussed on a 7.5 mm spot);<sup>57</sup> nitridation of finely disperse boron powder at 1200 °C for 16 h;<sup>58</sup> synthesis involving catalysts (FeB) (see Ref. 59), *etc.* Encapsulation of  $ZrO_2$  and cobalt nanorods inside the BN nanotubes was reported.<sup>60, 61</sup> It was pointed out that some methods allow nanotubes to be fabricated in gramme<sup>57</sup> and even kilogramme quantities.<sup>58</sup>

Boron nitride nanowires ~20 nm in diameter and several tens of micrometres long can be formed by the interaction of an  $N_2$  +  $NH_3$  vapour mixture with nanoscale iron boride ( $\alpha$ -FeB) particles at 1100 °C.<sup>62</sup> At this temperature, aluminium nitride nanowires are synthesised from a mixture of the aluminium and  $Al_2O_3$  powders and carbon nanotubes are obtained, which in this case play the role of not only the reducing agent but also a kind of template that specifies the shape and size of the nanowires.<sup>63</sup> Different methods of synthesis of nanotubes and nanowires (or nanofilaments) based on silicon carbide and silicon nitride have been reported.<sup>64, 65</sup> Figure 1 presents the electron micrographs of SiC specimens with different morphologies. Nanowires, nanofilaments, nanoporous materials and SiC nanoparticles were fabricated from a carbonaceous silicon precursor synthesised by the interaction of a phenol-formaldehyde polymer with tetraethoxysilane and treated in a different fashion.<sup>65</sup> However, the stability and reproducibility of the treatment regimes still remain unclear.

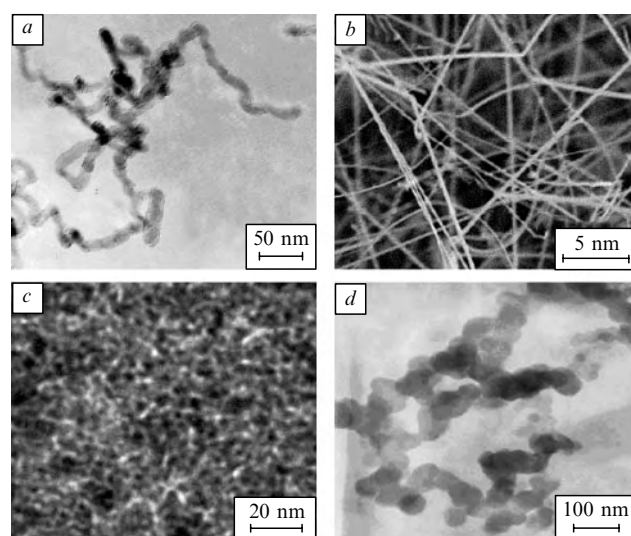


**Figure 1.** Electron micrographs of carbide silicon specimens with different morphologies:<sup>65</sup>

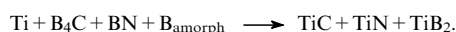
nanowires (*a*), nanofilaments (*b*), a nanoporous specimen with an average pore size of about 5 nm and a specific surface area of  $200 \text{ m}^2 \text{ g}^{-1}$  (*c*) and nanoparticles (*d*).

## 2. High-melting transition-metal compounds (WC, TiC, TiN, $TiB_2$ , *etc.*)

Tungsten carbide, as a base for widely used hard alloys, has attracted particular attention of researchers. A method of preparation of WC/Co nanopowders by low-temperature reduction and carbidisation of a mixture of ammonium metatungstate and cobalt chloride in a fluid bed reactor followed by spray drying (this favours good mixing of nanocomponents),<sup>66</sup> which was advertised in a big way in the early 1990s, this did not gain acceptance in industry. This was mainly due to the fact that at present it is impossible to retain the nanostructure in the course of subsequent sintering. Nevertheless, extensive searches for optimum methods of fabrication of WC and WC/Co nanopowders have been carried out with allowance for the general trend towards fabrication of strong, wear-resistant ultrafinely-disperse hard alloys. Doping tungsten carbide with vanadium carbide and with VC–TaC solid solution precludes grain-coarsening in the sintering stage.<sup>67, 68</sup> A process involving mechanochemical and plasma chemical syntheses has been reported.<sup>69–74</sup> Micro- and nanopowders of more complex compositions, *e.g.*, WC–35% TiC–Co (see Ref. 75) and  $Ti(C,N)$ –WC–Ni (see Ref. 76) were prepared by carbothermal reduction and co-milling. It should be kept in mind that nanopowders with particle sizes less

than 100 nm were not obtained by the authors of all the studies cited above;<sup>67–76</sup> often, characterisation of the powders with respect to the impurities and fraction distributions was also incomplete. Usually, the advertising circulars of most of big manufacturers of hard-alloy WC powders [H.C.Starck (Germany), Wolfram BHG (Austria), Dow Chemical Company (USA), *etc.*] indicate a particle size less than 0.2 to 0.3  $\mu\text{m}$ .<sup>68, 77, 78</sup> Inframat Corporation (IMC, USA) offers the WC and WC–(5%–15%)Co nanopowders characterised by a size 40–80 nm of the carbide grains, which are then agglomerated to form particles with the average size 0.2–0.4  $\mu\text{m}$ .<sup>79</sup> Agglomeration is carried out in order to prepare the charge material to pressing.

Various methods of synthesis of TiN, TiC, TiB<sub>2</sub> nanopowders and related high-melting compounds have been reported. Methods used in addition to the plasma-enhanced and laser-assisted syntheses, carbothermal reduction and conventional ball milling<sup>1, 2</sup> mentioned above include self-propagating high-temperature synthesis, mechanochemical synthesis, high-temperature vapour-phase reactions, high-energy ball milling and some others. As in the case of nanopowders of covalent high-melting compounds, the emphasis is placed on the preparation of multi-component and multicomposition nanoparticles. For instance, nanoparticles of TiN/TiB<sub>2</sub> composite are obtained by high-energy ball milling and mechanochemical synthesis of the starting Ti + TiB<sub>2</sub> mixtures in a nitrogen atmosphere of Ti + BN mixtures in a argon atmosphere.<sup>80–82</sup> A procedure proposed for the preparation of TiB<sub>2</sub>/TiN/Ti(C,N) nanocomposites included high-energy ball milling of the starting powders, (Ti + B<sub>4</sub>C) and (Ti + BN), to give products (TiC + B<sub>amorph</sub>) and (TiN + B<sub>amorph</sub>) and subsequent ball milling of the products to produce TiB<sub>2</sub> following the reaction



The final ball milling step followed by non-isothermal annealing to 1300 °C (at a heating rate of 10 °C/min) produces TiB<sub>2</sub> + TiN + Ti(C,N) nanoparticles of size 30–60 nm, which can be detected by XPA, X-ray analysis and TEM.<sup>83</sup> Methods of synthesis of transition-metal high-melting compounds are characterised in Table 2.

However, in spite of a large number of studies on the synthesis of nanocrystalline high-melting compounds (over 60 publications), in most cases the efficiency of different methods are difficult to compare. The reason is that many important details (impurity content, nanoparticle size distribution, pressing and sintering behaviour of ultradisperse powders, properties of consolidated compacts, *etc.*) are still out of researchers' eyeshot.

### 3. Selected properties of nanopowders and nanotubes

It should be noted that the particle and crystallite sizes reported in the most representative studies<sup>54, 70, 74, 83, 88, 91</sup> were obtained by at least two independent methods (*e.g.*, X-ray analysis and TEM). The results of specific surface area measurements and the estimates of the average particle size cannot be considered sufficient without analysing the particle size distribution. This can be explained by the fact that even a small amount of coarse grains can initiate significant grain growth in the course of subsequent sintering and thus favour the disappearance of the nanostructure.

Unfortunately, not all authors of synthetic studies report such characteristics of ultradisperse powders and nanoparticles as the content of impurities (especially, oxygen) and adsorbed gases, interfacial segregations and deviation from stoichiometry. An investigation<sup>99</sup> of WC, NbC, TiC, SiC, Si<sub>3</sub>N<sub>4</sub>, AlN and TaN nanopowders prepared by plasma chemical synthesis showed that the overall content of oxygen increases as the specific surface area increases, the major contribution to this increase coming from the oxygen-containing gases adsorbed on the surface. Studies of gas evolution in the course of high-vacuum annealing of TiN and Si<sub>3</sub>N<sub>4</sub> nanopowders showed that the vapour phase mainly con-

**Table 2.** Methods of preparation of high-melting compound nanopowders.

| Compound            | Nanoparticle size /nm      | Method of preparation                                                     | Ref.   |
|---------------------|----------------------------|---------------------------------------------------------------------------|--------|
| TiN                 | 5–10                       | sodium-thermal reduction in nitrogen atmosphere                           | 84     |
| ZrN                 | 30–100                     | magnesium-thermal reduction in nitrogen atmosphere                        | 85     |
| TiC                 | —                          | self-propagating high-temperature synthesis with magnesium additives      | 86     |
| TaC                 | 30–55                      | self-propagating high-temperature synthesis in electric field             | 87     |
| ZrC                 | < 500 (see <sup>a</sup> )  | high-energy mechanochemical synthesis                                     | 88     |
| TiB <sub>2</sub>    | < 15                       | vapour-phase synthesis<br>TiCl <sub>4</sub> + BCl <sub>4</sub>            | 89     |
|                     | 15–70                      | TiCl <sub>4</sub> + NaBH <sub>4</sub>                                     | 90     |
| ZrB <sub>2</sub>    | 15–70                      | vapour-phase synthesis<br>ZrCl <sub>4</sub> + NaBH <sub>4</sub>           | 91     |
| HfB <sub>2</sub>    | 15–70                      | vapour-phase synthesis<br>HfCl <sub>4</sub> + NaBH <sub>4</sub>           | 92     |
| NbB <sub>2</sub>    | 40–50                      | carbothermal reduction                                                    | 93     |
| VC <sub>0.875</sub> | ~ 1000 (see <sup>b</sup> ) | carbothermal reduction with ageing                                        | 94, 95 |
| WC                  | 50–200                     | self-propagating high-temperature synthesis                               | 96     |
| TiC                 | 75                         | carbothermal reduction involving titania                                  | 97     |
|                     | 30–60                      | as a result of TiCl <sub>4</sub> + CaC <sub>2</sub> interaction at 550 °C | 98     |

<sup>a</sup> Particles are comprised of 5-nm nanograins.

<sup>b</sup> Particles are comprised of nanocrystallites of size 400–600 nm and thickness 15–20 nm.

tains CO, nitrogen, water vapour and hydrogen and revealed two gas evolution maxima at ~300 and ~600 °C.<sup>1, 4, 100</sup> The distribution of impurities and gases across the surface of the Si<sub>3</sub>N<sub>4</sub> powder particles has been the subject of a detailed review.<sup>100</sup> The effect of annealing on the content of gases in this nanopowder (average particle size was about 15 nm) before and after annealing at 1200 °C (1 h) can be followed using the data listed below (both gas and water vapour content is given in mass %):

| Powder   | $V/\text{cm}^3 \text{ g}^{-1}$ | CO | H <sub>2</sub> | N <sub>2</sub> | H <sub>2</sub> O |
|----------|--------------------------------|----|----------------|----------------|------------------|
| Starting | 625                            | 59 | 11             | 21             | 9                |
| Annealed | 89                             | 79 | 7              | 10             | 4                |

( $V$  is the reduced total volume of the gases).<sup>100</sup>

The quantum-chemical methods suitable for prediction of the adsorption of gases (water vapours, ammonia, *etc.*) on the Si<sub>3</sub>N<sub>4</sub> surface have been considered.<sup>101</sup> Changes of the surface charge density in the interaction of ultradisperse Si<sub>3</sub>N<sub>4</sub> powder with nitrate solutions were analysed.<sup>102</sup>

The properties of nanotubes, nanowires and nanofilaments of high-melting compounds have become the subject of more and more extensive research (see, *e.g.*, Refs 103–106), but a considerable body of data available require an additional substantiation. Studies on boron nitride hold a leading position; in particular, it was revealed that the bandgap of the BN nanotubes is ~5.5 eV, being independent of the nanotube diameter. As to the elastic characteristics, there are at least two different results for the elastic modulus,  $E = 1.22 \pm 0.24 \text{ GPa}$ ,<sup>59</sup> which exceeds all the known  $E$  values for nanofilaments, and  $E = 722 \text{ GPa}$ .<sup>103</sup> Methods of synthesis and the properties of BN, BCN, SiC, AlN, Si<sub>3</sub>N<sub>4</sub>, TiC and BC<sub>x</sub> nanowires have been reviewed.<sup>106</sup>

### III. Consolidated compacts

#### 1. Consolidation processes: general

Conventional regimes of pressing and sintering of compounds are almost inapplicable to nanopowders.<sup>1,2</sup> No significant densification occurs even in the case of high-pressure pressing (at  $>1$  GPa), because the compactibility appreciably decreases due to the developed surface and strong intergrain friction forces.<sup>107</sup> The residual porosity of the TiN and Si<sub>3</sub>N<sub>4</sub> nanopowders pressed at 7–9 GPa exceeded 10%–15%; magnetic-pulse pressing of the TiN powder (particle size 70–80 nm) at pressures to 2–3 GPa also did not lead to significant decrease in porosity.<sup>108,109</sup> At the same time further sintering of powders is usually accompanied by intense grain growth due to recrystallisation occurring at high temperatures. As a result, the nanostructure disappears and the physicochemical and mechanical characteristics are not improved.

At present, there are a number of methods of consolidation of powder nano-objects, which make it possible to prepare materials with the desired nanostructure. These are high-pressure treatment at relatively moderate temperatures,<sup>4,5,110</sup> non-isothermal sintering,<sup>34,111</sup> reactive hot-pressing,<sup>112</sup> arc-discharge (plasma-assisted) sintering,<sup>88,113</sup> short-term liquid-phase sintering,<sup>66</sup> sintering activated by phase transitions<sup>114</sup> and some others. Here, recrystalli-

sation in the course of sintering and, correspondingly, grain growth are precluded due to either lowering the temperature and shortening the duration of sintering under high pressure,<sup>4,5,110</sup> activation of diffusion,<sup>88,112–114</sup> or optimisation of the shrinkage and recrystallisation processes in different temperature intervals.<sup>34,111</sup> Methods combining mechanochemical synthesis and consolidation deserve attention because of considerable promise for preparation of TiB<sub>2</sub>/TiN-type nanocomposite materials.<sup>81,112</sup>

The effect of the disorder–order transition on the sintering of silicon carbide is quite demonstrative.<sup>114</sup> The effect of temperature on the change (in the course of sintering) in the relative density of the SiC nanopowders prepared by mechanochemical synthesis under intense milling (grain size 5 to 10 nm, agglomeration into larger grains of size 100–150 nm) is illustrated by Fig. 2. For comparison, we present the data on the sintering of commercially available SiC nanopowder (grain size of about 30 nm). A dramatic increase in the relative density at  $\sim 1700$  °C was interpreted as a consequence of structural ordering in the ball milling synthesised SiC, which was confirmed by X-ray analysis data, namely, sharper reflections and the appearance of a peak at  $2\theta \sim 40^\circ$ . Besides, an analogy between the X-ray diffraction patterns of the commercially available SiC powder and the carbide sintered at 1800 °C is obvious (see the X-ray diffraction patterns in Fig. 2).

However, in practice the methods listed above always lead to nanomaterials with a grain size of at least about 30 nm and low residual porosity (at least  $\sim 2\%$ ), which of course affects the physicomechanical and physicochemical properties.

The laws of sintering of WC nanopowders are of particular interest (see, e.g., Refs 66–68, 4–78, 115) because of the wide use of this high-melting compound. It is known that the VC, Cr<sub>3</sub>C<sub>2</sub> and TaC additives act as inhibitors of grain growth in sintering of hard alloys. A dilatometric study of shrinkage of conventional WC + 7.8% Co + 0.7% VC powders and nanopowders of the same composition showed that shrinkage of the latter is carried out in the solid phase while that of the coarse-grain powders occurs under conditions of liquid-phase sintering.<sup>115</sup>

A method of synthesis of nanoporous materials based on SiC by reactive sintering of highly disperse silicon–colloidal graphite (Si + 30% C) mixtures at relatively moderate temperatures (1100–1200 °C) has been reported.<sup>116</sup> This technique permits preparation of micro- and nanomaterials with porosities ranging between 50% and 65% and a specific surface area of the order of 30 to 40 m<sup>2</sup> g<sup>−1</sup>; the calculated effective pore size in the materials is  $\sim 20$  nm and the maximum pore size is at most 300 nm.

#### 2. Structure and properties

The most widely used methods of studying the structure of nanomaterials include TEM, scanning electron microscopy (SEM), atomic force microscopy (AFM) and X-ray analysis. High resolution of the electron microscopy methods is necessary for the disclosure of such peculiar features as the presence of very small particles, pores and grains (of size less than 10–20 nm), observation of dislocations and establishment of the structure of interfaces (grain boundaries and phase boundaries) and the character of breakdown of nanostructures (see, e.g., Refs 117–119). Figure 3 presents a high-resolution TEM image of a TiN film.<sup>117</sup> A characteristic strip-like structure can be seen, which corresponds to the atomic planes, and a number of intracrystalline edge dislocations (the possibility for them to exist in the nanomaterials based on high-melting compounds was confirmed by the estimates<sup>117</sup> made with allowance for the concepts developed in another study<sup>120</sup>).

A bright-field electron micrograph of the structure of hot pressed ZrC nanopowders obtained by mechanochemical synthesis (crystallite size is about 5 nm, agglomerate size of nearly 3  $\mu$ m) and the grain size distribution are shown in Fig. 4.<sup>88</sup> As can be seen, hot pressing at relatively moderate temperatures is accompanied by intense grain growth. The specimens obtained were characterised by an average grain size of nearly 95 nm, which

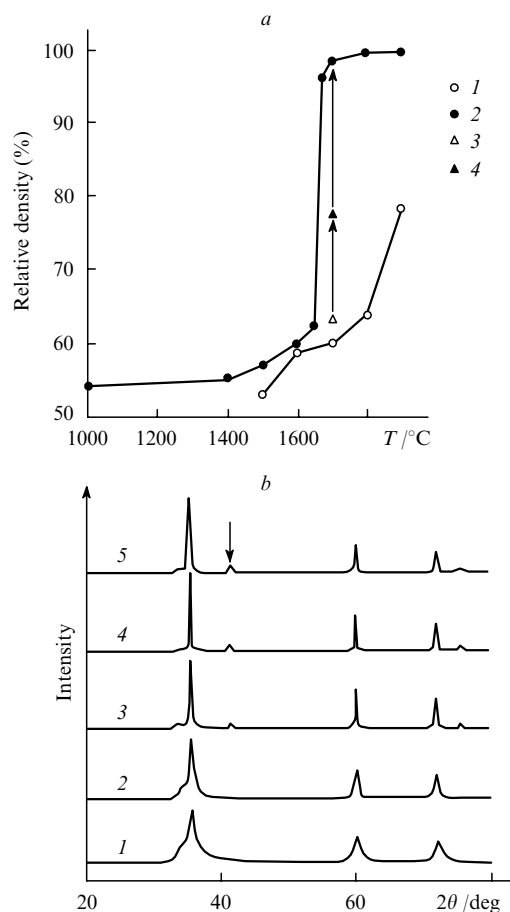


**Figure 2.** Relative densities of SiC nanopowders plotted vs. sintering temperature (a) and X-ray diffraction patterns of commercially available SiC powder and specimens sintered at different temperatures (b);<sup>114</sup>

(a): commercially available SiC powder (1); powder obtained by mechanochemical synthesis (2); the same powder sintered at 1700 °C for 0 (3) and 2 min (4). The duration of heating to corresponding sintering temperatures was the same for all specimens. The sintering time of specimens 1 and 2 was 10 min;

(b):  $T = 1400$  (1), 1600 (2), 1700 (3), 1800°C (4); commercially available powder (5).

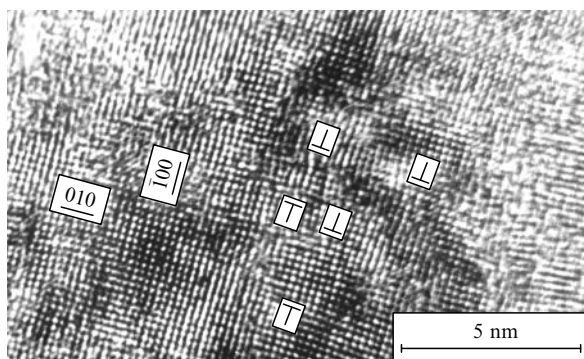


**Figure 3.** HRTEM image of TiN nanostructure obtained in the direct resolution mode.<sup>117</sup> Shown are the edge dislocations ( $\perp$ ).

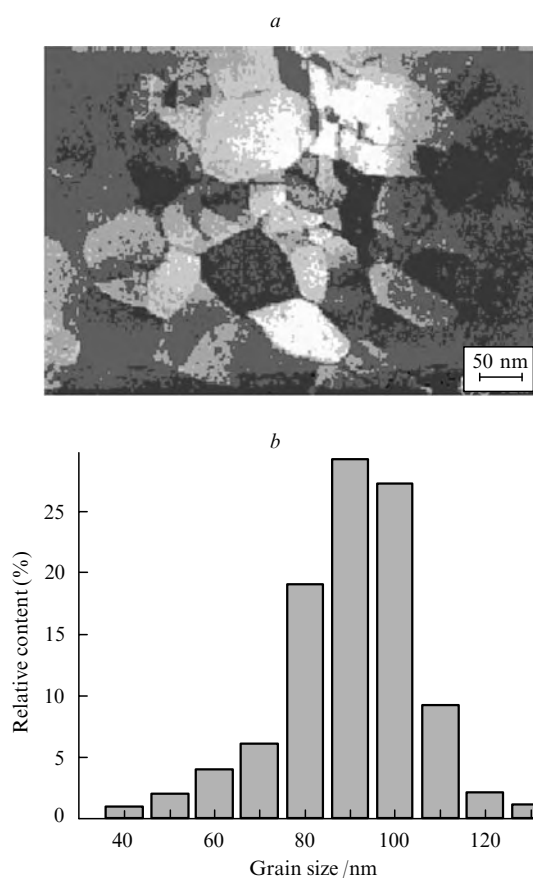


**Figure 4.** Bright-field electron micrograph of nanocrystalline zirconium carbide obtained by hot pressing at 1300 °C and a pressure of 1.5 GPa (a) and the grain size distribution (b).<sup>88</sup>

approaches the upper size limit for nanostructures, and a rather broad grain size distribution.

Electron energy dispersive analysis of the TEM and SEM images makes it possible to determine the chemical composition, but the most informative method of investigation of nanomaterials is electron energy loss spectroscopy, which provides information on the interfacial segregations. However, the necessary equipment is available in a few research laboratories and information on impurity segregations on grain boundaries of high-melting compounds is restricted to the data for silicon nitride and to some extent for WC–Co hard alloys.<sup>100, 121</sup>

Hardness is the best studied characteristic of nanomaterials based on high-melting compounds. This can be explained by the availability of measuring instruments and relative ease of speci-

men preparation. Knowledge of hardness is important in manufacturing of tool materials. Data on the hardness of nanocrystalline high-melting compounds have been the subject of several review articles (see, *e.g.*, Refs 9, 15, 21, 23, 30, 31, 122). These results, as well as the new data<sup>43, 67, 69, 77, 78, 88</sup> showed that the hardnesses of nanocrystalline titanium nitride<sup>110</sup> and tungsten carbide<sup>123</sup> ( $\sim 30$  and  $\sim 40$  GPa, respectively) are 1.5–2 times higher than those of conventional coarse-grained materials only if the specimens were thoroughly prepared and well-characterised. The hardnesses of nanocrystalline SiC,<sup>‡</sup> Si<sub>3</sub>N<sub>4</sub>, ZrC, TiC, *etc.* specimens were comparable with those of polycrystals and single crystals, which can be explained by porosity and poorly developed nanostructures. For instance, the hardness of the ZrC specimens with the morphology shown in Fig. 4a was  $\sim 27$  GPa,<sup>88</sup> while the corresponding polycrystals and single crystals showed 24 to 26 GPa.<sup>37</sup> Thus, methods of fabrication of certain consolidated nanomaterials based on high-melting compounds are still far from being perfect.

The effect of the relative density on the microhardness and elastic modulus of the specimens prepared from TiN nanopowders of different dispersity can be followed using the data shown in Fig. 5. As can be seen, hardness depends on the porosity and grain size, while the elastic modulus depends only on porosity in this range of grain sizes. From simple estimates it follows that a decrease in the elastic modulus of nanomaterials can be expected at grain sizes less than 10 nm, where the proportion of interfaces (grain boundaries) exceeds 20% of the total volume.

The dependences of hardness ( $H_V$ ) and elastic modulus on porosity  $\vartheta$  ( $\vartheta = 1 - \tau$ , where  $\tau$  is the relative density) have the form

$$H_V = H_{V_c}(1 - 4.7\vartheta) \text{ for } d = 70 - 80 \text{ nm,}$$

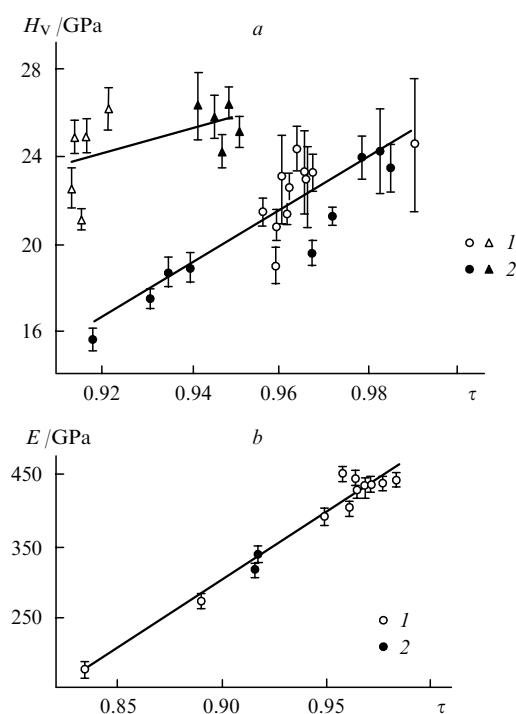


**Figure 5.** Microhardness (a) and elastic modulus (b) plotted vs. relative density ( $\tau$ ) of TiN nanocrystalline specimens obtained at 4–7.7 GPa and  $T = 1200$ – $1400$  °C from ultradisperse powders with the particle size 16–18 (1) and 70–80 nm (2).<sup>110</sup> The open and solid circles denote the results of two series of experiments.

<sup>‡</sup> Even greater hardness, 32–41.5 GPa, was reported<sup>124</sup> for superstoichiometric silicon carbide specimens (grain size  $\sim 330$  nm) obtained at high pressures and high temperatures.

$$H_V = H_{V_c}(1 - 2.1 \vartheta) \text{ for } d = 16 - 18 \text{ nm},$$

$$E = E_c(1 - 3.9 \vartheta),$$

where  $H_{V_c}$  and  $E_c$  are the hardness and the elastic modulus for the compacted state ( $\vartheta = 0$ ,  $\tau = 1$ ), which are respectively equal to 26.2 ( $d = 70 - 80$  nm), 28.8 ( $d = 16 - 18$  nm) and 490 GPa ( $d$  is the average initial particle size of the TiN nanopowder).

The linear character of the plots shown in Fig. 5 is typical of many powder materials characterised by narrow porosity ranges.<sup>37</sup>

In discussing the properties of nanomaterials one should take into account not only the role of the nanostructure but also the impurity content and the possibility of interfacial impurity segregations; porosity, residual stress, nonequilibrium phases and structural vacancies (deviation from stoichiometry); interface states and many other factors (as applied to hardness, these are, *e.g.*, the measuring technique, load magnitude and surface roughness). Taken altogether, this makes the interpretation of the properties of nanomaterials a complicated task and the results reported should be accompanied by detailed discussion and conclusions should be thoroughly substantiated.<sup>8</sup>

A fracture toughness study of nanostructured materials based on high-melting compounds revealed an intercrystallite character of crack propagation. This can be confirmed by the micrographs of the TiN fracture surface and the crack (Fig. 6).<sup>10</sup> As can be

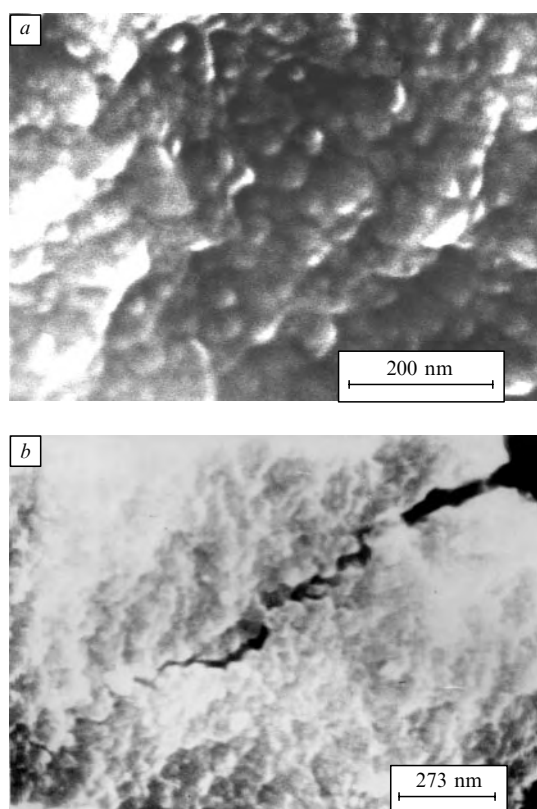


**Figure 6.** SEM micrographs of the surface of nanocrystalline TiN.<sup>10</sup> Fracture surface (a) and crack propagation (b).

§ For instance, the microhardness values of 60–80 GPa reported<sup>95</sup> for the specimens with ~30% porosity, sintered from vanadium carbide (VC<sub>0.875</sub>) nanopowders at 1700 °C cast some doubt. Extrapolation of these data to zero porosity leads to a microhardness of about 200 GPa, which seems to be unrealistic (the hardness of diamond is ~100 GPa).

seen, the fracture occurs at grain boundaries. The intercrystallite character of fractures provides an explanation for the fact that such an important characteristic of brittle single-phase materials as the crack resistance, remains almost unchanged as the grain size decreases.<sup>10</sup>

Information on the high-temperature strength of nanostructured high-melting compounds is scarce. The possibility for superplasticity (high creep rates) to occur in microcrystalline composites of the Si<sub>3</sub>N<sub>4</sub>/TiB<sub>2</sub> type at 1600 °C was pointed out.<sup>125</sup> At the same time extremely low creep rates were found in Si<sub>3</sub>N<sub>4</sub>/SiC nanocomposites (see Ref. 126) and in amorphous ternary (Si/C/N) and quaternary (Si/B/C/N) specimens synthesised by pyrolysis of organosilicon polymers.<sup>56</sup>

The effect of the TiN content on the resistivity ( $\rho$ ) of Si<sub>3</sub>N<sub>4</sub>/TiN composite (grain size 100–600 nm) is illustrated in Fig. 7.<sup>47</sup> As the TiN concentration in this composite changes, the  $\rho$  value changes by nearly fifteen orders of magnitude, from the values characteristic of dielectrics (Si<sub>3</sub>N<sub>4</sub>) to those typical of metals and metal-like compounds (TiN), the latter being observed at the TiN concentrations of less than 20 vol. %.

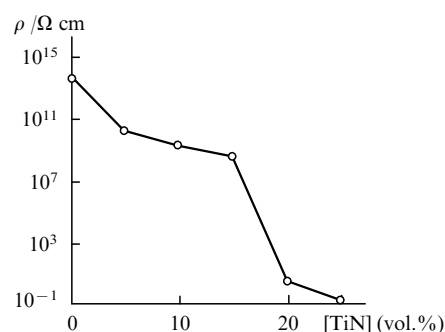


**Figure 7.** Resistivity of Si<sub>3</sub>N<sub>4</sub>–TiN system plotted vs. its composition.<sup>47</sup>

Numerous interfaces in nanomaterials produce natural barriers to the motion of charge carriers. Therefore, a decrease in the grain size is accompanied by a decrease in the resistivity and thermal conductivity. A good example of the latter is provided by SiC.<sup>22</sup> At room temperature, the thermal conductivities of nanocrystalline (grain size about 70 nm) and coarse-grained SiC (grain size 3 to 5  $\mu$ m) specimens differed by a factor of 8. At 1400 °C, only a twofold difference was observed, due to the change in the contribution of phonon–phonon scattering.

Numerous interfaces in nanomaterials can favour enhancement of their radiation stability due to the increase in the number of escape channels of radiation-induced defects and, hence, lower degree of swelling of specimen.<sup>22</sup>

An interesting size effect related to the superconducting properties was found in a number of high-melting compounds. The effect of the particle size of nanopowders on the change in the critical magnetic field in TiN, NbN, VN, Nb (N,C) and V<sub>3</sub>Si,<sup>127</sup> which seems to be related to the evolution of the phonon spectrum of nanoparticles, is illustrated in Fig. 8.

However, the physical, mechanical and physicochemical properties of nanomaterials based on high-melting compounds are still poorly understood. Owing to limited quantities of well-characterised specimens, studies of the size effects (*e.g.*, evaluation of the familiar Hall–Petch relation for strength and hardness) are in the early stage of development. Data on the constitutional diagrams of these materials in the nanocrystalline state are almost unavailable. This important information is limited to the old estimates obtained in the simplest regular approximation for the ZrC–C, TiN–AlN, TiN–TiB<sub>2</sub> and TiC–TiB<sub>2</sub> systems.<sup>128–130</sup>

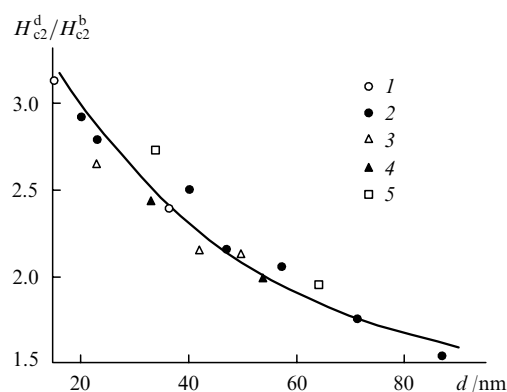


**Figure 8.** Critical magnetic field plotted vs. grain size of high-melting compounds obtained by plasma chemical synthesis.<sup>127</sup>  $H_{c2}^d$  is the second critical field strength for nanopowders and  $H_{c2}^b$  is the same for the coarse-grained specimen. Nb(N, C) (1), TiN (2), NbN (3),  $V_3Si$  (5) and VN (5).

## IV. Nanostructured films

### 1. Methods of fabrication: general

General information concerning physical and chemical methods of fabrication of films and coatings has been reported in a number of review articles (see, *e.g.*, Refs 1–5, 9, 15, 30, 31). Division of methods into physical and chemical ones is conditional because chemical reactions play a significant role in a number of physical methods (*e.g.*, physical deposition of films) while chemical methods involve many physical phenomena. The most widely used methods of fabrication of nanostructured films belong to the so-called physical deposition techniques, namely, reactive and non-reactive magnetron sputtering (high-frequency and d.c. modes), cathode (or arc-ion) sputtering, laser ablation and ion beam treatment of surface. High-temperature chemical deposition methods are employed more rarely. Coatings several tens of micrometres thick are fabricated using gas-thermal (plasma and detonation) deposition. Therefore, a variety of technological procedures for fabrication of nanostructured films and coatings are available; many of them have found large-scale applications. For instance, very hard multilayered (Ti,Al,Y)N/VN nitride films used as wear-resistant coatings for metal-working instruments are manufactured on large-scale high-vacuum multicathode magnetron sputtering equipment.<sup>30</sup>

The use of an additional magnetic field in the course of deposition permits efficient control of the crystallite sizes and the crystallite size distribution (Table 3).<sup>131, 132</sup> Mention may be made that nanostructured films can have much smaller grain sizes

**Table 3.** Average crystallites size (nm) in nitride/boride films prepared by non-reactive magnetron sputtering with  $\sim 400$  G external magnetic field switched off and on.<sup>131, 132</sup>

| Target                       | Field off     | Field on       |
|------------------------------|---------------|----------------|
| TiB <sub>2</sub>             | $3.6 \pm 1.8$ | $3.3 \pm 1.1$  |
| 75 TiB <sub>2</sub> + 25 TiN | $2.3 \pm 1.1$ | not determined |
| 50 TiB <sub>2</sub> + 50 TiN | $2.9 \pm 1.5$ | $1.8 \pm 0.3$  |
| 25 TiB <sub>2</sub> + 75 TiN | $5.9 \pm 4.0$ | $6.5 \pm 2.5$  |
| TiN                          | $29 \pm 15$   | $8.8 \pm 2.2$  |

compared to powder compacts. The lattice constant of a titanium nitride film with the NaCl-type structure is  $\sim 0.42$  nm; the crystallite of size  $\sim 2$  nm contains only  $\sim 5^3 = 125$  unit cells, *i.e.*, such films can be treated as cluster-consolidated materials.<sup>133</sup>

### 2. Investigation of the structure and composition

In addition to the methods of investigation of the structure of powders mentioned above (TEM, SEM, XPA, X-ray analysis and AFM), films are also studied by X-ray photoelectron spectroscopy, Auger electron spectroscopy (AES), Rutherford back-scattering spectroscopy, positron annihilation spectroscopy, secondary ion mass spectrometry, local electron diffraction, *etc.*

Table 4 lists the characteristics of some films we have studied.<sup>134</sup> The dark-field TEM image of the structure of the film fabricated in regime IV and the crystallite size distribution are shown in Fig. 9.<sup>133</sup> The size distribution in the case of magnetic field assisted deposition is shifted towards smaller sizes and becomes narrower (see Table 3). Approximate chemical formulae listed in Table 4 were calculated based on the AES data. Table 4 shows that the films deposited can be both superstoichiometric (regimes IV–VI for the TiN-based films) and understoichiometric (regimes I–III for the TiB<sub>2</sub>-based films); some films were amorphous after deposition. Considerable attention should be given to high solubility of components in the metallic and non-metallic sublattices. For instance, an equilibrium pseudobinary system TiB<sub>2</sub>–TiN is characterised by low mutual solubility of the components at room temperature.<sup>37</sup> However, in the film state the degree of mutual solubility of the boride and nitride becomes high (regimes III–V lead to single-phase composites) due to highly non-equilibrium character of the films deposited.

Thus, the properties of nanostructured films should be analysed with allowance for the possibility of high solubility of metallic and non-metallic components and for the non-stoichiometry of specimens, which is much higher than that of coarse-grained specimens of high-melting compounds. Yet another feature of such films is that their deposition and subsequent cooling to room temperature is accompanied by production of

**Table 4.** Composition and structures of films (1–3  $\mu$ m thick) plated in the d.c. regime (I) and in high-frequency regimes (II–X).<sup>134</sup>

| Target                         | Sputtering regime | Approximate formula                                                                          | Grain size/nm | Type of structure | Lattice constant/nm |                |
|--------------------------------|-------------------|----------------------------------------------------------------------------------------------|---------------|-------------------|---------------------|----------------|
|                                |                   |                                                                                              |               |                   | <i>a</i>            | <i>c</i>       |
| TiB <sub>2</sub>               | I                 | Ti(B <sub>0.73</sub> N <sub>0.2</sub> O <sub>0.05</sub> C <sub>0.02</sub> ) <sub>1.56</sub>  | 4–8           | AlB <sub>2</sub>  | 0.3060              | 0.3201         |
| TiB <sub>2</sub>               | II                | Ti(B <sub>0.69</sub> N <sub>0.24</sub> O <sub>0.04</sub> C <sub>0.03</sub> ) <sub>1.64</sub> | $3.6 \pm 1.8$ | AlB <sub>2</sub>  | 0.3083              | 0.3246         |
| TiB <sub>2</sub> /25 TiN       | III               | Ti(B <sub>0.56</sub> N <sub>0.29</sub> O <sub>0.05</sub> C <sub>0.1</sub> ) <sub>1.32</sub>  | $2.3 \pm 1.1$ | AlB <sub>2</sub>  | 0.3005              | 0.3263         |
| TiB <sub>2</sub> /50 TiN       | IV                | Ti(B <sub>0.34</sub> N <sub>0.49</sub> O <sub>0.12</sub> C <sub>0.05</sub> ) <sub>1.49</sub> | $2.9 \pm 1.5$ | NaCl              | $\sim 0.42$         |                |
| TiB <sub>2</sub> /75 TiN       | V                 | not determined                                                                               | $5.9 \pm 4.0$ | NaCl              | 0.4307              |                |
| TiN                            | VI                | Ti(N <sub>0.6</sub> O <sub>0.2</sub> C <sub>0.2</sub> ) <sub>1.58</sub>                      | $29 \pm 15$   | NaCl              | 0.4292              |                |
| AlN                            | VII               | Al(N <sub>0.78</sub> O <sub>0.15</sub> C <sub>0.07</sub> ) <sub>0.98</sub>                   | 5–10          | ZnS               | not determined      | not determined |
| AlN/50 TiN                     | VIII              | see <sup>a</sup>                                                                             | 3–10          | NaCl              | "                   |                |
| AlN/50 TiB <sub>2</sub>        | IX                | not determined                                                                               |               |                   | amorphous film      |                |
| AlN/20 SiC/10 TiB <sub>2</sub> | X                 | "                                                                                            |               |                   | "                   |                |

<sup>a</sup> Approximate formula (Ti<sub>0.55</sub>Al<sub>0.37</sub>Fe<sub>0.08</sub>)(N<sub>0.73</sub>O<sub>0.11</sub>C<sub>0.16</sub>)<sub>1.075</sub>.

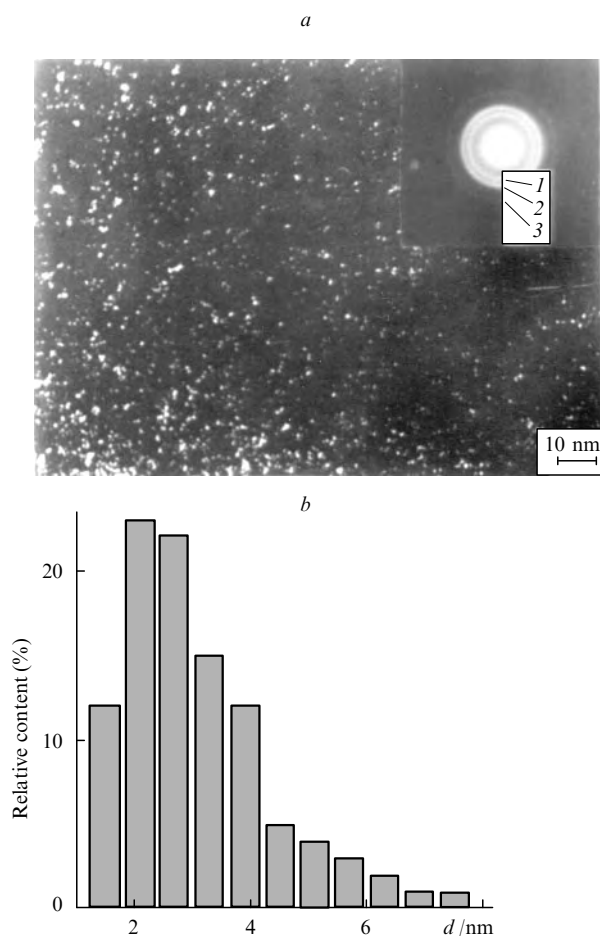


**Figure 9.** Dark-field TEM image of a Ti(B,N) film (regime IV, see Table 4) (a) and the grain size distribution (b).<sup>133</sup> Reflection: 111 (I), 200 (2) and 220 (3).

large residual stress (most often, compressive stress), which can be as high as several GPa;<sup>9</sup> this also affects the film properties.

In the text above we listed not all factors responsible for the properties of nanostructured films of high-melting compounds. But even a brief look at them revealed the need for thorough and comprehensive studies of such films by independent methods. Unfortunately, it does not always happen.

### 3. Properties of films

Complete information on the hardness, resistivity and elastic characteristics of single- and multilayered films of high-melting carbides, borides and nitrides is available from review articles.<sup>9, 23</sup> These data can be complemented with the following results.

The record hardness values (80–100 GPa) were obtained for (Ti, Si)N films fabricated using plasma-assisted chemical deposition.<sup>15</sup> However, these results appeared to be poorly reproducible. This was explained<sup>135</sup> by possible film degradation caused by impurities, in particular, oxygen.

High hardnesses (50 to 70 GPa) of single-layer films based on TiB<sub>2</sub> and B<sub>4</sub>C and of multilayered (Ti,Al)N/VN, TiN/TiB<sub>2</sub> and ZrN/ZrB<sub>2</sub> films have been reported (see, e.g., Refs 9, 15, 29, 30, 131–138). Earlier,<sup>23, 122</sup> it was pointed out that progress made in the field of fabrication of films of novel ultrahard materials based on nanostructured high-melting compounds is more pronounced compared to fabrication of consolidated powder compacts. This is due to the possibility of forming nanostructures with a crystallite size of less than 10 nm in films.

Layered nanocomposites of the TiC/C<sub>amorphous</sub> and WC/C<sub>amorphous</sub> types, characterised by low and stable friction coef-

ficients and high wear resistance, have been developed.<sup>139</sup> These properties are of paramount importance for fabrication of elements of highly efficient friction units used in various fields of technology.

Coatings with a hardness of about 10.6 GPa (under a load of 300 g) were fabricated by gas-thermal (plasma-assisted) deposition of nanopowders of WC–Co hard alloys agglomerated into grains of size 0.3–0.5 μm.<sup>140</sup>

High-resolution SEM and AFM studies of the film behaviour revealed two types of deformation, homogeneous and inhomogeneous.<sup>10, 117, 118, 141, 142</sup> The former is mainly observed in films having a columnar structure, e.g., TiN films. Localised inhomogeneous deformation is accompanied by indentation, which is particularly pronounced in the case of TiB<sub>2</sub> films.

As mentioned above, the use of an additional external magnetic field in the course of sputtering<sup>131, 132</sup> permits fabrication of films with different grain size, which enhances the possibilities of studying the size effects in nanomaterials. It is also noteworthy that the magnetic field has a strong effect on the roughness of film surface (roughness appreciably decreases) and affects the properties of not only the nanocrystalline but also amorphous films, which can be seen by taking films of boron carbide based nanomaterials as examples (Table 5).

**Table 5.** Average crystallite sizes and microhardness values of films of boron carbide based materials with external magnetic field switched off (I) and on (II).

| Target                                     | Average crystallite size /nm |           | Microhardness H <sub>0</sub> /GPa |       |
|--------------------------------------------|------------------------------|-----------|-----------------------------------|-------|
|                                            | I                            | II        | I                                 | II    |
| TiB <sub>2</sub>                           | 3.6 ± 1.8                    | 3.3 ± 1.1 | 32–39                             | 42–48 |
| 75% TiB <sub>2</sub> /25% B <sub>4</sub> C | 8.5 ± 4                      | 2.9 ± 0.3 | 40–46                             | 54–58 |
| 50% TiB <sub>2</sub> /50% B <sub>4</sub> C | amorphous films              |           | 44–50                             | 60–68 |
| 25% TiB <sub>2</sub> /75% B <sub>4</sub> C | the same                     |           | 44–50                             | 62–71 |
| B <sub>4</sub> C                           | "                            |           | 42–50                             | 48–56 |

A study of the galvanomagnetic and electrical properties of TiN films with grain sizes of 29 ± 15 and 8.8 ± 2.2 nm showed that only the charge carrier (electron) mobility and, correspondingly, the conductivity of these films changes, while the charge carrier concentration remains unchanged.<sup>143</sup> These results also indicate a possible absence of large oxygen and carbon segregations at grain boundaries in these films.

A study of high-temperature oxidation of AlN–TiN, AlN–TiB<sub>2</sub> and AlN–SiC–TiB<sub>2</sub> films revealed high thermal stabilities and scale resistances, which exceed those of coarse-grained bulk materials.<sup>144</sup> The results obtained by differential thermal (DTA) and thermogravimetric (TG) analyses at temperatures below 1500°C are presented in Fig. 10. AlN–SiC–TiB<sub>2</sub> films having a self-reinforced nanostructure and aluminium-enriched surface were found to show the highest scale resistance.

Nanostructured boride films and films of some other high-melting compounds are thermally stable up to 1000–1100 °C.<sup>26, 132–136, 144–147</sup> Changes in the microhardness of multilayered TiN/AlN films after annealing in argon atmosphere for 2 h can be followed using the data presented in Fig. 11.<sup>144</sup> As can be seen, films having thinner individual layers are more thermally stable.

An interesting method of improving the thermal stability of multicomponent nanocrystalline high-melting compounds involves the use of spinodal decomposition accompanied by the formation of ultradisperse thermally stable binary structures. The temperature dependences of the microhardness of the coatings based on titanium nitride and zirconium nitride (systems TiN–ZrN and TiN–AlN in amorphous Si<sub>3</sub>N<sub>4</sub> matrix) are

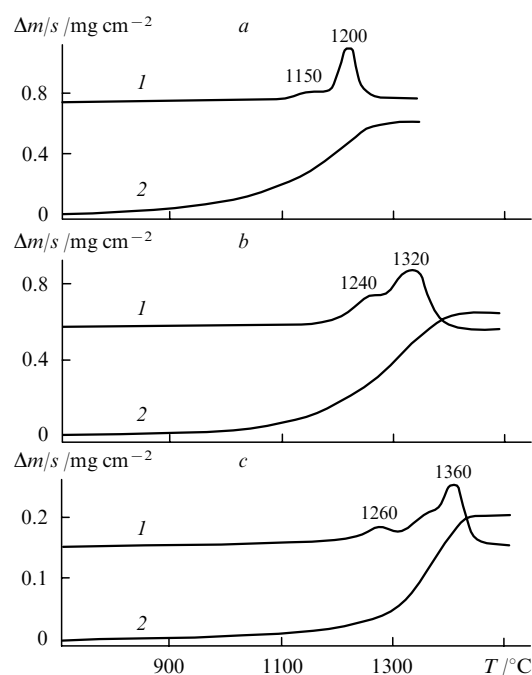


**Figure 10.** DTA (1) and TG (2) curves for AlN–TiN (a), AlN–TiB<sub>2</sub> (b) and AlN–TiB<sub>2</sub>–SiC (c) films.<sup>143</sup>

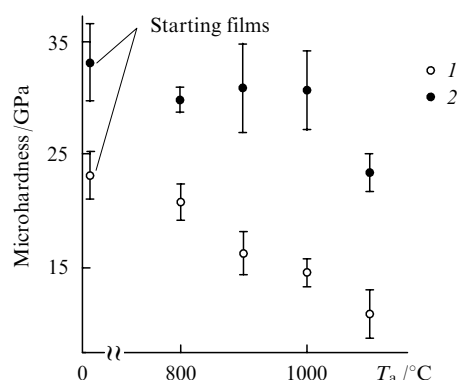


**Figure 11.** Effect of annealing temperature on microhardness of multi-layered TiN/AlN films (overall thickness is 300 nm).<sup>144</sup> Thickness of individual layers is 16 (1) and 2.9 nm (2).

shown in Fig. 12. In the former case the hardness of the alloyed (Ti,Zr)N films considerably increases (see Fig. 12a); the corresponding solid solution decomposes into finely disperse phases on heating, which was detected by X-ray analysis.<sup>147</sup> In the latter case the increase in microhardness is not so large (see Fig. 12b); nevertheless, it affects the thermal stabilities of the films based on titanium nitride and aluminium nitride.<sup>135</sup>

The effect of annealing at 900 °C on the composition and structure of films of silicon carbonitride based materials was studied.<sup>148</sup> Using various methods (IR spectroscopy, X-ray photoelectron spectroscopy, X-ray analysis, Raman spectroscopy, etc.), the post-annealing changes in the crystallite size and a decrease in the proportion of the amorphous component were revealed.

## V. Conclusion

In essence, each type of the nanomaterials (powders, compacts and films) considered in this review deserves a relevant comprehensive analysis. For instance, powders obtained by plasma

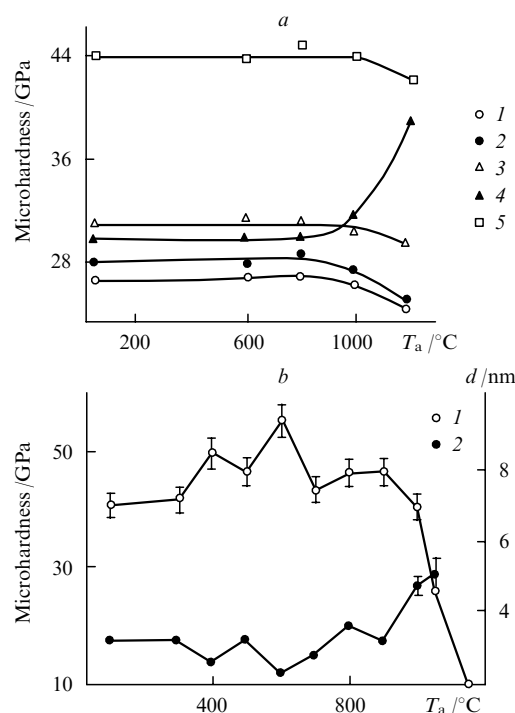


**Figure 12.** Effect of annealing temperature on microhardness of the coatings based on the TiN–ZrN (a) and (Al<sub>1-x</sub>Ti<sub>x</sub>)N/a-Si<sub>3</sub>N<sub>4</sub> systems (b). (a): ZrN (1); TiN (2); TiN–ZrN, 10 layers (3); alloyed films: (Ti,Zr)N (4) and TiN–ZrN, 20 layers (5); (b): microhardness (1), crystallite size (2).

chemical synthesis have been the subject of a monograph.<sup>149</sup> A joint study makes it possible to compare the results obtained for different types of nanomaterials; however, we had to leave some details out of consideration and only refer to original publications because of limitations on the length of the article. In the text below we present the key results obtained in the last decade in the field under study.

Methods for preparation of nanopowders, nanotubes and nanowires, nanostructured compacts and films of practically important high-melting compounds have been elaborated on a laboratory scale (and in some cases on a large scale). Films have been the best studied and can serve as the basis for fabrication of nanomaterials (grain size of 2 to 3 nm; cluster-consolidated objects) possessing the highest physicochemical characteristics. It was shown that application of an external magnetic field in the course of film deposition has a strong effect on the film structure and hardness.

The self-propagating high-temperature synthesis and mechanochemical synthesis have found wide use in the preparation of nanopowders. However, a comparison of the cost–performance ratios for different methods of production of ultradisperse powders and disclosure of optimum ones is complicated by the lack of many necessary characteristics.

A number of methods for consolidation of powder nanomaterials have been elaborated, which allow the nanostructure (with a grain size of about 50 nm) to be retained and specimens of low porosity to be obtained. Of particular interest are the methods that combine mechanochemical synthesis and densification of nanopowders. There is a need in comparing the efficiency of these techniques.

The hardness of nanostructured films based on high-melting compounds can compete with that of the classical ultrahard (> 50 GPa) materials. It was shown that the nanostructures of the films based on borides, nitrides and carbides are thermally stable up to 1000–1100 °C. Highly wear-resistant, nanostructured, single- and multilayered coatings based on high-melting



compounds (with a hardness of at least 40–50 GPa) for tool applications are now produced in the United Kingdom, Germany, Czech Republic and other countries.<sup>30, 31, 135</sup>

A considerable body of information on the structure, physicochemical and physicomechanical properties of nanocrystalline high-melting compounds has been accumulated; selected data on their properties have been reported in a collection of studies.<sup>150</sup> However, there are still many 'blind spots' due to insufficient knowledge of fundamental characteristics of these species (*e.g.*, the electronic structure and constitutional diagrams, the semiconductor and thermodynamic properties, radiation-induced and other types of defects, *etc.*).

Prospects for the design of and research into nanomaterials based on high-melting compounds are associated with both investigation of the nature of the size effects and stability of nanostructures<sup>151</sup> and disclosure of novel (compared to traditional tool and tribotechnical applications) fields of application. For instance, the possibility of using films based on molybdenum and tungsten carbides for electrocatalysis was pointed out;<sup>152, 153</sup> however, by and large the catalytic properties of nanostructured high-melting compounds are poorly studied.

It was shown (see, *e.g.*, Refs 154–158) that nanocrystalline films based on high-melting compounds can be used not only as coatings for tool materials but also for biomedical applications and in data storage systems. There is increasing interest in these compounds from specialists working in electronics and nuclear engineering. Particular attention has been given to silicon carbide, silicon nitride and aluminium nitride. Silicon carbide is thought to be quite promising high-temperature semiconductor material for the Schottky diode type devices,<sup>65</sup> while silicon nitride and aluminium nitride are considered as efficient barrier materials. It is of interest to study the possibility of synthesis and the properties of semiconductor heterostructures based on SiC and other high-melting compounds. The high mechanical and dielectric properties of nanocrystalline films based on, *e.g.*, Si<sub>3</sub>N<sub>4</sub> are attractive for the design of novel types of microbolometric devices for various measuring systems in transport, in biological studies and in industrial and environmental monitoring. Nanocrystalline silicon carbide is considered as a promising structural material for pressurised water-cooled nuclear reactors and boiling water-cooled reactors. Materials based on SiC can be used as the matrix and shell components and for production of units for the fuel core and the plasma-faced wall of a thermal reactor (see, *e.g.*, Refs 159–161).

Clearly, realisation of these promising avenues will require extensive technological and materials science investigations of nanocrystalline structures based on the high-melting compounds described above.

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<sup>g</sup> — *Phys. Met. Metallogr. (Engl. Transl.)*

<sup>h</sup> — *Russ. J. Appl. Chem. (Engl. Transl.)*

<sup>i</sup> — *Phys. Solid State (Engl. Transl.)*

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<sup>l</sup> — *Dokl. Phys. Chem. (Engl. Transl.)*

<sup>m</sup> — *Chem. Sustain. Devel. (Engl. Transl.)*

# Asymmetric induction in the nucleophilic addition in the series of aromatic azines

I N Egorov, G V Zyryanov, V L Rusinov, O N Chupakhin

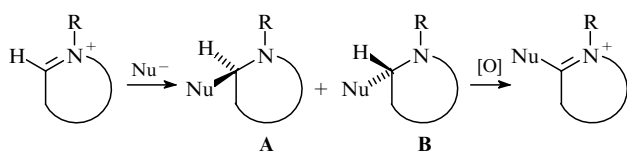
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**Abstract.** Stereoselective reactions of nucleophilic addition to the C=N bond in aromatic azines resulting in chiral products are reviewed. Various methods of inducing the optical activity are discussed. The bibliography includes 60 references.

## I. Introduction

Reactions of nucleophilic substitution of a hydrogen atom ( $S_N^H$ ) in  $\pi$ -electron deficient (hetero)aromatic compounds and azines in particular belong to the abundant class of two-step addition–elimination processes.<sup>1</sup> The initial formation of nucleophilic addition products —  $\sigma^H$ -adducts of **A** and **B** — as a result of a direct attack of C-, N-, O-, P-, S- and other nucleophiles on a non-substituted carbon atom of the azine ring is a general feature of these reactions. The intermediates **A** and **B** themselves are of great synthetic and sometimes industrial interest.



R = H, Ac, R\* (R\* is a chiral substituent); Nu is a nucleophile.

The pro-chiral  $sp^2$ -carbon atom of the C=N bond of the azine ring acquires  $sp^3$ -hybridisation upon formation of  $\sigma^H$ -adducts and therefore becomes chiral. In most cases, these intermediates are mixtures of *R*- and *S*-enantiomers.<sup>2</sup> The adducts exist in the form of diastereomeric pairs where a symmetric carbon is present in either the substrate or the nucleophile. The attack of an achiral nucleophile on the chiral substrate should result in stereoselective

formation of a new chiral centre. In the ideal case, the addition yields an individual stereoisomer.

Numerous publications (see, for example, reviews<sup>3–7</sup>) on the synthesis of alkaloids and on nucleophilic addition reactions in the series of azines (chiral azines as well) neither specially emphasised nor systematised chiral transformations with asymmetric induction. Nor were stereochemical aspects of the formation of the type **A** or **B** intermediates discussed in the book<sup>1</sup> on the reactions of nucleophilic substitution of the aromatic hydrogen atom. The present review is intended to fill this gap. The results of the studies on stereoselective nucleophilic addition to the carbon atom of the azine C=N bond published over the last 15 years are presented.

## II. Stereochemical effects in the attack of an achiral nucleophile on an optically active azine

In spite of the fact that a pyridine-type nitrogen atom increases the  $\pi$ -deficiency of heterocycles, very few examples of the direct introduction of neutral C-nucleophiles into non-activated azines are known.<sup>1</sup> Activated forms of azine substrates, *viz.*, azinium cations, and highly reactive nucleophiles, primarily organometallic compounds, are used as a rule in the induction of chirality upon the nucleophilic attack. In this section, some examples of stereoselective reactions of azines with other C-nucleophiles (cyanide ions, enolates, indoles) as well as with Si- and O-nucleophiles are discussed.

### 1. Reactions of azines with chiral substituents at the nitrogen atom

#### a. The effect of a chiral substituent on the diastereoselectivity of the reaction

The reactions of C-nucleophiles with azinium cations containing nitrogen atoms quaternised with chiral substituents are the best studied. The corresponding salts are usually synthesised by alkylation or acylation (often *in situ*) of an azine substrate with an optically active reagent. The fragments of chiral hydrocarbons, alcohols (including natural ones), amino acids and heterocyclic compounds may be used as the asymmetric inductors. The electrophilicity of the azinium cation depends on the nature of the substituent at the nitrogen atom: less reactive *N*-alkyl-substituted salts react only with carbanions (organometallic compounds), while for *N*-acyl derivatives there is a wide range of potential nucleophiles. The data presented in this Section are ordered according to the type of the nucleophilic agent and in the order of increasing complexity of the azine substrate.

Stereoselective addition reactions of cyanide to chiral isoquinolinium salts have been described.<sup>8</sup> The starting salts have been

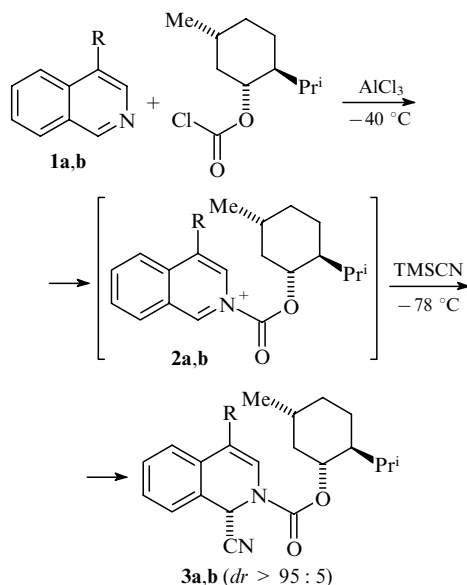
I N Egorov, G V Zyryanov, V L Rusinov Urals State Technical University, ul. Mira 19, 620002 Ekaterinburg, Russian Federation. Fax (7-343) 374 04 58, tel. (7-343) 375 45 01, e-mail: egorov@htf.ustu.ru (I N Egorov), grigoryz@hotmail.com (G V Zyryanov), rusinov@htf.ustu.ru (V L Rusinov)  
O N Chupakhin I Ya Postovsky Institute of Organic Synthesis, Urals Branch of the Russian Academy of Sciences, ul. S Kovalevskoy 20, 620219 Ekaterinburg, Russian Federation. Fax (7-343) 374 11 89, tel. (7-343) 374 11 89, e-mail: chupakhin@ios.uran.ru

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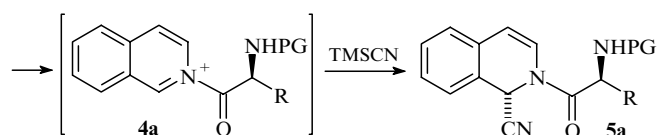
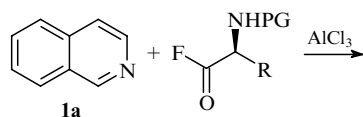
synthesised *in situ* by acylation of isoquinolines with optically active (–)-menthyl chloroformates in the presence of Lewis acids. Trimethylsilyl cyanide (TMSCN) was used as a C-nucleophile.

Thus isoquinolines **1a,b** in the reaction with (–)-(*R*)-menthyl chloroformate yield optically active salts **2a,b**, which add the CN group with high diastereoselectivity. The diastereomeric ratio (*dr*) in the products **3a,b** exceeds 95 : 5.<sup>8</sup>



R = H [**a** (98%)], Br [**b** (96%)].

Isoquinolinium salts **4a** obtained from protected amino acid fluorides react with TMSCN in a similar way.<sup>8</sup> In these reactions, the stereoselective formation of Reissert compounds **5a** was observed. The diastereomeric ratio of the reaction products depends on the structure of the original amino acid.



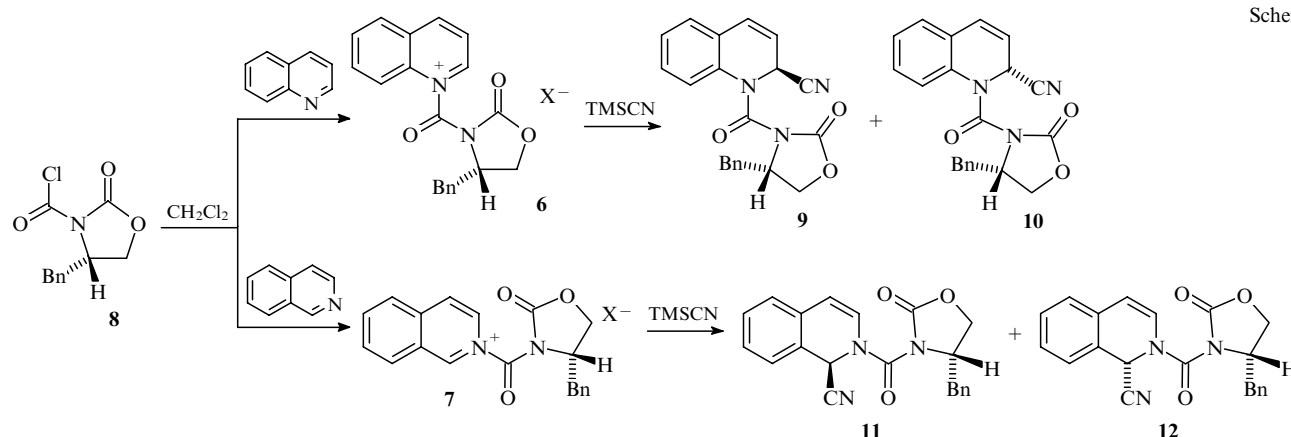
PG is protection group (Z is benzyloxycarbonyl, Fmoc is 9-fluorenylmethyloxycarbonyl).

| R                  | PG   | Yield of <b>5a</b> (%) | <i>dr</i> |
|--------------------|------|------------------------|-----------|
| Me                 | Z    | 89                     | > 95 : 5  |
| Me                 | Fmoc | 44                     | 71 : 29   |
| Pr <sup>i</sup>    | Fmoc | 47                     | 70 : 30   |
| CH <sub>2</sub> Ph | Z    | 51                     | 82 : 18   |

The chiral *N*-acylazinium salts of the quinoline (compounds **6**) and isoquinoline (compounds **7**) series were obtained by acylation of the corresponding heterocycles with an optically active derivative of 2-oxooxazolidine-3-carbonyl chloride **8**.<sup>9</sup> The study of their reactions with TMSCN has revealed a different diastereomeric ratio of the resulting diastereomeric Reissert compounds **9**, **10** and **11**, **12**. The stereoselectivity of this reaction depends not only on the structure of the anion X<sup>–</sup>, but on the temperature of the reaction as well (Scheme 1).

It was suggested<sup>9</sup> that the reason for the observed diastereoselectivity of the reaction is that *N*-acylazinium triflates **6** and **7** adopt the most favourable conformation with maximum  $\pi$ – $\pi$ -interaction between the (iso)quinolinium aromatic ring and the phenyl ring of the acyl substituent. Such a conformation results in shielding of one of the diastereotopic sides of the reacting C=N<sup>+</sup> bond. Two possible conformations **A1**, **A2** and **B1**, **B2** can be suggested for the iminium salts **6** and **7**, respectively (Scheme 2). In contrast to the conformers **A2** and **B2**, the *trans*-configuration (relative to the single N<sup>+</sup>–CO bond) of the iminium and carbonyl groups in conformers **A1** and **B1** makes the  $\pi$ – $\pi$ -interaction possible. The attack of the cyanide-ion (the front side is marked by a solid arrow in Scheme 2, the rear side, by dashed one) on the less sterically hindered side of the conformers **A1** (salt **6**) and **B1** (salt **7**) leads to the predominant formation of the diastereomers **9** and **12**, respectively.

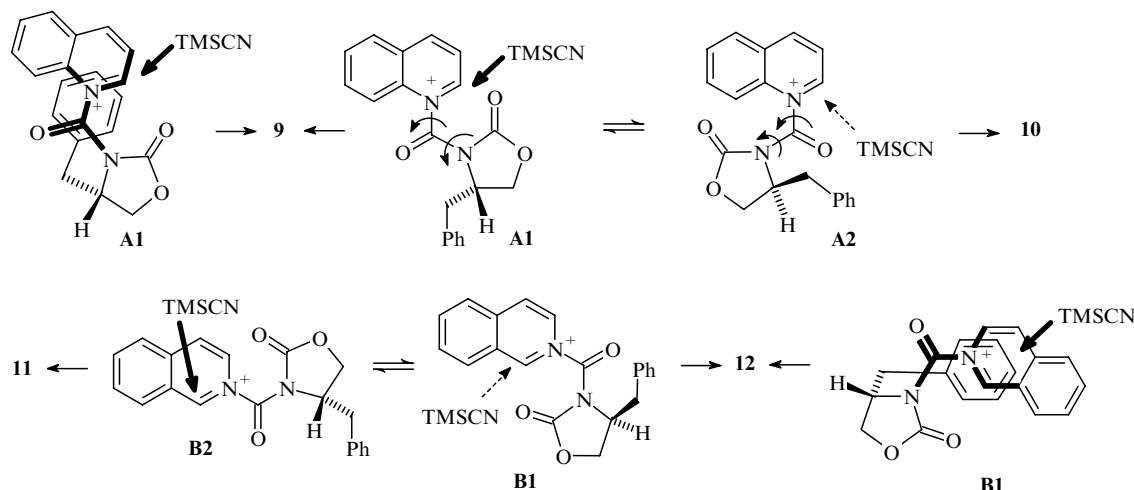
The triflate anion also favours the  $\pi$ – $\pi$ -interactions in the acylazinium intermediate due to weaker interaction with the iminium part of the molecule than in the case of the chloride



Scheme 1

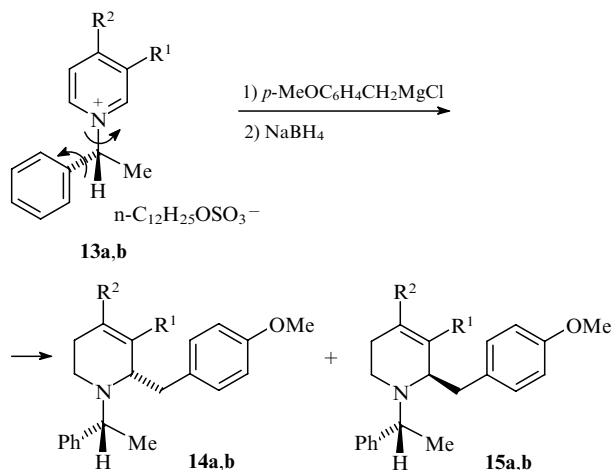
| X <sup>–</sup>   | T/°C | Reagent | Diastereomer ratio |         | Total yield (%) |         |
|------------------|------|---------|--------------------|---------|-----------------|---------|
|                  |      |         | 9 : 10             | 11 : 12 | 9 + 10          | 11 + 12 |
| Cl <sup>–</sup>  | 20   | —       | 55 : 45            | 60 : 40 | 88              | 76      |
| TfO <sup>–</sup> | 20   | TMSOTf  | 83 : 17            | 15 : 85 | 70              | 35      |
| TfO <sup>–</sup> | 40   | TMSOTf  | 84 : 16            | 29 : 71 | 60              | 95      |

Scheme 2



anion. As a consequence, the stereoselectivity of the addition increases.<sup>9</sup>

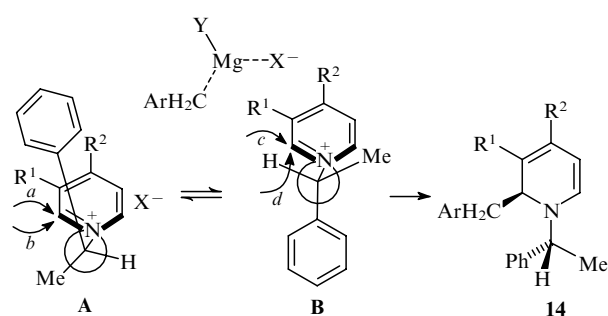
Azines may be quaternised not only by chiral acyl groups, but by alkyl groups as well. Thus chiral *N*-alkylpyridinium salts **13a,b** show a high degree of diastereoselectivity in reactions with benzyl-type Grignard reagents.<sup>10</sup> The reduction of the products with sodium borohydride leads to diastereomeric tetrahydropyridines **14a,b** (the main product) and **15a,b**.



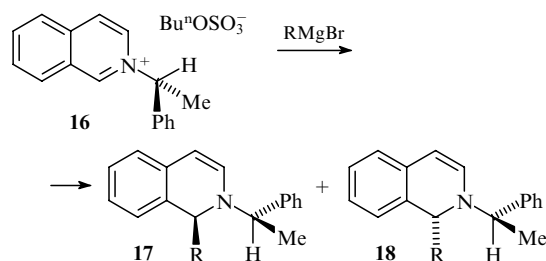
$R^1 = R^2 = \text{Me}$  (**a**, *de*† 82%);  $R^1 - R^2 = (\text{CH}_2)_4$  (**b**, *de* 78%).

Such a relatively high selectivity was rather unexpected for the authors,<sup>10</sup> because the chiral alkyl group in the starting salt **13** is quite mobile and relatively freely rotates around the N–C bond.

The structures **A** and **B**, in which the C–H bond of the chiral group is coplanar to the plane of the pyridine ring, are probably the most energetically favourable conformations of the salts **13**. In such a case, there are several possible directions of the nucleophilic attack: pathways *a* and *b* for the conformation **A** and pathways *c* and *d* for the conformation **B**. But only the pathway *c* leads effectively to stereoisomers **14**, because only in this case is the approach of the nucleophile to the pyridine ring unhindered by the small- (H atom) and medium-sized (methyl group) substituents of the chiral alkyl fragment.<sup>10</sup>



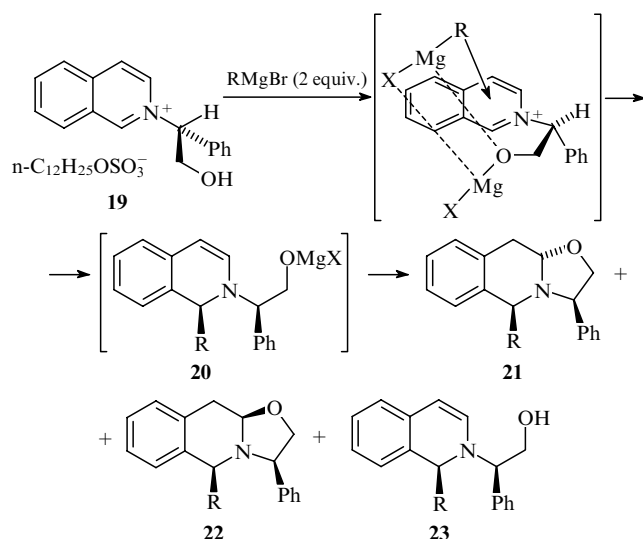
The reaction of the chiral isoquinolinium salts **16** with the Grignard reagents afforded unstable 1-substituted 1,2-dihydroisoquinolines **17** and **18** in good yields (90%–95%).<sup>11</sup> However, the observed diastereoselectivity of this reaction is lower than that in the case of 3,4-disubstituted pyridinium salts.



| R                                                          | Ratio <b>17</b> : <b>18</b> |
|------------------------------------------------------------|-----------------------------|
| Me                                                         | 64:36                       |
| Ph                                                         | 87:13                       |
| <i>m</i> -MeOC <sub>6</sub> H <sub>4</sub>                 | 90:10                       |
| <i>m</i> -MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> | 62:38                       |

In a similar reaction of the Grignard reagents with the isoquinolinium salt **19**, which contains a chiral hydroxy(phenyl)ethyl group at the nitrogen atom, the 1,2-dihydroisoquinoline intermediates **20** cyclise spontaneously upon hydrolysis.<sup>11</sup> The main reaction products are tetrahydrooxazoloisoquinolines **21** and **22**. Small amounts of dihydroisoquinolines **23** are also isolated.

† *de* is diastereomeric excess.

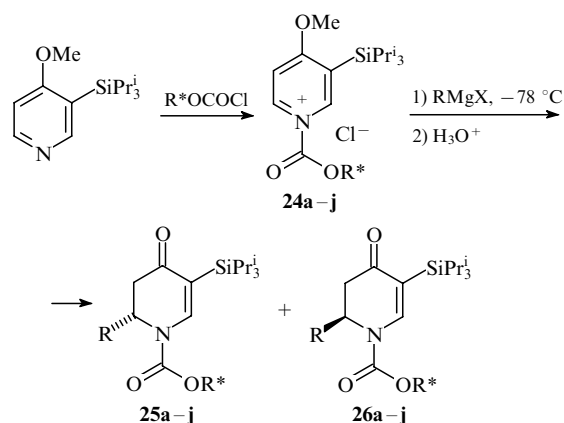


| R                                          | Ratio <b>21</b> : <b>22</b> : <b>23</b> |
|--------------------------------------------|-----------------------------------------|
| Me                                         | 51 : 37 : 12                            |
| Ph                                         | 64 : 29 : 7                             |
| Pr <sup>i</sup>                            | 49 : 34 : 17                            |
| <i>m</i> -MeOC <sub>6</sub> H <sub>4</sub> | 72 : 20 : 8                             |

Presumably,<sup>11</sup> the destabilising steric interactions between the phenyl groups of the oxazolidine ring and the substituent R at C(5) are responsible for the preferable formation of the oxazolidines **22** rather than of their stereoisomers **23**.

A series of papers on the influence of chiral substituents at the nitrogen atom of azine substrates on the stereoselectivity of the reactions with organometallic reagents have been published by the Comins group. Thus 1-acylpyridinium salts **24** containing a

residue of an optically active alcohol (R\*OH) have been studied.<sup>12–16</sup> These salts have been synthesised from 4-methoxy-3-(triisopropylsilyl)pyridine and the corresponding chiral chloroformates. The salts **24a,b** react with organomagnesium compounds under very mild conditions.<sup>13</sup> Acid hydrolysis of the reaction mixture yields mainly dihydropyridones **25a,b**. The stereoselectivity of the reaction is relatively high, stereoisomers **26a,b** are the minor products.



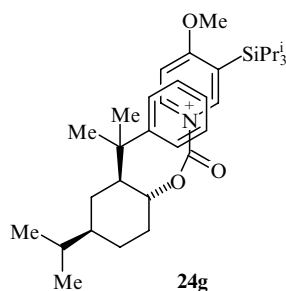
The effect of chiral acyl groups on the stereoselectivity of the addition reaction may be increased by introducing aromatic substituents into the alcohol residue.<sup>14,15</sup> Thus the diastereoselectivities of the reactions of *trans*-2-( $\alpha$ -cumyl)cyclohexyl derivatives of the salts **24c–f** with *p*-tolyl- and cyclohexylmagnesium halides were equal to 83%–93%. Acylpyridinium salts **24g–i**, containing an isopropyl group in a similar chiral substituent, appeared to be slightly more effective as asymmetric inductors in this stereoselective synthesis (Table 1).<sup>15</sup>

**Table 1.** Reaction of 1-acylpyridinium salts **24a–j** with Grignard reagents.

| Compo-<br>unds<br><b>24–26</b> | R* | R                                                                                                                                                                                                      | Total<br>yield<br>(%)                        | de<br>(%)<br>(see <sup>a</sup> )             | Compo-<br>unds<br><b>24–26</b> | R* | R                                       | Total<br>yield<br>% | de<br>(%)<br>(see <sup>a</sup> ) |
|--------------------------------|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|----------------------------------------------|--------------------------------|----|-----------------------------------------|---------------------|----------------------------------|
| <b>a</b>                       |    | Ph                                                                                                                                                                                                     | 87                                           | 44                                           | <b>e</b>                       |    | <i>p</i> -Tol<br>Cy (see <sup>b</sup> ) | 93<br>84            | 83<br>83                         |
| <b>b</b>                       |    | Me<br>Bu <sup>i</sup> (see <sup>b</sup> )<br>Cy (see <sup>b</sup> )<br>Ph<br><i>o</i> -Tol<br><i>p</i> -Tol<br><i>p</i> -MeOC <sub>6</sub> H <sub>4</sub><br><i>p</i> -ClC <sub>6</sub> H <sub>4</sub> | 92<br>95<br>90<br>88<br>81<br>90<br>77<br>78 | 91<br>92<br>81<br>94<br>60<br>82<br>73<br>81 | <b>f</b>                       |    | <i>p</i> -Tol<br>Cy (see <sup>b</sup> ) | 71<br>82            | 89<br>86                         |
| <b>c</b>                       |    | <i>p</i> -Tol<br>Cy (see <sup>b</sup> )                                                                                                                                                                | 89<br>95                                     | 89<br>82                                     | <b>g</b>                       |    | <i>p</i> -Tol<br>Ph                     | 89<br>82            | 92<br>86                         |
| <b>d</b>                       |    | <i>p</i> -Tol<br>Cy (see <sup>b</sup> )                                                                                                                                                                | 91<br>92                                     | 93<br>86                                     | <b>h</b>                       |    | <i>p</i> -Tol<br>Cy (see <sup>b</sup> ) | 64<br>81            | 94<br>90                         |
|                                |    |                                                                                                                                                                                                        |                                              |                                              | <b>i</b>                       |    | <i>p</i> -Tol<br>Cy (see <sup>b</sup> ) | 95<br>80            | 79<br>85                         |
|                                |    |                                                                                                                                                                                                        |                                              |                                              | <b>j</b>                       |    | Ph                                      | 80                  | 4                                |

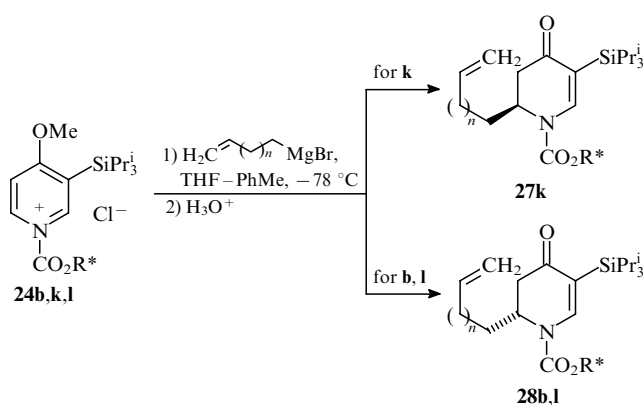
<sup>a</sup> Compound **25** is the predominant stereoisomer; <sup>b</sup> in these cases X = Br, in other examples X = Cl; Cy is cyclo-C<sub>6</sub>H<sub>11</sub>.

Presumably,<sup>15</sup> it is the steric shielding of one side of the pyridinium ring of salt **24** by bulky chiral acyl groups that determines the predominant direction of the nucleophilic attack. The process is enhanced by aryl substituents in these groups. The  $\pi$ - $\pi$ -donor-acceptor interaction (further in the text,  $\pi$ - $\pi$ -interaction) between the substituent and the pyridinium cation stabilises the staggered conformation.<sup>16,17</sup> The positive effect of the isopropyl group of the 8-arylmethyl moiety on the stereoselectivity of the process is more difficult to rationalise. It was suggested<sup>15,16</sup> that the isopropyl group might affect the ratio of the possible rotamers leading to the optimum  $\pi$ - $\pi$ -interaction between the aromatic rings.



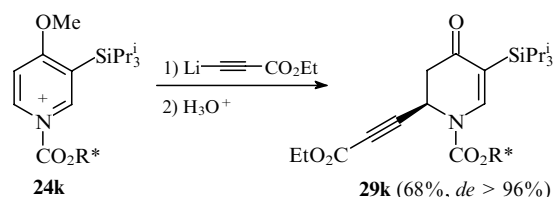
The non-stereoselectivity of the reaction of phenylmagnesium bromide with the salt **24j** where *vic*-substituents in the cyclohexane ring adopt a *cis*-configuration may be explained by the same reason.

The configuration of the optical centre of the acyl group determines the ratio of the diastereomeric products. Thus the reaction of a homochiral 1-acylpyridinium salt **24k**, obtained by the reaction of chloroformate (as the acylating agent),  $R^* = (+)$ -*trans*-2-( $\alpha$ -cumyl)cyclohexyl [(+)-TCC], with alkenylmagnesium bromides yielded dihydropyridones **27k**.<sup>18,19</sup> In the case of its optical antipode, *i.e.*, (–)-TCC-chloroformate, the reaction of acylpyridinium salt **24l** leads to the diastereomer of **27**, *i.e.*, dihydropyridone **28l**.<sup>20,21</sup> A similar result has been observed in the reaction of substrate **24b** containing a (–)-8-phenylmethyl substituent.<sup>22</sup>



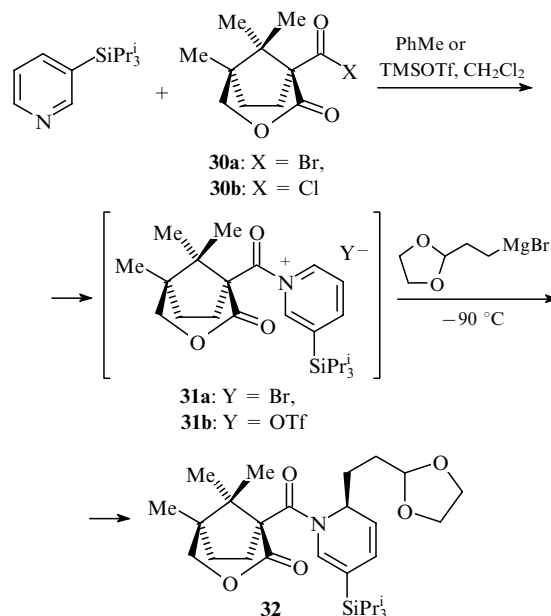
| Salt <b>24</b> | $R^*$            | Reaction product |     |           |          | Ref.   |
|----------------|------------------|------------------|-----|-----------|----------|--------|
|                |                  | compound         | $n$ | yield (%) | $de$ (%) |        |
| <b>b</b>       | (–)-8-Ph-menthyl | <b>28b</b>       | 2   | 100       | 91       | 18     |
| <b>k</b>       | (+)-TCC          | <b>27k</b>       | 1   | 91        | 90       | 14     |
|                |                  | <b>27k</b>       | 2   | 95        | 93       | 15     |
| <b>l</b>       | (–)-TCC          | <b>28l</b>       | 1   | —         | 90       | 16, 17 |

Similar stereochemistry of the addition products was observed with lithium acetylides used as C-nucleophiles instead of alkenylmagnesium bromides. Thus treatment of the salt **24k** with a Li-derivative of ethyl propiolate leads to dihydropyridone **29**.<sup>23</sup>

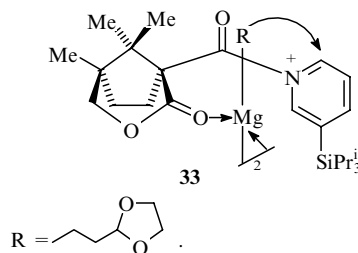


$R^* = (+)$ -TCC.

The reaction of 3-(triisopropylsilyl)pyridine with chiral bicyclic acyl bromide **30a** in pyridine yields solid *N*-acylpyridinium salt **31a**.<sup>24</sup> The addition of 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide at  $-90^\circ C$  to this heterogeneous system affords 6-substituted *N*-acyl-1,6-dihydropyridine **32**. The reaction is regio- and diastereoselective (yield 41%,  $de$  100%). An analogous reaction was carried out with acyl chloride **30b** under homogeneous conditions,<sup>24</sup> which are more suitable for this reaction. In presence of trimethylsilyl triflate (TMSOTf), the addition product **32** is formed *via* intermediate salt **31b**. The yield of the product increased to 62%, but the diastereoselectivity of the process decreased to 88%.

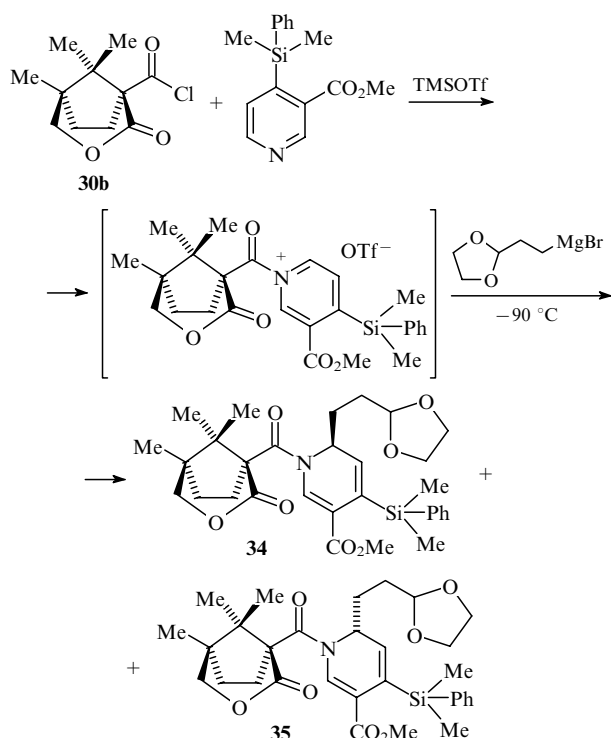


The asymmetric induction in the considered processes may be explained by preliminary complex formation. The reaction mechanism includes the initial coordination and addition of organometallic reagent to the carbonyl group of the chiral acyl substituent with formation of complex **33**. Judging from the stereochemistry of the addition product **32**, the attack of the nucleophilic agent on the iminium moiety proceeds as follows:



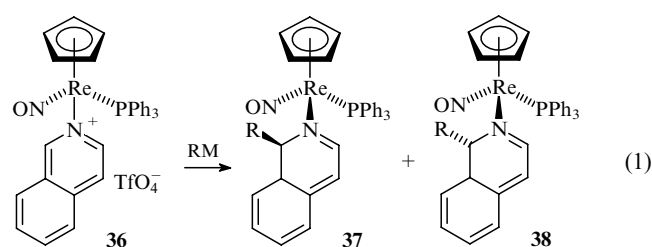
Later, this reaction was extended<sup>25</sup> to methyl dimethyl(phenyl)silylnicotinate in order to avoid addition at position 4. Compound **34** was isolated as the main product, while the stereoisomer **35** was a minor product (ratio **34**:**35** = 87.2:12.8).





An example of diastereoselective addition of C-nucleophile to isouquinoline **36**, activated by a chiral rhenium complex, has been described.<sup>26</sup> The reactions of compound **36** with organometallic compounds occur under very mild conditions and start at a temperature as low as  $-100^{\circ}\text{C}$ . The metallocomplex **37** is the main reaction product (*de* 46%–88%); small amounts of the diastereomer **38** were observed [reaction (1)].

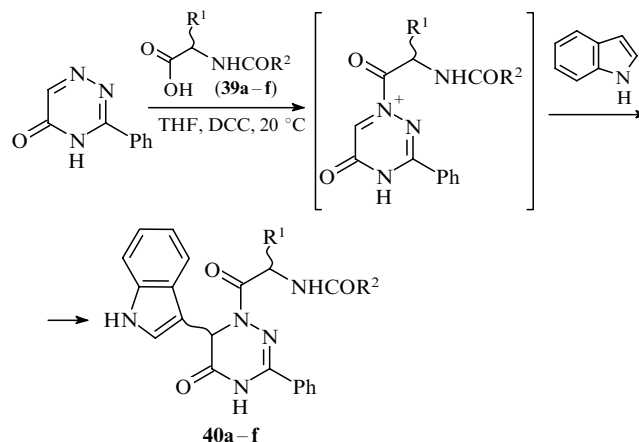
This reaction with  $\text{Me}_3\text{SiCH}_2\text{MgCl}$  is significantly slower than that with  $\text{Me}_3\text{SiCH}_2\text{Li}$ . In the former case, the diastereoselectivity noticeably decreases with an increase in temperature. However, the Grignard reagent containing the secondary alkyl group, *viz.*,  $\text{Pr}^i\text{MgCl}$ , reacts with the complex **36** rapidly even at  $-100^{\circ}\text{C}$ . It is worth noting that  $\text{MeMgCl}$  is the least reactive nucleophile in this reaction.<sup>26</sup>



| RM                                    | Temperature / $^{\circ}\text{C}$ | Ratio <b>37</b> : <b>38</b> |
|---------------------------------------|----------------------------------|-----------------------------|
| $\text{Me}_3\text{SiCH}_2\text{Li}$   | $-55$                            | 94 : 6                      |
| $\text{Me}_3\text{SiCH}_2\text{MgCl}$ | 20                               | 80 : 20                     |
| $\text{Pr}^i\text{MgCl}$              | $-100$                           | 89 : 11                     |
| $\text{EtMgBr}$                       | $-100$                           | 89 : 11                     |
| $\text{PhCH}_2\text{MgCl}$            | $-100$                           | 88 : 12                     |
| $\text{Pr}^n\text{MgCl}$              | $-100$                           | 87 : 13                     |
| $\text{MeMgCl}$                       | 20                               | 84 : 16                     |
| $\text{Bu}^n\text{MgCl}$              | $-100$                           | 82 : 18                     |
| $\text{AlEtMgBr}$                     | $-100$                           | 73 : 27                     |

$\pi$ -Electron-donating heterocycles can be used as C-nucleophiles in reactions with azines. Thus 3-phenyl-1,2,4-triazin-5(4*H*)-one was acylated with *N*-protected  $\alpha$ -amino acids **39a–f** activated by dicyclohexylcarbodiimide (DCC) and reacted with indole.<sup>27</sup> The addition products at the position 3 of indole, compounds

**40a–f**, were obtained with high diastereoselectivity (*dr* > 95 : 5). The predominant formation of only one pair of diastereomers in this reaction was explained by a significant steric hindrance for the attack of the triazine ring caused by the amino acid residue. However, it is the same circumstances that are the reason for the low yields.<sup>27</sup>

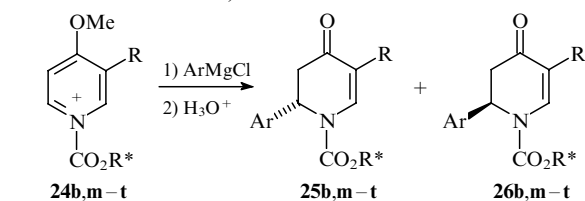


| Compound <b>40</b> | Starting amino acid <b>39</b>  | Yield (%) |
|--------------------|--------------------------------|-----------|
| <b>a</b>           | <i>N</i> -Boc-glycine ‡        | 42        |
| <b>b</b>           | <i>N</i> -Bn-D,L-leucine       | 26        |
| <b>c</b>           | <i>N</i> -Ac-D-alanine         | 28        |
| <b>d</b>           | <i>N</i> -Ac-L-tryptophan      | 21        |
| <b>e</b>           | <i>N</i> -Ac-L-valine          | 17        |
| <b>f</b>           | <i>N</i> -Ac-D,L-phenylalanine | 22        |

These examples illustrate the significant influence of chiral substituents at the azine nitrogen atom on the stereoselectivity of the reactions with C-nucleophiles.

#### b. The effect of an achiral substituent at a carbon atom of the azine ring on the reaction diastereoselectivity

The most detailed investigation into the effect of the character and size of a 3-substituent in the pyridine ring on the diastereoselectivity of the addition of the Grignard reagents was carried out by Comins *et al.*<sup>14</sup> The authors of the cited paper studied the reactions of a series of optically active 4-methoxy-*N*-[(–)-menthyloxycarbonyl]pyridinium salts **24b,m–t** with arylmagnesium chlorides leading to 6-substituted compounds **25** and **26** (**25** being the main stereoisomer).



| Compounds <b>24–26</b> | R                 | R*                  | Ar            | Yield (%) | <i>de</i> (%) |
|------------------------|-------------------|---------------------|---------------|-----------|---------------|
| <b>b</b>               | $\text{SiPr}_3^i$ | (–)-8-phenylmenthyl | Ph            | 88        | 94            |
|                        |                   |                     | <i>o</i> -Tol | 81        | 60            |
| <b>m</b>               | H                 | (–)-menthyl         | Ph            | 79        | 34            |
|                        |                   | (–)-8-phenylmenthyl | Ph            | 83        | 30            |
| <b>n</b>               | $\text{SiMe}_3$   | (–)-menthyl         | Ph            | 88        | 50            |
|                        |                   | (–)-8-phenylmenthyl | Ph            | 82        | 65            |
|                        |                   |                     | <i>o</i> -Tol | 90        | 30            |
| <b>o</b>               | $\text{SiPr}_3^n$ |                     | <i>o</i> -Tol | 88        | 40            |

‡ Boc is *tert*-butoxycarbonyl.

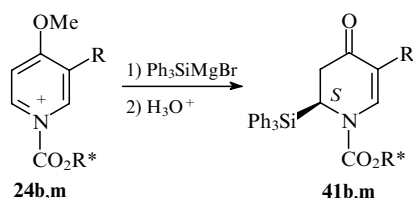
| Compo-<br>unds <b>24–26</b> | R                              | R* | Ar            | Yield<br>(%) | de<br>(%) |
|-----------------------------|--------------------------------|----|---------------|--------------|-----------|
| <b>p</b>                    | SiBu <sub>3</sub> <sup>i</sup> |    | <i>o</i> -Tol | 89           | 34        |
| <b>q</b>                    | SiPh <sub>3</sub>              |    | <i>o</i> -Tol | 85           | 18        |
| <b>r</b>                    | SnBu <sub>3</sub> <sup>i</sup> |    | Ph            | 84           | 60        |
| <b>s</b>                    | SnPr <sub>3</sub> <sup>i</sup> |    | Ph            | 80           | 84        |
| <b>t</b>                    | SnCy <sub>3</sub>              |    | Ph            | 75           | 80        |

The original idea<sup>14</sup> was to increase the regioselectivity of the reaction by introducing a 3-substituent in the pyridinium ring, which would prevent nucleophilic attack on C(2). However, the substituent also affected the stereochemistry. Although no rigorous regularities were established, some qualitative conclusions could be drawn. The best diastereoselectivity (*de* 94%) was obtained in the reaction of 4-methoxy-3-(triisopropylsilyl)-pyridinium salt **24b** with phenylmagnesium chloride. The use of pyridinium salts with less bulky 3-alkylsilyl substituents in the reactions with aromatic Grignard reagents resulted in a decrease in *de* (in the range of 34%–40%). The triphenylsilyl substituent reduced the diastereoselectivity of the process even more (down to 18%).<sup>14</sup>

### c. The effect of the character of the nucleophile on the stereochemistry of addition reactions of nucleophilic reagents to chiral *N*-acylazinium salts

As was mentioned above, a broad spectrum of addition products have been obtained in reactions of chiral *N*-acylpyridinium salts with Grignard reagents.<sup>13,28,29</sup> Derivatives of indolizine,<sup>21,30</sup> quinolizidine,<sup>31</sup> piperidine<sup>30,32–36</sup> and *cis*- and *trans*-decahydroquinoline<sup>19,22</sup> alkaloids were synthesised from other optically active *N*-acylazinium salts and organometallic compounds. Only one of the possible diastereomers is formed predominantly in these reactions and its stereochemistry depends on the configuration of the chiral acyl group.<sup>13,14,22</sup> Examples of the effect of the character and stereochemistry of the attacking nucleophilic reagent on the product configuration are given below.

**Characteristic features of the introduction of the triphenylsilyl group into chiral *N*-acyl-4-methoxypyridinium salts.** The reaction of triphenylsilylmagnesium bromide (Si-nucleophile) with chiral *N*-acyl-4-methoxypyridinium salt **24b** at –78 °C is stereoselective and results in diastereomerically pure *N*-acyl-2-(triphenylsilyl)-2,3-dihydropyridin-4-one **41b** (yield 73%, *de* 96%).<sup>37</sup> The reaction of this nucleophile with 3-unsubstituted salt **24m** leads to compound **41m** (*de* 96%) in 88% yield. It appeared that the absolute configuration of the newly formed chiral centre C(2) of dihydropyridones **41b,m** is opposite to that of the main reaction product of pyridinium salts **1** with arylmagnesium chlorides as C-nucleophiles (see above). In addition, it was shown that the trimethylsilyl group at position 3 of the starting salt did not affect the asymmetric induction in this reaction.<sup>37,38</sup>



R = Me<sub>3</sub>Si (**b**), H (**m**); R\* = (–)-8-phenylmenthyl.

The preferential formation of *S*-isomer is explained<sup>38</sup> by the interaction of the magnesium atom of the Grignard reagent with the carbonyl group of the acyl fragment (Fig. 1). This coordination results in the alteration of the direction of the nucleophilic attack, which was confirmed by quantum-chemical calculations.

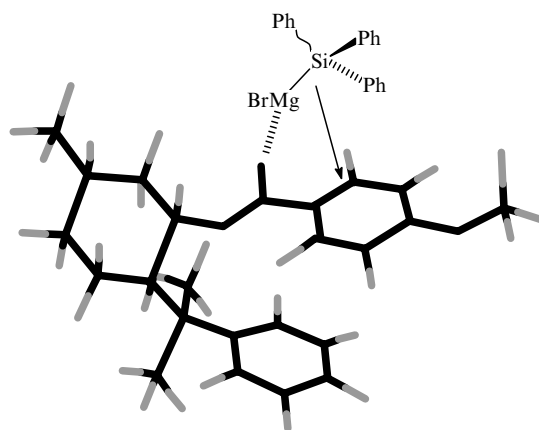
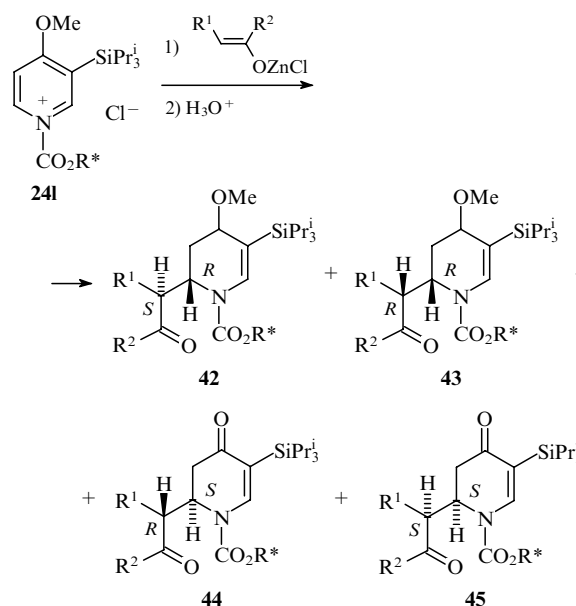


**Figure 1.** The molecular mechanic model of addition of triphenylsilyl-magnesium bromide to chiral *N*-acyl-4-methoxypyridinium salts **24**.<sup>38</sup>

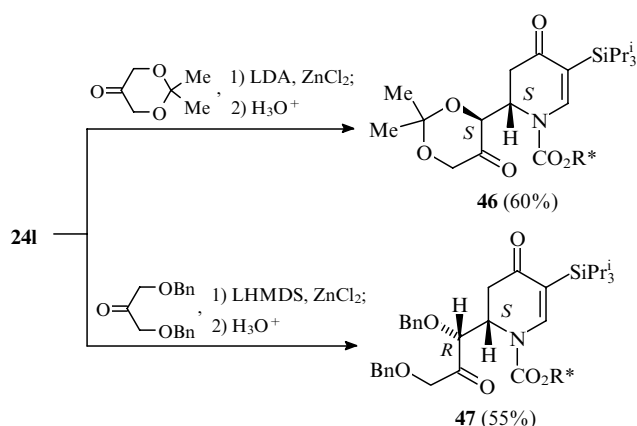
**Characteristic features of the addition of metalloenolates to chiral *N*-acylpyridinium salts** The addition reactions of prochiral metalloenolates of ketones and lactones with salts **24** are highly stereoselective and result in the formation of two new chiral centres.<sup>3,39</sup> The *2R,2'S*-diastereomer **42** is the main reaction product, while (*R,R*)-**43**, (*S,R*)-**44** and (*S,S*)-**45** stereoisomers were obtained in minor amounts.



R\* = (–)-TCC.

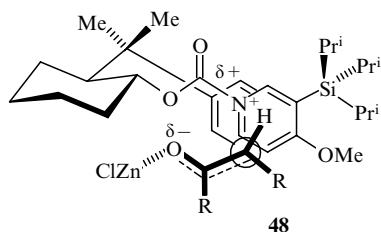
| R <sup>1</sup>                                                     | R <sup>2</sup> | Ratio<br><b>42</b> : ( <b>43</b> + <b>44</b> + <b>45</b> ) | Yield of <b>42</b> (%) |
|--------------------------------------------------------------------|----------------|------------------------------------------------------------|------------------------|
| –CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> –                 |                | 88 : 12                                                    | 82                     |
| –CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> – |                | 86 : 14                                                    | 79                     |
| Me                                                                 | Et             | 92 : 8                                                     | 83                     |

Interestingly, this reaction with the enol form of 2,2-dimethyl-1,3-dioxan-5-one (*E*-isomer) yields compound **46** with (*2S,2'S*)-configurations of chiral centres. Compound (*2S,2'R*)-**47** with the opposite configuration is formed as the main product in a similar reaction with 1,3-bis(benzyloxy)propan-2-one in the enol form, which exists as *Z*-isomer due to formation of a chelate.<sup>39</sup>



R\* is (–)-TCC, LDA is lithium diisopropylamide, LHMDs is lithium hexamethyldisilazide.

The selectivity of the addition of *E*-enolate may be explained by the existence of a transition state

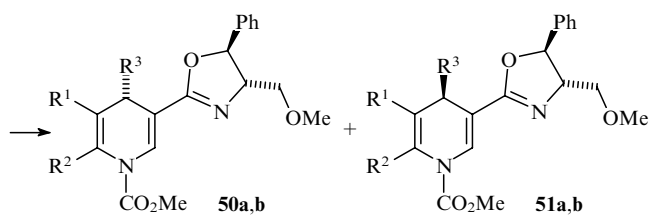
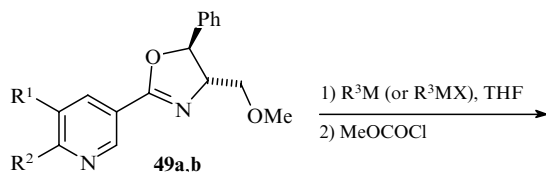


This transition state is the most probable due to a non-covalent interaction between the pyridinium ring and the phenyl ring of the chiral acyl group ( $\pi$ – $\pi$ -interaction) and also due to electrostatic attraction between the positively charged nitrogen atom and the negatively charged enolate oxygen atom.<sup>39</sup>

## 2. Reactions of azines containing a chiral atom in the ring

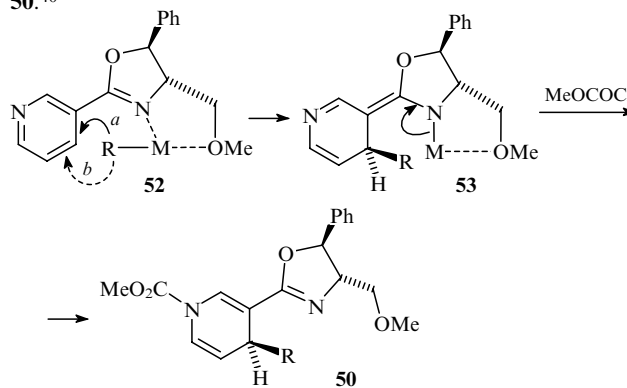
The presence in the azine ring of substituents capable of coordinating the attacking particle is an important factor determining the stereochemical composition of products of a nucleophilic reaction on a carbon atom of a double C=N bond in azines. Thus examples of insertion of functional groups capable of complexation with nucleophiles at the  $\beta$ -position of pyridine and quinoline rings are given in papers<sup>40–42</sup>.

One of the first reported reactions of diastereoselective nucleophilic addition to pyridinium salts and quinolinium salts with initial complexation is the reaction of chiral 2-(3-pyridyl)- (49a) and 2-(3-quinolyl)oxazolines (49b) with organolithium and -magnesium reagents followed by treatment with methyl chloroformate.<sup>42</sup> This reaction affords the corresponding 1,4-dihydro-derivatives 50a,b and 51a,b in good yields and high diastereomer ratio (*de* > 95%). Replacement of pyridine by quinoline increases the diastereoselectivity of the process. Thus in the reaction of compound 49a with methyl lithium the ratio of the corresponding diastereomers 50a:51a is 93:7, while in the case of quinoline derivative 49b this ratio is equal to 98:2.



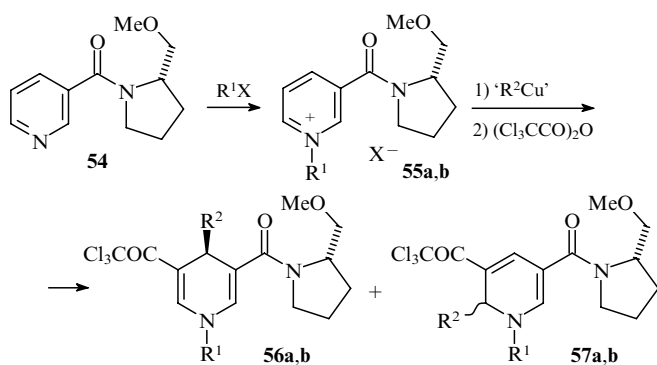
| Compounds 49–51 | R <sup>1</sup> , R <sup>2</sup> | R <sup>3</sup> M or R <sup>3</sup> MX | T / °C | Ratio 50:51 | Total yield (yield of 50) (%) |
|-----------------|---------------------------------|---------------------------------------|--------|-------------|-------------------------------|
| a               | H                               | MeLi                                  | –40    | 93:7        | 79                            |
|                 |                                 |                                       | –78    | 94:6        | 79 (63)                       |
|                 |                                 | MeMgCl                                | 0      | 91:9        | 88                            |
|                 |                                 | EtMgBr                                | 0      | 92:8        | 63                            |
|                 |                                 | Bu <sup>n</sup> Li                    | –78    | 97:3        | (92)                          |
|                 |                                 | Bu <sup>n</sup> MgCl                  | 0      | 95:5        | 98                            |
| b               | C <sub>6</sub> H <sub>4</sub>   | PhLi                                  | –78    | 92:8        | 94                            |
|                 |                                 |                                       | –78    | 98:2        | 84 (70)                       |

The high stereoselectivity of the addition was explained by initial coordination of an organometallic compound (RM or RMX) to the nitrogen atom and the methoxy group of oxazoline, which leads to the formation of a complex 52 followed by the attack of the group R on the position 4 of the pyridine ring. The addition of RM (or RMX) from different sides of the plane of the ring (paths *a* and *b*) results in products with different stereochemistry. High stereoselectivity of the studied reactions implies that the most common reaction pathway is the path *a*. It was suggested that lithium or magnesium derivatives 53, formed upon addition of organometallic compound RM (or RMX) to pyridine 49a, are acylated with methyl chloroformate to afford compound 50.<sup>40</sup>



However, an alternative mechanism for the formation of adducts 50 and 52 was suggested:<sup>13</sup> the initial *in situ* formation of *N*-acylazinium salts upon acylation with chloroformate with consequent addition of an alkyl or phenyl group R to the C(4) atom of the pyridine heterocycle. Obviously, the reaction mechanism depends on the order of addition of the reagents.

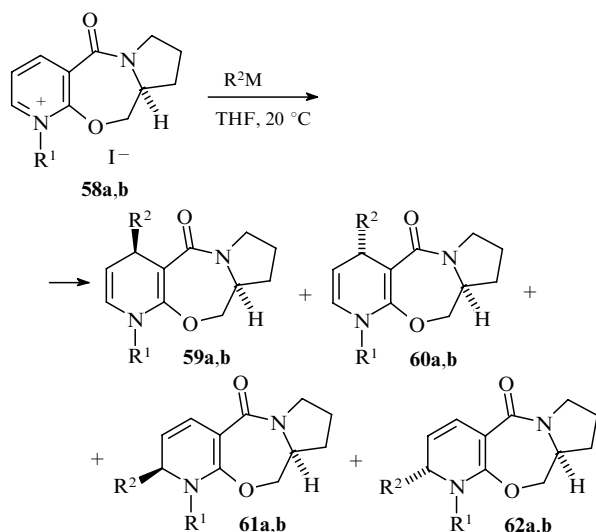
Pyridinium salts 55a,b were obtained by alkylation of nicotinamide 54 with methyl iodide and benzyl bromide, respectively, and then reacted with lithium organocuprates.<sup>43</sup> The expected adducts 56a,b (diastereomer ratio varies from 2.5:1 to 9:1, only the main product is shown in the Scheme) and 57a,b (*dr* = 1:1) were isolated after acylation of the reaction mixture with trichloroacetic anhydride.



$R^1 = \text{Me (a), Bn (b)}$ ;  $X = \text{I (a), Br (b)}$ ;  $R^2 = \text{Me, Bu}^n, \text{Ph}$ .

| Compo- und 55 | ' $R^2\text{Cu}$ '             | Reaction products (ratio)  | $dr$ (for 56) | Total yield (%) |
|---------------|--------------------------------|----------------------------|---------------|-----------------|
| a             | $\text{Me}_2\text{CuLi}$       | <b>56a + 57a</b> (2 : 1)   | 4 : 1         | 43              |
|               | $\text{Bu}_2^n\text{CuLi}$     | <b>56a</b>                 | 9 : 1         | 62              |
|               | $\text{Ph}_2\text{Cu(CN)Li}_2$ | <b>56a + 57a</b> (4.5 : 1) | 5 : 1         | 50              |
| b             | $\text{Bu}_2^n\text{CuLi}$     | <b>56b</b>                 | 4 : 1         | 34              |
|               | $\text{Ph}_2\text{Cu(CN)Li}_2$ | <b>56b + 57b</b> (1.6 : 1) | 2.5 : 1       | 37              |

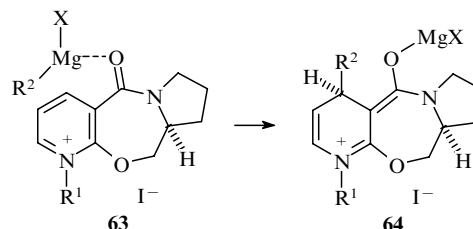
An example of the complexation effect on the stereoselective addition of nucleophiles to pyridinium salts is documented.<sup>41</sup> Reactions of 1-methyl- (**58a**) and 1-benzylpyridoxazepinone (**58b**) salts with alkyl-, alkenyl- and phenyl-magnesium bromide result in the products **59a,b** with high stereoselectivity and in good yields. Stereo- and regioisomers **60a,b**–**62a,b** are found in minor amounts. The process becomes less selective where organolithium compounds are used instead of the Grignard reagents.



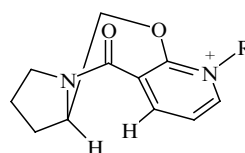
$R^1 = \text{Me (a), Bn (b)}$ .

| Compo- unds 58–62 | $R^2\text{M}$                            | Product ratio         |         |         | Yield of 59 (%) |
|-------------------|------------------------------------------|-----------------------|---------|---------|-----------------|
|                   |                                          | (59 + 60) : (61 + 62) | 59 : 60 | 61 : 62 |                 |
| a                 | $\text{MeLi}$                            | 1 : 1                 | 3 : 1   | 3 : 1   | —               |
|                   | $\text{Bu}^n\text{Li}$                   | 3 : 1                 | 2 : 1   | 1 : 0   | —               |
|                   | $\text{MeMgBr}$                          | 19 : 1                | 19 : 0  | 1 : 0   | 72              |
|                   | $\text{Bu}^n\text{MgBr}$                 | 57 : 1                | 57 : 0  | 1 : 0   | 60              |
|                   | $\text{Bu}^i\text{MgBr}$                 | > 99 : 1              | 99 : 0  | 1 : 0   | 95              |
|                   | $\text{CH}_2 = \text{CHMgBr}$            | > 99 : 1              | 99 : 0  | 1 : 0   | 74              |
|                   | $\text{CH}_2 = \text{CHCH}_2\text{MgBr}$ | 5.5 : 1               | 4 : 1.5 | 1 : 0   | —               |
|                   | $\text{PhMgBr}$                          | 98 : 0                | 98 : 0  | 2 : 0   | 88              |
| b                 | $\text{MeLi}$                            | 1.75 : 1              | 3 : 0.5 | 1 : 1   | —               |
|                   | $\text{MeMgBr}$                          | 15 : 1                | 75 : 0  | 4 : 1   | 87              |
|                   | $\text{PhMgBr}$                          | > 99 : 1              | 99 : 0  | 1 : 0   | 83              |

In this case, the high regio- and stereoselectivity of the reaction is explained by the coordination of the Grignard reagent to the amide oxygen atom, which leads to the formation of complex **63**. The transfer of the organic fragment from the magnesium atom to C(4) of the pyridine ring results in the enolate **64**; its hydrolysis leads to compounds **59**–**62**.<sup>41</sup>

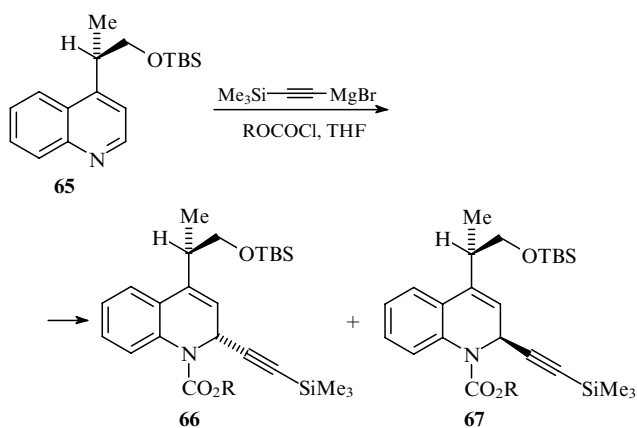


Studies on the conformational behaviour of compounds **58a,b** reveal that the seven-membered ring is relatively rigid and only two energetically favourable conformations are possible (only one is shown).<sup>41</sup>



In this conformation, the amide carbonyl group is located above the pyridinium ring plane in an *anti*-position relative to the hydrogen atom in the chiral centre, while in the second conformer the carbonyl group and the pyridinium ring are coplanar. It is remarkable that the conformations of compounds **58** where the carbonyl amide group is arranged under the pyridinium ring are energetically unfavourable. Therefore, the intermolecular shift of the group  $R^2$  of the complex **63** through a six-membered transition state can lead predominantly to the isomer **64**.<sup>43</sup>

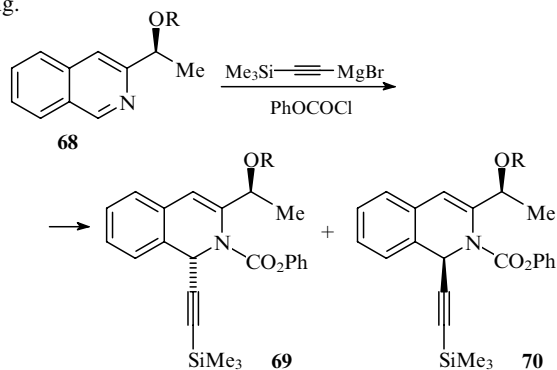
Diastereoselective addition of (trimethylsilyl)ethynylmagnesium bromide to optically active quinolines **65** in the presence of alkyl (or aryl) chloroformates produces compounds **66** and **67** in good yields and moderate diastereoselectivity.<sup>44,45</sup> This is the result of steric hindrance created by bulky substituents at position 4 of the quinoline ring.



| R  | Temperature /°C | Total yield (%) | Ratio (±)-66 : (±)-67 |
|----|-----------------|-----------------|-----------------------|
| Me | 0               | 78              | 66 : 34               |
| Bn | –78 to –2       | 72              | 59 : 41               |
| Ph | –78 to 0        | 87              | 68 : 32               |
| Ph | –78             | 66              | 67 : 33               |

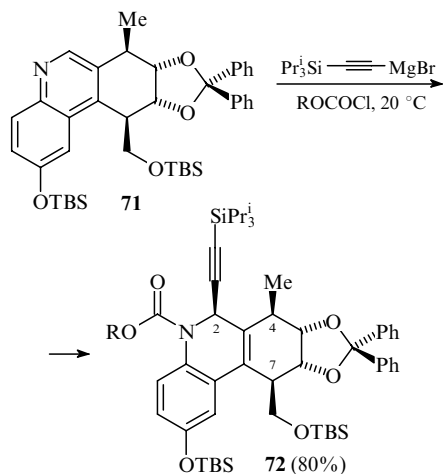
An example of nucleophilic addition to isoquinoline with a chiral substituent at position 3 is known.<sup>46</sup> Diastereoselective addition of (trimethylsilyl)ethynylmagnesium bromide to isoqui-

nolines **68** in the presence of aryl chloroformates yields compounds **69** and **70** with high diastereoselectivities due to the presence of a chiral substituent at position 3 of the isoquinoline ring.



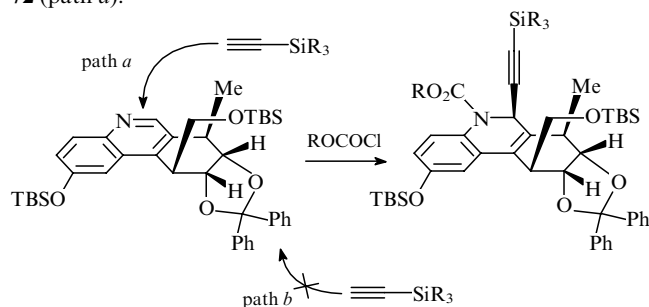
| R                                 | Total yield (%) | Ratio <b>69</b> : <b>70</b> |
|-----------------------------------|-----------------|-----------------------------|
| SiMe <sub>2</sub> Bu <sup>t</sup> | 88              | 87.3 : 12.7                 |
| SiPh <sub>2</sub> Bu <sup>t</sup> | 82              | 94.6 : 5.4                  |
| CPh <sub>3</sub> (Tr)             | 30              | 90.4 : 9.6                  |

In the total synthesis of antibiotic dynemycin A, alkyne radicals were introduced into a substituted tetrahydrophenanthridine containing chiral centres in the cyclohexane moiety.<sup>42</sup> A mixture of diastereomers in the ratio of 9 : 1 was obtained upon treatment of compound **71** with chloroformate in the presence of the Grignard reagent, (triisopropylsilyl)ethynylmagnesium bromide. Compound **72** was the main isomer, which was formed as a result of *cis*-addition (relative to the 4- and 7-substituents) of the alkyne fragment to the pyridinium C(2) atom.<sup>42</sup>

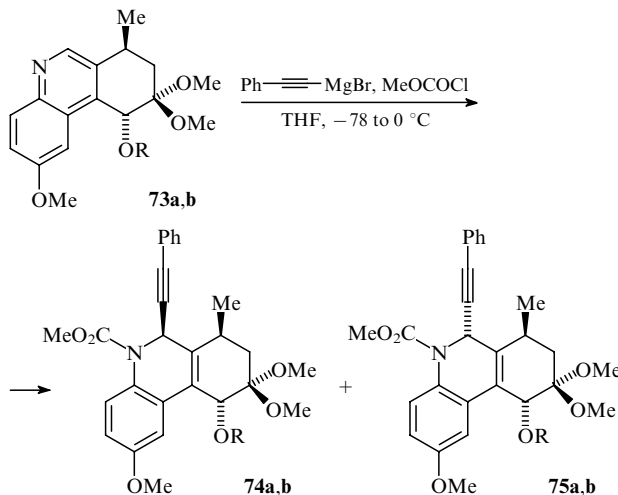


TBS is *tert*-butyldimethylsilyl; R = Me, All.

The starting compound **71** is sterically severely hindered for the attack along the path *b*; therefore, the addition is stereoselective and proceeds with predominant formation of compound **72** (path *a*).<sup>42</sup>

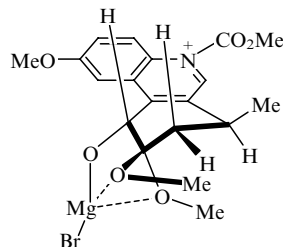


Tetrahydrophenanthridines **73a,b** react similarly with phenylethynylmagnesium bromide in the presence of methyl chloroformate. It was found<sup>47</sup> that the non-protected compound **73a** forms predominantly a *cis*-addition product **74a** (relative to the methyl group), the ratio **74a** : **75a** = 11 : 1, while TBS-protected analogue **73b** produces a diastereomer mixture in which *trans*-addition product **75b** is dominant (ratio **74b** : **75b** = 1 : 1.5).

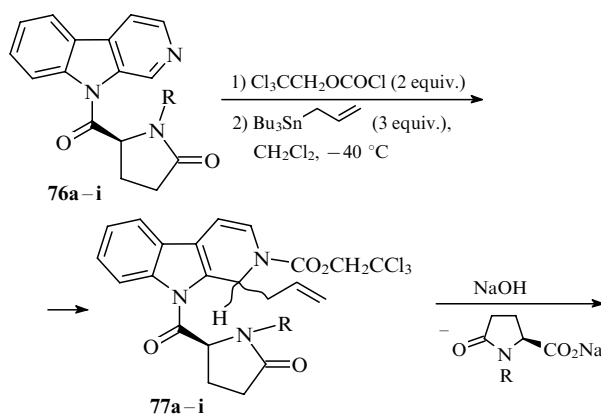


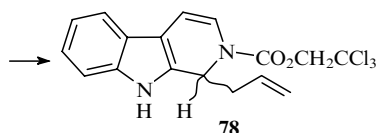
R = H (**a**), TBS (**b**).

This fact was explained by a half-chair conformation of the intermediate alkoxide formed from compound **73a** in which the magnesium counterion is chelated by one or two oxygen atoms of the methoxy groups. This leads to *pseudo*-equatorial orientation of the methyl substituent in compound **74a**. As a result, the axial addition of acetylide at the *cis*-position relative to this Me group is facilitated.<sup>47</sup>



The reaction of 9-acyl- $\beta$ -carboline **76a-i** activated by 2,2,2-trichloroethyl formate with allyl(tri-*n*-butyl)tin produces 1,2-dihydroadducts **77a-i**; their subsequent hydrolysis occurs with elimination of optically active sodium salt of 5-oxoproline.<sup>48,49</sup> The configuration of the remaining chiral centre in the obtained alkylated dihydro- $\beta$ -carboline **78a-i** depends on the character of substituent R in the adduct **77**.





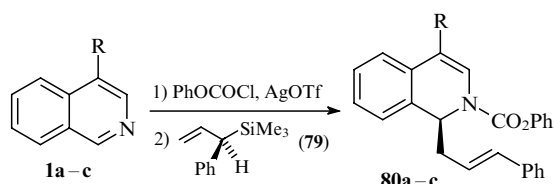
| Compounds <b>76, 77</b> | R                                                          | Yield of <b>77</b> (%) | Product <b>78</b> |        |
|-------------------------|------------------------------------------------------------|------------------------|-------------------|--------|
|                         |                                                            |                        | configuration     | ee (%) |
| <b>a</b>                | Me                                                         | 22                     | <i>S</i>          | 7      |
| <b>b</b>                | Bn                                                         | 95                     | <i>S</i>          | 21     |
| <b>c</b>                | 1-naphthylmethyl                                           | 87                     | <i>S</i>          | 58     |
| <b>d</b>                | 2-naphthylmethyl                                           | 100                    | <i>S</i>          | 66     |
| <b>e</b>                | 9-anthrylmethyl                                            | 98                     | <i>S</i>          | 91     |
| <b>f</b>                | MeCO                                                       | 100                    | <i>R</i>          | 89     |
| <b>g</b>                | PhCO                                                       | 92                     | <i>R</i>          | 83     |
| <b>h</b>                | 9-anthrylcarbonyl                                          | 56                     | <i>R</i>          | 83     |
| <b>i</b>                | <i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CO | 100                    | <i>R</i>          | 88     |

The stereoselectivity of the addition reaction of  $\beta$ -carboline **76a–e** containing *N*-alkylpyroglutaminy fragments linearly increases with an increase in the size of the substituent R. One side of the  $\beta$ -carboline molecule is shielded, probably due to steric hindrance. In the case of *N*-acylpyroglutaminy derivatives **76f–i**, stereoisomers with opposite configuration of the chiral centre are formed with virtually the same enantioselectivity.<sup>48</sup> One can suggest that in this case another conformation of the adduct **77** is more favourable and therefore the size of the substituent little affects the selectivity of the process.

### III. Stereoselective addition of an optically active nucleophile to an achiral azine

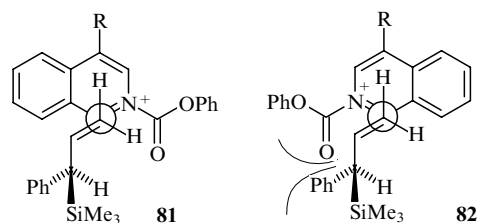
In all previously discussed cases, optically active azine substrates reacted with nucleophilic agents. Steric factors caused by the presence of a chiral azine substituent effectively determined the asymmetric character of the synthesis. Another variant of obtaining optically active azine derivatives where a chiral nucleophile reacts with an achiral amine is rather interesting and much less investigated. In this case, the direction of a nucleophilic attack mostly depends on the structure of the attacking species. It is possible to achieve stereoselective formation of products with the desired configuration by varying the reaction conditions.

Yamaguchi and co-authors<sup>50</sup> have performed the enantioselective addition of chiral (*R*)-phenyl-3-trimethylsilylprop-1-ene (**79**) with *N*-acylisoquinolinium salts obtained from isoquinolines **1a–c**. (*S*)-1-[(*E*)-3-phenylprop-2-enyl]-1,2-dihydroisoquinolines **80a–c** are formed in this process with high enantioselectivity.

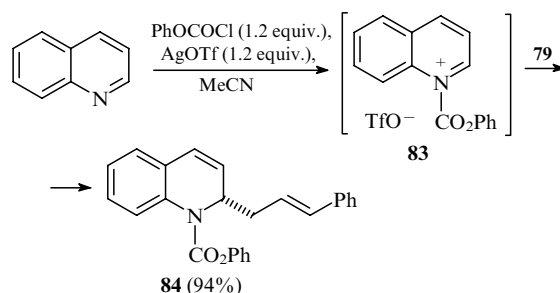


| Compounds <b>7, 80</b> | R                  | Yield (%) | ee (%) |
|------------------------|--------------------|-----------|--------|
| <b>a</b>               | H                  | 54        | 95     |
| <b>b</b>               | Br                 | 86        | 94     |
| <b>c</b>               | CO <sub>2</sub> Me | 78        | 93     |

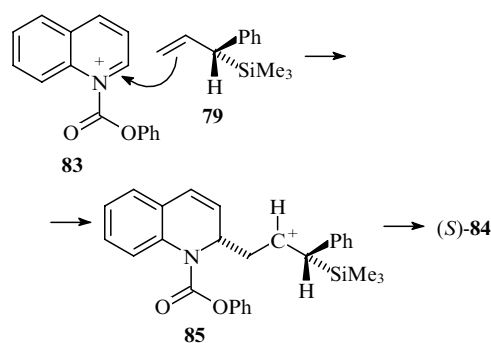
The authors suggest<sup>50</sup> that this addition proceeds with formation of an antiperiplanar transition state **81**, which leads to the *S*-adduct. The transition state **82**, which is a precursor of the *R*-adduct, is less energetically favourable.



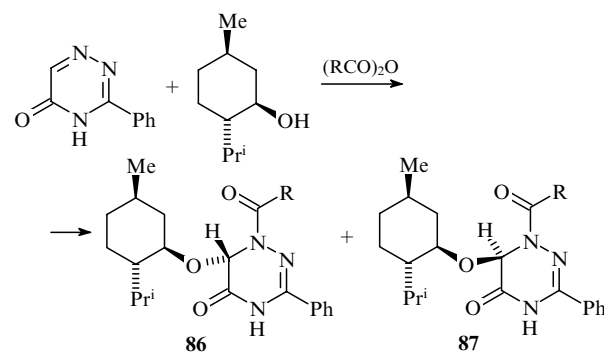
Stereoselective addition of chiral allylsilane **79** to activated quinolines has been described.<sup>51</sup> As a result of the reaction with quinolinium salt **83**, an optically active 2-substituted 1,2-dihydroquinoline **84** (ee 77%) is formed.



Several possible reaction pathways have been proposed.<sup>51</sup> The most preferential is believed to be that including the formation of intermediate **85**. Elimination of the trimethylsilyl group yields the product with *S*-configuration of the chiral centre.



No reactions of stereoselective addition of chiral C-nucleophiles to triazines have been described yet; however, a reaction with an optically active O-nucleophile, viz., a natural alcohol L-menthol is known. Thus the addition of enantiomerically pure L-menthol at the unsubstituted carbon atom of 3-phenyl-1,2,4-triazin-5(4*H*)-one activated by acid anhydrides yields a mixture of diastereomers **86** and **87**,<sup>52, 53</sup> the diastereomers **86** being the major products. It was also established that the diastereoselectivity of the reaction depends on the size of the acylating agent. In the case of acetic anhydride (R = Me), the diastereomer ratio **86**:**87** is equal to 60:40, while with the more sterically hindered isobutyric anhydride (R = Pr<sup>i</sup>) this ratio is increased to 85:15.<sup>52, 53</sup>



R = Me, Pr<sup>i</sup>.

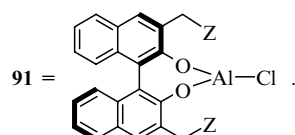
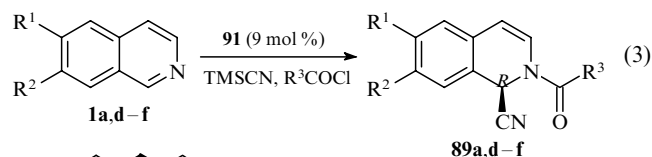
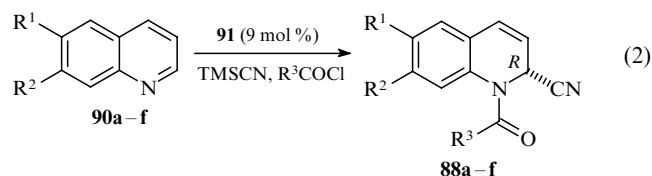
The predominant formation of stereoisomers **86** is explained<sup>53</sup> by steric factors.

#### IV. Asymmetric induction in the attack of an achiral nucleophile at an achiral azine

Asymmetric induction in a reaction of an achiral nucleophile with an achiral azine substrate is possible only where optically active solvents, additives or catalysts are used.

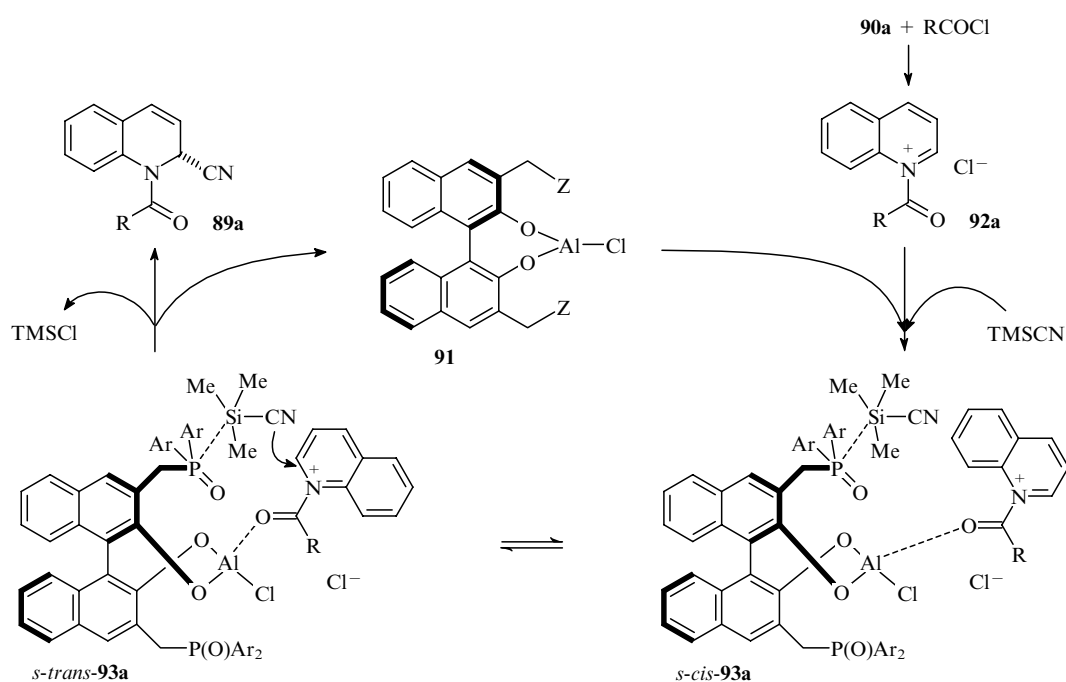
Shibasaki *et al.*<sup>54–57</sup> have investigated the formation of Reissert compounds **88a–f** and **89a,d–f** from quinolines **90a–f** and isoquinolines **1a,d–f** catalysed by chiral bifunctional catalysts based on binaphthyl **91**. The enantioselectivity of the reactions (2) and (3) is believed to depend on the character of the substituent  $R^3$  in the acyl chloride. For example, in the presence of the electron-rich and, therefore, relatively inert 2-furoyl chloride the reactions are more selective than in the case of acetyl chloride. The polarity of the solvent also strongly affects the enantioselectivity. Thus it was found that the *ee* of the reaction of quinoline with the most reactive benzoyl chloride in non-polar solvents (toluene, benzene) increases from 71% to 78%, although the yield decreases. The use of more polar acetonitrile in this reaction results in a decrease in *ee* down to 37%. The substitution of  $P(O)(o-Tol)_2$  for  $P(O)Ph_2$  (**Z**) in the catalyst **91** makes it a stronger Lewis base and as a result the yield and the enantioselectivity of reaction (2) increase.

Although the mechanisms of reactions (2) and (3) have not been elucidated so far, it is obvious that the reactions should be accelerated due to double activation of *N*-acyl(iso)quinolinium ion and of TMSCN by the catalyst **91**. Azinium ion is activated by the Lewis acid (an Al atom) and TMSCN, by the Lewis base (an oxygen atom of the P=O group), which are constituents of the structure of catalyst **91**. In a control run with the catalyst **91** where  $Z = CHPh_2$ , which provides only steric restrictions, the direction of the addition process changes and enantioselectivity decreases significantly. Thus the reaction of quinoline with TMSCN in the presence of benzoyl chloride and catalyst **91** ( $Z = CHPh_2$ ), which is not a Lewis base, leads to the formation of 1-benzyl-1,2-dihydroquinoline-2-carbonitrile mainly with *S*-configuration of the chiral centre (yield 73%, *ee* 24%).



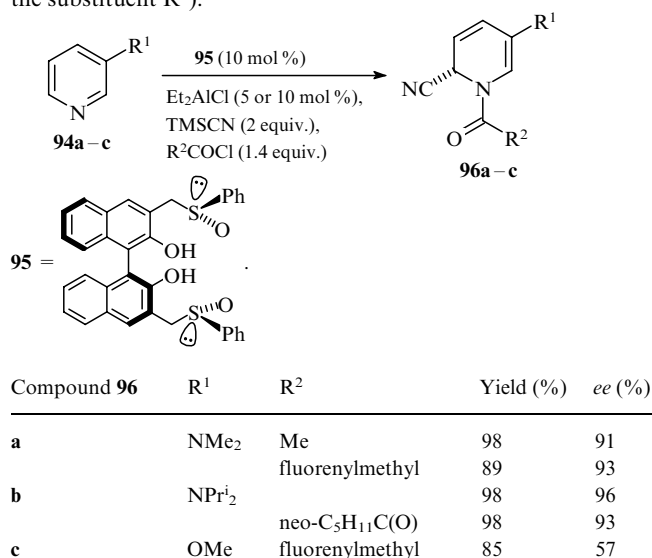
| Azine      | R <sup>1</sup>   | R <sup>2</sup>     | R <sup>3</sup> | Z                                 | Yield (%) | ee (%) |
|------------|------------------|--------------------|----------------|-----------------------------------|-----------|--------|
| <b>90a</b> | H                | H                  | Ph             | P(O)Ph <sub>2</sub>               | 70        | 71     |
|            |                  |                    | Me             | P(O)Ph <sub>2</sub>               | 42        | 58     |
|            |                  |                    | 1-naphthyl     | P(O)Ph <sub>2</sub>               | 63        | 46     |
|            |                  |                    | 2-furyl        | P(O)Ph <sub>2</sub>               | 58        | 73     |
|            |                  |                    |                | P(O)( <i>o</i> -Tol) <sub>2</sub> | 91        | 85     |
| <b>90b</b> | OMe              | H                  |                | P(O)( <i>o</i> -Tol) <sub>2</sub> | 74        | 89     |
| <b>90c</b> | NMe <sub>2</sub> | H                  |                | P(O)( <i>o</i> -Tol) <sub>2</sub> | 72        | 89     |
| <b>90d</b> | OMe              | OMe                |                | P(O)( <i>o</i> -Tol) <sub>2</sub> | 99        | 91     |
| <b>90e</b> |                  | OCH <sub>2</sub> O |                | P(O)( <i>o</i> -Tol) <sub>2</sub> | 77        | 83     |
| <b>90f</b> | Cl               | H                  |                | P(O)( <i>o</i> -Tol) <sub>2</sub> | 57        | 67     |
| <b>1a</b>  | H                | H                  | Me             | P(O)Ph <sub>2</sub>               | 99        | 71     |
|            |                  |                    | 2-furyl        | P(O)( <i>o</i> -Tol) <sub>2</sub> | 91        | 85     |
| <b>1d</b>  | OMe              | H                  |                | P(O)( <i>o</i> -Tol) <sub>2</sub> | 74        | 89     |
| <b>1e</b>  |                  | OCH <sub>2</sub> O |                | P(O)( <i>o</i> -Tol) <sub>2</sub> | 77        | 83     |
| <b>1f</b>  | Cl               | H                  |                | P(O)( <i>o</i> -Tol) <sub>2</sub> | 57        | 67     |

A scheme of the catalytic cycle with unsubstituted quinoline as a model compound has been suggested<sup>54–57</sup> (Scheme 3). In the first step, the reaction of quinoline with acyl chloride results in formation of *N*-acylquinolinium intermediate **92a**. Then the acylquinolinium ion is activated due to complexation of the

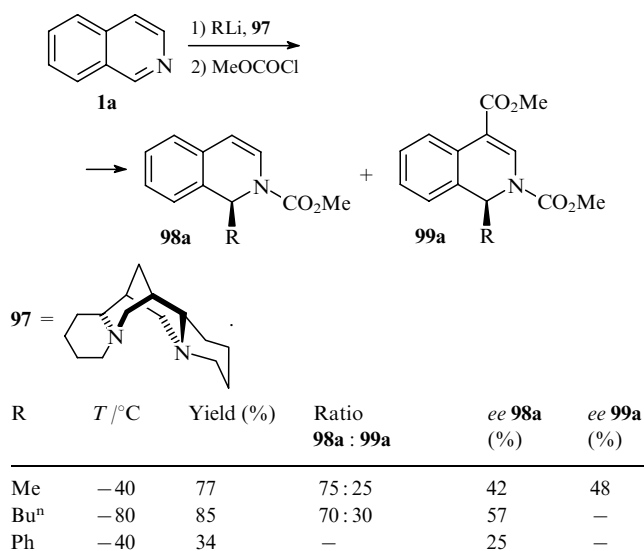


amide oxygen with the Lewis acid (Al atom of chiral catalyst). Two conformers, *s-trans*-**93** and *s-cis*-**93**, exist in equilibrium. However, the reaction will occur with preferable formation of compound *s-trans*-**93** upon activation of TMSCN with the catalyst **91**. The distance between the coordinated TMSCN and the electrophilic carbon atom in the *s-cis*-isomer is too large for successful catalytic reaction. Hypothetical transition state *s-trans*-**93** explains the formation of the product with *R*-configuration.

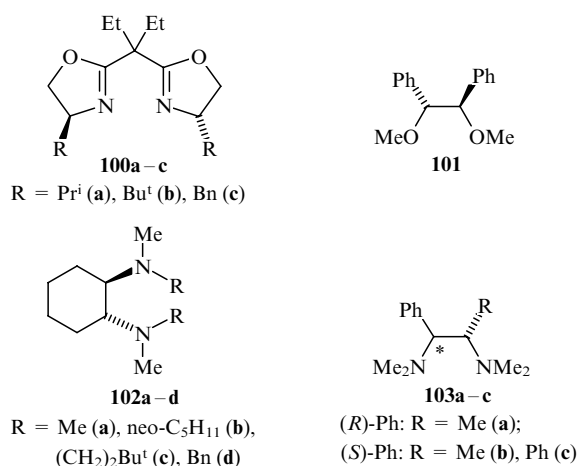
Later, the asymmetric bifunctional catalyst **91** was modified, which provided the possibility of performing similar reactions with pyridine derivatives **94a–c**. Thus the reaction of pyridine **94b** with TMSCN catalysed by chiral binaphthyl **91** [Z = P(O)Ph<sub>2</sub>] in the presence of carboxylic acid chlorides occurs with low enantioselectivity (*ee* < 9%) to give a mixture of addition products with the cyano group at positions 2 and 6 of the pyridine ring in a ratio of 2.3 : 1.<sup>57</sup> The use of the catalyst **95** increased the regioselectivity of the process. 2-Cyano-substituted pyridines **96a–c** with *S*-configuration (*ee* 96%) were predominantly formed (the ratio of 2- and 6-addition products varied from 12 : 1 to 50 : 1 depending on the substituent R<sup>1</sup>).<sup>54–57</sup>



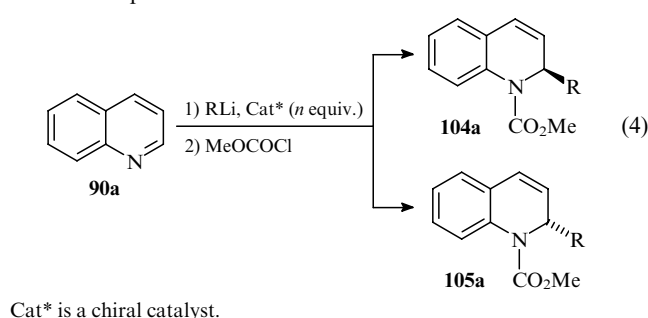
Enantioselective addition of organolithium compounds to isoquinoline under very mild conditions in the presence of a chiral ligand (–)-sparteine (**97**) has been described.<sup>58</sup> These reactions produce either a mixture of chiral dihydroisoquinolines **98a**, **99a** (for R = Me, Bu<sup>n</sup>) or compound **98a** (R = Ph) alone.



Later, the reactions of azines with organolithium reagents were studied in detail<sup>59,60</sup> using non-substituted quinoline (**90a**) as a substrate. Not only were the conditions (temperature, solvent) varied, but also a large number of chiral catalysts were used including sparteine (**97**), bisoxazolines **100**, chiral diether **101**, as well as symmetrical (**102**) and non-symmetrical (**103**) 1,2-diamines.



Treatment of the reaction mixture with methyl chloroformate affords dihydroisoquinolines **104a** or **105a**, the chiral centre formed having *R*- or *S*-configuration depending on the type of the chiral catalyst and the nature of the radical R in the organolithium compound.



The results of these investigations are listed in Table 2. The following conclusions can be drawn on the basis of data obtained.

(*R,R*)-Dimethoxydiphenylethane (**101**) appeared to be an inefficient chiral catalyst: dihydroquinolines **104a** were obtained in reasonable yields but with low enantioselectivity (*ee* 2%–26%). Dihydroquinolines **105a** with opposite configuration of the chiral centre were prepared using (–)-sparteine (**97**) as the catalyst; the enantioselectivity of this process increased (especially in the reaction with phenyllithium) and in some cases (R = Bu<sup>n</sup>) the yield of the product was quantitative. Bis(oxazolines) showed the best selectivity as chiral catalysts; in the reaction of quinoline with methyllithium and catalyst **100a**, *ee* was equal to 63%; the resulting dihydroquinolines had *S*-configurations.<sup>59,60</sup>

The use of *N,N'*-tetramethylcyclohexane-1,2-diamine **102a** (TMCDa) was rather successful with 1-naphthyllithium as a nucleophile: the yield of dihydroquinoline **105a** (R = 1-naphthyl) was 75% (*ee* 64%). Replacement of methyl substituents at the nitrogen atoms of the catalyst **102a** by bulkier alkyl groups (compounds **102b–d**) resulted in reduction of the yields and a sharp decrease in diastereoselectivity of the reaction (4).<sup>60</sup>

The study of *N,N'*-tetramethylethane-1,2-diamines **103a–c** as chiral catalysts gave the following results. Catalysis by the diamine **103a** resulted in virtually racemic product. The reaction in the presence of the diamine **103c** (symmetry C<sub>2</sub>) produced the addition products with moderate enantioselectivity. And, finally, the catalyst **103b** operated as a pseudo-C<sub>2</sub>-diamine, because the



**Table 2.** Reaction of quinoline (**90a**) with organolithium compounds RLi in the presence of a chiral catalyst.<sup>59, 60</sup>

| R               | Catalyst    | Solvent           | <i>T</i> / °C | <i>n</i> | Yield (%) | Product          | Configuration | <i>ee</i> (%) |
|-----------------|-------------|-------------------|---------------|----------|-----------|------------------|---------------|---------------|
| Me              | <b>97</b>   | Et <sub>2</sub> O | −20           | 1        | 69        | <b>105a</b>      | <i>S</i>      | 5             |
|                 | <b>100a</b> | PhMe              | −40           | 1        | 47        | <b>105a</b>      | <i>S</i>      | 63            |
|                 | <b>100a</b> | PhMe              | −40           | 0.2      | 43        | <b>105a</b>      | <i>S</i>      | 30            |
|                 | <b>100b</b> | PhMe              | −40           | 0.2      | < 5       | <b>105a</b>      | <i>S</i>      | —             |
|                 | <b>100c</b> | PhMe              | −40           | 0.2      | 69        | <b>105a</b>      | <i>S</i>      | 21            |
|                 | <b>100c</b> | Et <sub>2</sub> O | −40           | 0.2      | 86        | <b>105a</b>      | <i>S</i>      | 22            |
|                 | <b>101</b>  | Et <sub>2</sub> O | −20           | 1        | 67        | <b>104a</b>      | <i>R</i>      | 20            |
|                 | <b>102a</b> | PhMe              | −20           | 1        | 93        | <b>105a</b>      | <i>S</i>      | 13            |
| Bu <sup>n</sup> | <b>97</b>   | PhMe              | −40           | 1        | 98        | <b>105a</b>      | <i>S</i>      | 18            |
|                 | <b>97</b>   | Et <sub>2</sub> O | −40           | 1        | 98        | <b>105a</b>      | <i>S</i>      | 16            |
|                 | <b>100a</b> | PhMe              | −60           | 1        | 63        | <b>105a</b>      | <i>S</i>      | 72            |
|                 | <b>100a</b> | PhMe              | −70           | 1        | 85        | <b>105a</b>      | <i>S</i>      | 79            |
|                 | <b>100b</b> | PhMe              | −70           | 1        | 80        | <b>105a</b>      | <i>S</i>      | 32            |
|                 | <b>100b</b> | PhMe              | −70           | 0.2      | 70        | <b>105a</b>      | <i>S</i>      | 37            |
|                 | <b>100c</b> | PhMe              | −70           | 1        | 57        | <b>105a</b>      | <i>S</i>      | 69            |
|                 | <b>100c</b> | PhMe              | −70           | 0.2      | 79        | <b>105a</b>      | <i>S</i>      | 41            |
|                 | <b>101</b>  | Et <sub>2</sub> O | −60           | 0.2      | 86        | <b>104a</b>      | <i>R</i>      | 4             |
|                 | <b>101</b>  | PhMe              | −78           | 0.2      | 53        | <b>104a</b>      | <i>R</i>      | 4             |
|                 | <b>102a</b> | PhMe              | −78           | 1        | 83        | <b>105a</b>      | <i>S</i>      | 10            |
|                 | <b>102b</b> | PhMe              | −70           | 0.2      | 53        | see <sup>a</sup> | —             | < 4           |
|                 | <b>102c</b> | PhMe              | −70           | 0.2      | 67        | <b>105a</b>      | <i>S</i>      | 63            |
|                 | <b>102d</b> | PhMe              | −70           | 0.2      | 58        | see <sup>a</sup> | —             | 5             |
|                 | <b>103a</b> | PhMe              | −70           | 0.2      | 55        | <b>104a</b>      | <i>R</i>      | 5             |
| Ph              | <b>97</b>   | PhMe              | −78           | 1        | 82        | <b>105a</b>      | <i>R</i>      | 66            |
|                 | <b>97</b>   | PhMe              | −78           | 0.2      | 38        | <b>105a</b>      | <i>R</i>      | 7             |
|                 | <b>97</b>   | Et <sub>2</sub> O | −78           | 1        | 55        | <b>105a</b>      | <i>R</i>      | 67            |
|                 | <b>100a</b> | PhMe              | −78           | 1        | 6         | <b>105a</b>      | <i>R</i>      | < 4           |
|                 | <b>100a</b> | Et <sub>2</sub> O | −44           | 0.2      | 57        | <b>105a</b>      | <i>R</i>      | < 4           |
|                 | <b>101</b>  | Et <sub>2</sub> O | −78           | 1        | 16        | <b>104a</b>      | <i>S</i>      | < 2           |
|                 | <b>101</b>  | PhMe              | −78           | 1        | 7         | <b>104a</b>      | <i>S</i>      | 26            |
|                 | <b>102a</b> | PhMe              | −78           | 1        | 29        | <b>105a</b>      | <i>R</i>      | 45            |
|                 | <b>102b</b> | PhMe              | −70           | 0.2      | 47        | <b>105a</b>      | <i>R</i>      | 10            |
|                 | <b>102c</b> | PhMe              | −70           | 0.2      | 39        | <b>105a</b>      | <i>R</i>      | 17            |
| Ph              | <b>103a</b> | PhMe              | −70           | 0.2      | 68        | see <sup>a</sup> | —             | < 4           |
|                 | <b>103b</b> | PhMe              | −78           | 1        | 44        | <b>104a</b>      | <i>S</i>      | 27            |
|                 | <b>103c</b> | PhMe              | −78           | 0.2      | 14        | <b>104a</b>      | <i>S</i>      | 23            |
| 1-Naphthyl      | <b>97</b>   | PhMe              | −50           | 1        | 37        | <b>105a</b>      | <i>R</i>      | 16            |
|                 | <b>97</b>   | Et <sub>2</sub> O | −78           | 1        | 86        | <b>105a</b>      | <i>R</i>      | 28            |
|                 | <b>100a</b> | PhMe              | −70           | 0.2      | 20        | <b>105a</b>      | <i>R</i>      | 8             |
|                 | <b>100a</b> | PhMe              | −50           | 0.2      | 55        | <b>105a</b>      | <i>R</i>      | 0             |
|                 | <b>101</b>  | PhMe              | −50           | 1        | 57        | <b>104a</b>      | <i>S</i>      | < 4           |
|                 | <b>101</b>  | PhMe              | −50           | 0.2      | 45        | <b>104a</b>      | <i>S</i>      | 5             |
|                 | <b>102a</b> | PhMe              | −78           | 1        | 75        | <b>105a</b>      | <i>R</i>      | 64            |
|                 | <b>103a</b> | PhMe              | −70           | 0.2      | 46        | see <sup>a</sup> | —             | < 4           |
|                 | <b>103b</b> | Et <sub>2</sub> O | −70           | 1        | 70        | <b>104a</b>      | <i>S</i>      | 58            |
|                 | <b>103c</b> | PhMe              | −70           | 0.2      | 35        | <b>104a</b>      | <i>S</i>      | 23            |
| 2-Naphthyl      | <b>102a</b> | PhMe              | −78           | 1        | 19        | <b>105a</b>      | <i>R</i>      | 28            |

<sup>a</sup> Stereochemical data are unavailable.

results with this catalyst are similar to those obtained with the diamine **103c**.<sup>60</sup>

## V. Conclusion

Thus, the nucleophilic addition reactions with aromatic azines are stereoselective in most cases due to either steric effects of chiral groups in the azine or in a nucleophile, or the presence of optically active catalyst. The stereoselectivity of the process is affected by a number of factors. Among them, the most important are the character and stereochemistry of the nucleophile, the configuration of the chiral centre of the azine, the ability of the nucleophile to form complexes with the substrate and also the possibility of using chiral catalysts in these reactions.

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# Coordination compounds of rare-earth metals with organic ligands for electroluminescent diodes

M A Katkova, A G Vitukhnovsky, M N Bochkarev

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**Abstract.** Data on lanthanide coordination compounds with organic ligands used in the design of electroluminescent diodes are summarised and systematically represented. The molecular and electronic structures and spectroscopic characteristics of these compounds are considered. A comparative analysis of the properties of organic electroluminescent diodes with different compositions of emitting and conductive layers is presented. The bibliography includes 147 references.

## I. Introduction

The design of organic electroluminescent diodes (or organic light-emitting diodes, OLEDs) for the construction of planar multicolour information displays and high-value-in-use multicolour indicators, as well as of low-cost and efficient light sources, is a new field of investigation in molecular electronics and applied synthetic chemistry. Organic electroluminescent diodes are multilayer sandwich structures capable of converting electrical energy into light energy. There is good reason to expect that, in the near future, this unique property of OLEDs will make it possible to construct planar lightweight and very cheap displays and display panels, which will be superior to liquid-crystal analogues in the main parameters, and produce unconventional light sources for different purposes. The following two most important aspects of this area of scientific research should be mentioned: the development and construction of radically new superthin flexible polychromatic displays and a gradual change from luminescent bulbs and incandescent lamps to organic and hybrid light-emitting diodes as illuminants. Nowadays, the power efficiency of laboratory light sources based on organic materials is already better than the light output of incandescent lamps ( $15\text{--}20\text{ lm W}^{-1}$ ) and is in excess of  $50\text{ lm W}^{-1}$ , the theoretically possible efficiency being higher than  $300\text{ lm W}^{-1}$ . The service lifetime of these lamps

(10 000 hours) is more than 50 times longer than that of modern incandescent lamps. The light efficiency of gas luminescent tubes is slightly higher than that of modern OLED sources. However, these tubes are essentially inferior to OLED devices in many respects (explosion hazard, toxicity, inadequacy of perception of light by human eye, etc.).

Lanthanide complexes with organic ligands (hereinafter referred to as lanthanide complexes) belong to one of the most promising classes of compounds for the design of electroluminescent devices owing to specific electronic structures of these metals. Although these complexes have found application in the design of OLEDs about 10 years ago, this aspect has been already considered in several exhaustive reviews published in leading journals.<sup>1–4</sup> Investigations in this field are progressing so rapidly that, although a short period of time has passed since the latest review publication,<sup>4</sup> a need has arisen to generalise and analyse the available data once again. The present review summarises data on the molecular structures and spectroscopic characteristics of luminescent-active rare-earth complexes. The principles of selection and combination of such complexes in the design of OLED devices are considered. Problems in the design of light-emitting diodes on the basis of these compounds, which are associated with optimisation of their compositions by introducing additional luminescent and transport layers, are discussed. The review covers all data published in this area up to the present day. The data are classified and represented according to the nature of the ligand. In some cases, the photoluminescent properties of complexes are used as the key feature.

## II. Main characteristics of electroluminescent devices based on organic compounds

Electroluminescence was discovered by Losev (Nizhny Novgorod Radiolaboratory),<sup>5</sup> who found electrically induced light emission in silicon carbide crystals. However, during the period of vigorous development of semiconductor physics, light-emitting recombination in semiconductors seemed to be unlikely, at least from practical point of view. The situation changed radically after the discovery of intense light emission in p–n transitions in gallium arsenide. In the early 1960s, the General Electric Company produced a commercial light-emitting device (LED) based on the inorganic semiconductor GaAsP.

Electroluminescence of organic compounds was described for the first time for anthracene in 1963.<sup>6</sup> However, the efficiency of these devices was too low for practical applications, and this discovery did not stimulate research on light-emitting devices. Only in the late 1980s, after the construction of a new type of light-

**M A Katkova, M N Bochkarev** G A Razuvaev Institute of Organometallic Chemistry, Russian Academy of Sciences, ul. Tropinina 49, 603950 Nizhny Novgorod, Russian Federation. Fax (7-8312) 62 74 97, tel. (7-8312) 62 77 95, e-mail: marina@iomc.ras.ru (M A Katkova), mboch@iomc.ras.ru (M N Bochkarev)

**A G Vitukhnovsky** P N Lebedev Physical Institute, Russian Academy of Sciences, Leninsky prosp. 53, 119991 Moscow, Russian Federation. Fax (7-495) 135 78 60, tel. (7-495) 132 63 64, e-mail: alexei@sci.lebedev.ru

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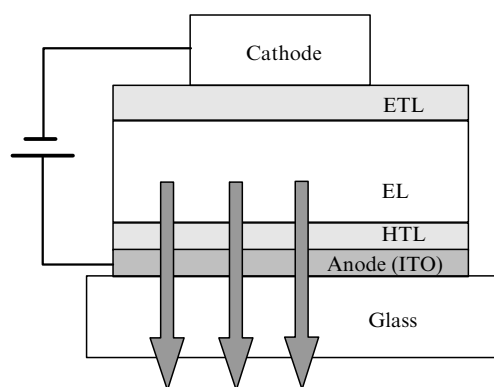


Figure 1. Scheme of an organic light-emitting diode (see the text).

emitting diode based on aluminium hydroxyquinolate ( $\text{Alq}_3$ )<sup>7</sup> and poly(*p*-phenylenevinylene) (PPV),<sup>8</sup> was a new line of investigation aimed at designing and studying organic light-emitting diodes opened.

Typical OLED devices have single-layer or multilayer sandwich structures  $\sim 100$  nm thick (Fig. 1).

Cells consist of the following sequence of components: a glass support coated with a transparent conducting layer of indium tin oxide (ITO) serving as the anode; an organic hole-transport layer (HTL), an emitting layer (EL), an electron-transport layer (ETL) and a metallic cathode as an aluminium film.

Below are given the formulas of organic and complex compounds, which are most often used in lanthanide-containing OLED devices (these abbreviations are used hereinafter).

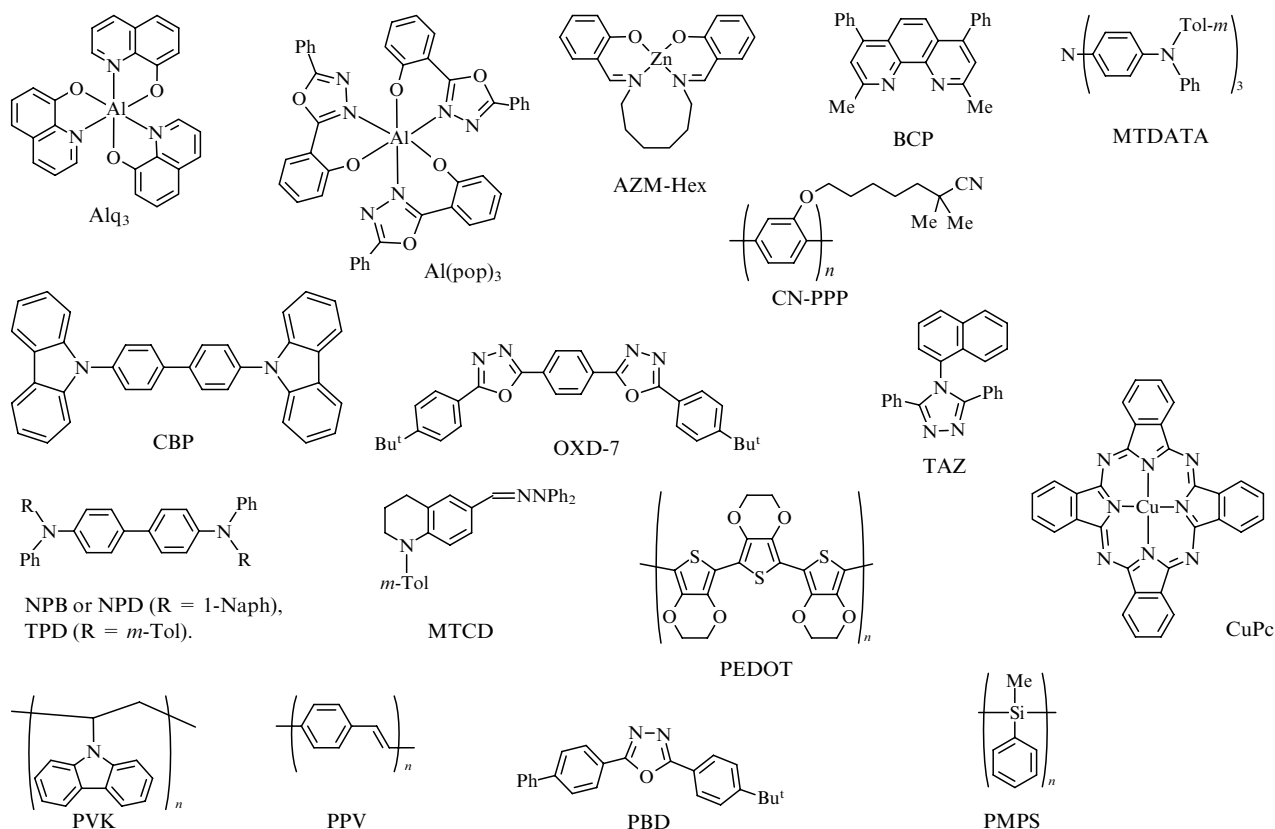
Theoretical models of charge transport in these compounds were considered in detail.<sup>9–11</sup>

Lanthanide complexes studied as emitters, OLED devices constructed on the basis of these compounds, and the maximum brightnesses of the latter are presented in Table 1.

The efficiency of conversion of absorbed energy into light emission is characterised mainly by the luminescence quantum yield, *e.g.*, the number of photons per absorbed light quantum (in the case of photoluminescence) or per injected electron–hole pair (in the case of electroluminescence). The quantum yield, which ignores the possibility of absorption of this emission in the device, is called the internal quantum yield, whereas the external quantum yield is associated with directly measured light emission from the device. The external quantum efficiency of a light-emitting diode is determined as a ratio of the number of quanta emitted from the material to the number of charge carriers passing through the light-emitting diode during the same period of time.<sup>72</sup>

Nowadays, cells based on the organic compound rubrene (5,6,11,12-tetraphenyltetracene) exhibit the highest electroluminescence efficiency of all the known OLED devices. In these cells, the maximum brightness exceeds  $200\,000\text{ cd m}^{-2}$  and the light emission efficiency is  $\sim 8\text{ lm W}^{-1}$ .<sup>73</sup> Of complex compounds, tris(2-phenylpyridine)iridium has the best characteristics in cells: the maximum brightness is  $100\,000\text{ cd m}^{-2}$ , the light emission efficiency being the same ( $\sim 8\text{ lm W}^{-1}$ ).<sup>74</sup> The maximum brightness of the best lanthanide-containing device based on terbium pyrazolone complex **51(Tb)** is  $20\,000\text{ cd m}^{-2}$ , and the efficiency of this device is  $3.24\text{ lm W}^{-1}$ .<sup>66</sup>

However, in spite of the fact that rare-earth complexes are considerably less efficient than organic compounds, they have attracted great attention because of specific features of the mechanism of luminescence providing monochromatic radiation. Electronic spectra of lanthanide ions are associated with *f–f* transitions in the 4*f* layer shielded from external fields by the closed 5*s* and 5*p* shells. This provides narrowing of the emission line to 10 nm, which is inaccessible for other luminophores. At the same time, the fact that transitions within the same electronic configuration are parity-forbidden results in low absorptivity of *f–f* transitions ( $\epsilon \leq 10\text{ mol}^{-1}\text{ litre cm}^{-1}$ ) and, as a consequence, in low luminescence efficiency of free ions.<sup>75</sup> Interactions of 4*f* electrons with the crystal field lead to a change in the radius of the *f*



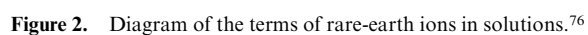


**Table 1.** Emitting lanthanide complexes with organic ligands.

| Type of complex          | Formula                                    | Structure | OLED Device                                                                                                                                                     | Maximum brightness /cd m <sup>-2</sup>          | Ref.                       |
|--------------------------|--------------------------------------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|----------------------------|
| <b>1(Ln)</b>             | Ln(acac) <sub>3</sub>                      |           | ITO/TPD/ <b>1(Tb)</b> /Al<br>ITO/PVK/PVK: <b>1(Tb)</b> :PBD/PBD/Al                                                                                              | 7 (at 0.4 mA cm <sup>-2</sup> )<br>17 (at 13 V) | 12<br>13                   |
| <b>2(Ln)</b>             | Ln(dbm) <sub>3</sub>                       |           | ITO/TPD/ <b>2(Eu)</b> /Al                                                                                                                                       | —                                               | 14                         |
| <b>3(Ln)</b>             | Ln(tfac) <sub>3</sub>                      |           | ITO/PVK/PVK: <b>3(Tb)</b> :PBD/PBD/Al                                                                                                                           | 25 (at 11 V)                                    | 13                         |
| <b>4(Ln)</b>             | Ln(acac-OXD) <sub>3</sub>                  |           | ITO/PVK:PBD: <b>4(Tb)</b> /Al(pop) <sub>3</sub> /CsF/Al                                                                                                         | 550 (at 20 V)                                   | 15                         |
| <b>5(Ln)</b>             | Ln(tta) <sub>3</sub>                       |           | ITO/PMPS: <b>5(Eu)</b> /PBD/Mg/Ag                                                                                                                               | 0.3 (at 18 V)                                   | 16                         |
| <b>6(Ln)</b>             | MLn(tta) <sub>4</sub>                      |           | ITO/PVK: <b>6(NaEu)</b> /OXD-7/Alq <sub>3</sub> /Al                                                                                                             | 36.7 (at 26 V)                                  | 17                         |
| <b>7(Ln)<sup>a</sup></b> | [Ln(acac-azin) <sub>3</sub> ] <sub>2</sub> |           | ITO/PVK: <b>7(Tb)</b> /PBD/LiF/Al                                                                                                                               | 0.65 (at 13 V)                                  | 18                         |
| <b>8(Ln)</b>             | Ln(acac) <sub>3</sub> (phen)               |           | ITO/PVK/ <b>8(Tb)</b> /Al<br>ITO/PVK/PVK: <b>8(Tb)</b> :PBD/PBD/Al<br>ITO/PVK/ <b>8(Tm)</b> /Al<br>ITO/PVK/ <b>8(Dy)</b> /Al<br>ITO/PVK: <b>8(Er)</b> /Al:Li/Ag | 210<br>36 (at 10 V)<br>6 (at 16 V)<br>20<br>—   | 19<br>13<br>20<br>21<br>22 |
| <b>9(Ln)</b>             | Ln(acac) <sub>3</sub> -(Cl-phen)           |           | ITO/TPD/ <b>9(Tb)</b> /Alq <sub>3</sub> /Li:Al                                                                                                                  | 95 (at 0.65 A m <sup>-2</sup> )                 | 23,<br>24                  |
| <b>10(Ln)</b>            | Ln(tfac) <sub>3</sub> (phen)               |           | ITO/PVK/PVK: <b>10(Tb)</b> :PBD/PBD/Al                                                                                                                          | 58 (at 8 V)                                     | 13                         |
| <b>11(Ln)</b>            | Ln(mppd) <sub>3</sub> (phen)               |           | ITO/PVK/ <b>11(Eu)</b> /Al                                                                                                                                      | —                                               | 25                         |

Table 1 (continued).

| Type of complex | Formula                       | Structure | OLED Device                                                                                                                                                                                                                                                                                      | Maximum brightness /cd m <sup>-2</sup>                                                               | Ref.                                       |
|-----------------|-------------------------------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|--------------------------------------------|
| <b>12(Ln)</b>   | Ln(bfa) <sub>3</sub> (phen)   |           | ITO/PVK/PVK: <b>12(Sm)</b> :PBD/Al                                                                                                                                                                                                                                                               | 135 (at 10 V)                                                                                        | 26                                         |
| <b>13(Ln)</b>   | Ln(dbm) <sub>3</sub> (phen)   |           | ITO/TPD/ <b>13(Eu)</b> :PBD/Alq <sub>3</sub> /Mg:Ag<br>ITO/ <b>13(Eu)</b> /Alq <sub>3</sub> / <b>8(Gd)</b> /Alq <sub>3</sub> /Al<br>ITO/TPD/ <b>13(Eu)</b> /Mg:Ag/Ag<br>ITO/TPD/ <b>13(Eu)</b> /BCP/Alq <sub>3</sub> /Mg:Ag/Ag<br>ITO/TPD/ <b>13(Tm)</b> /Mg:Ag<br>ITO/TPD/ <b>13(Er)</b> /Mg:Ag | 460 (at 16 V)<br>—<br>3.7 (at 17 V)<br>42 (at 16 V)<br>—<br>—                                        | 27<br>28<br>29<br>29<br>30<br>30           |
| <b>14(Ln)</b>   | Ln(dbm) <sub>3</sub> (bath)   |           | ITO/TPD/ <b>14(Eu)</b> /Mg:Ag<br>ITO/TPD/TPD: <b>14(Eu)</b> / <b>14(Eu)</b> /Mg:Ag<br>ITO/PVK/ <b>14(Eu)</b> /Mg:Ag<br>ITO/ <b>14(Gd)</b> / <b>14(Eu)</b> / <b>14(Gd)</b> /Ag:Mg<br><br>ITO/TPD/ <b>14(Ho)</b> /Mg:Ag<br>ITO/TPD/ <b>14(Tm)</b> /Mg:Ag<br>ITO/TPD/ <b>14(Er)</b> /Mg:Ag          | 150 (at 18 V)<br>820 (at 18 V)<br>400 (at 15 V)<br>100 (at 0.01 mA cm <sup>-2</sup> )<br>—<br>—<br>— | 31<br>31<br>32<br>31<br><br>33<br>30<br>30 |
| <b>15(Ln)</b>   | Ln(dfip) <sub>3</sub> (phen)  |           | ITO/TPD/ <b>15(Eu)</b> /AlLi                                                                                                                                                                                                                                                                     | 34 (at 12 V)                                                                                         | 34                                         |
| <b>16(Ln)</b>   | Ln(mdfip) <sub>3</sub> (phen) |           | ITO/TPD/ <b>16(Eu)</b> /AlLi                                                                                                                                                                                                                                                                     | 32.0 (at 9 V)                                                                                        | 35                                         |
| <b>17(Ln)</b>   | Ln(dtp) <sub>3</sub> (bath)   |           | ITO/TPD/ <b>17(Eu)</b> /Alq <sub>3</sub> /AlLi                                                                                                                                                                                                                                                   | 450 (at 15 V)                                                                                        | 36                                         |
| <b>18(Ln)</b>   | Ln(tta) <sub>3</sub> (phen)   |           | ITO/TPD/ <b>18(Eu)</b> /BCP/Alq <sub>3</sub> /Mg:Ag<br>ITO/TPD/ <b>18(Eu)</b> :CBP/BCP/Alq <sub>3</sub> /MgAg<br><br>ITO/TPD/ <b>18(Eu)</b> :PBD/PBD/Mg<br>ITO/TPD/ <b>18(YEu)</b> /Alq <sub>3</sub> /Mg:Ag                                                                                      | 32<br>500 (at 100 mA cm <sup>-2</sup> )<br>320<br>99 (at 11 V)                                       | 37<br>37<br>38<br>39                       |
| <b>19(Ln)</b>   | Ln(dnm) <sub>3</sub> (phen)   |           | ITO/PVK/ <b>19(Eu)</b> /Al                                                                                                                                                                                                                                                                       | —                                                                                                    | 25                                         |
| <b>20(Ln)</b>   | Ln(hfnh) <sub>3</sub> (phen)  |           | ITO/TPD/ <b>20(Eu)</b> :CBP/BCP/Alq <sub>3</sub> /LiF/Al<br>ITO/TPD/ <b>20(Sm)</b> :CBP/BCP/Alq <sub>3</sub> /LiF/Al                                                                                                                                                                             | 967<br>42                                                                                            | 40<br>40                                   |

Table 1 (continued).

| Type of complex | Formula                             | Structure | OLED Device                                                                | Maximum brightness /cd m <sup>-2</sup> | Ref.     |
|-----------------|-------------------------------------|-----------|----------------------------------------------------------------------------|----------------------------------------|----------|
| <b>21(Ln)</b>   | Ln(flta) <sub>3</sub> (phen)        |           | ITO/TPD/ <b>21(Eu)</b> :AZM-Hex/Mg                                         | —                                      | 14       |
| <b>22(Ln)</b>   | Ln(flpa) <sub>3</sub> (phen)        |           | ITO/TPD/ <b>22(Eu)</b> :AZM-Hex/Mg                                         | —                                      | 14       |
| <b>23(Ln)</b>   | Ln(flha) <sub>3</sub> (phen)        |           | ITO/TPD/ <b>23(Eu)</b> :AZM-Hex/Mg                                         | —                                      | 14       |
| <b>24(Ln)</b>   | Ln(flha) <sub>3</sub> (bath)        |           | ITO/TPD/ <b>24(Eu)</b> :AZM-Hex/Mg                                         | 10                                     | 14       |
| <b>25(Ln)</b>   | Ln(dbm) <sub>2</sub> -(danac)(phen) |           | ITO/TPD/ <b>25(Eu)</b> /Al                                                 | 924 (at 380 mA cm <sup>-2</sup> )      | 41       |
| <b>26(Ln)</b>   | Ln(dbm) <sub>3</sub> (TPPO)         |           | ITO/TPD/ <b>26(Eu)</b> /BCP/Alq <sub>3</sub> /Mg:Ag                        | 320 (at 14.5 V)                        | 42       |
| <b>27(Ln)</b>   | Ln(dbm) <sub>3</sub> (hpbm)         |           | ITO/TPD/ <b>27(Eu)</b> /Al                                                 | 1.14 (at 23 V)                         | 43       |
| <b>28(Ln)</b>   | Ln(dbm) <sub>3</sub> (epbm)         |           | ITO/TPD/ <b>28(Eu)</b> /Al<br>ITO/TPD/ <b>28(Eu)</b> /Alq <sub>3</sub> /Al | 29 (at 11 V)<br>180 (at 18 V)          | 43<br>43 |
| <b>29(Ln)</b>   | Ln(dbm) <sub>3</sub> -(pybm-OXD)    |           | ITO/TPD/ <b>29(Eu)</b> /LiF/Al                                             | 322 (at 21 V)                          | 44       |



Table 1 (continued).

| Type of complex           | Formula                                   | Structure | OLED Device                                                                                                                        | Maximum brightness /cd m <sup>-2</sup>            | Ref.           |
|---------------------------|-------------------------------------------|-----------|------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|----------------|
| <b>30(Ln)</b>             | Ln(dbm) <sub>3</sub> (tpip)               |           | ITO/ <b>30(Eu)</b> /MgAg/Ag<br>ITO/TPD/ <b>30(Eu)</b> /BCP/Alq <sub>3</sub> /MgAg/Ag                                               | 19 (at 13.5 V)<br>1305 (at 16 V)                  | 43<br>45       |
| <b>31(Ln)</b>             | Ln(dbm) <sub>3</sub> (cpip)               |           | ITO/TPD/ <b>31(Eu)</b> /MgAg/Ag<br>ITO/TPD/ <b>31(Eu)</b> /14(Eu)/MgAg/Ag<br>ITO/TPD/ <b>31(Eu)</b> /BCP/Alq <sub>3</sub> /MgAg/Ag | 537 (at 13 V)<br>1050 (at 16 V)<br>1460 (at 14 V) | 46<br>46<br>46 |
| <b>32(Ln)</b>             | Ln(tta) <sub>3</sub> (hpbm)               |           | ITO/TPD/ <b>32(Eu)</b> /Alq <sub>3</sub> /Al                                                                                       | < 7 (at 16 V)                                     | 47             |
| <b>33(Ln)</b>             | Ln(tta) <sub>3</sub> (epbm)               |           | ITO/TPD/ <b>33(Eu)</b> /Alq <sub>3</sub> /Al                                                                                       | 36.6 (at 21 V)                                    | 47             |
| <b>34(Ln)</b>             | Ln(tta) <sub>3</sub> (dppz)               |           | ITO/TPD/ <b>34(Eu)</b> :CBP/BCP/Alq <sub>3</sub>                                                                                   | 1670 (at 13.6 V)                                  | 48             |
| <b>35(Ln)<sup>b</sup></b> | Ln(tta) <sub>2</sub> (pmbbp)-(phen)       |           | ITO/TPD/ <b>35(Eu)</b> /Alq <sub>3</sub> /Mg:Al                                                                                    | 16 (at 12.5 V)                                    | 49             |
| <b>36(Ln)</b>             | Ln(tta) <sub>3</sub> (TPPO) <sub>2</sub>  |           | ITO/MTCD/ <b>36(Sm)</b> /Alq <sub>3</sub> /Al<br>ITO/MTCD/ <b>36(Sm)</b> /Al<br>ITO/TPD/ <b>36(Eu)</b> /Alq <sub>3</sub> /Al       | 0.5<br>—<br>10 (at 18 V)                          | 50<br>50<br>51 |
| <b>37(Ln)</b>             | Ln(stta) <sub>3</sub> (TPPO) <sub>2</sub> |           | —                                                                                                                                  | —                                                 | 52             |
| <b>38(Ln)</b>             | Ln(as) <sub>3</sub>                       |           | ITO/PVK/PVK:PBD: <b>38(Tb)</b> /PBD/Alq <sub>3</sub> /Al<br>ITO/PVK/PVK:PBD: <b>38(Tb)</b> /PBD/Al                                 | —<br>4.0 (at 22 V)                                | 53<br>53       |

Table 1 (continued).

| Type of complex | Formula                                    | Structure | OLED Device                                                                                            | Maximum brightness /cd m <sup>-2</sup> | Ref.           |
|-----------------|--------------------------------------------|-----------|--------------------------------------------------------------------------------------------------------|----------------------------------------|----------------|
| <b>39(Ln)</b>   | Ln(mebb) <sub>3</sub>                      |           | ITO/PVK:PBD: <b>39(Tb)</b> /CaAl                                                                       | 0.7                                    | 54             |
| <b>40(Ln)</b>   | Ln(meobb) <sub>3</sub>                     |           | ITO/PVK:PBD: <b>40(Tb)</b> /CaAl                                                                       | 7                                      | 54             |
| <b>41(Ln)</b>   | Ln(as) <sub>3</sub> (TPPO) <sub>2</sub>    |           | ITO/PEDOT/PVK: <b>41(Tb)</b> /Al                                                                       | —                                      | 55             |
| <b>42(Ln)</b>   | Ln(as) <sub>3</sub> (phen)                 |           | ITO/PVK: <b>42(Tb)</b> /Al                                                                             | —                                      | 56             |
| <b>43(Ln)</b>   | Ln(mdp) <sub>3</sub>                       |           | ITO/PVK/PVK:PBD: <b>43(Tb)</b> /Alq <sub>3</sub> /Al                                                   | 16 (at 24 V)                           | 57             |
| <b>44(Ln)</b>   | Ln(mhp) <sub>3</sub>                       |           | ITO/PPV/PVK: <b>44(Tb)</b> :PBD/Alq <sub>3</sub> /Al                                                   | 74 (at 18 V)                           | 58             |
| <b>45(Ln)</b>   | Ln(mtp) <sub>3</sub> (phen)                |           | ITO/PPV/PVK: <b>45(Tb)</b> :PBD/Alq <sub>3</sub> /Al                                                   | 152 (at 24 V)                          | 59             |
| <b>46(Ln)</b>   | Ln(ahb) <sub>3</sub>                       |           | ITO/PPV/PVK: <b>46(Tb)</b> :PBD/Alq <sub>3</sub> /Al<br>ITO/PVK: <b>46(Tb)</b> :PBD/Al                 | 35 (at 20 V)<br>18 (at 14 V)           | 60<br>60       |
| <b>47(Ln)</b>   | Ln(pmip) <sub>3</sub> -(TPPO) <sub>2</sub> |           | ITO/TPD/ <b>47(Tb)</b> /Alq <sub>3</sub> /Al<br>ITO/TPD/ <b>47(Lu)</b> /BCP/Alq <sub>3</sub> /Mg:Ag/Ag | 920 (at 18 V)<br>119 (at 19 V)         | 61<br>62       |
| <b>48(Ln)</b>   | Ln(tbpmp) <sub>3</sub> -(TPPO)             |           | ITO/MTDATA/TPD/ <b>48(Tb)</b> /TAZ/Al<br>ITO/ <b>48(Tb)</b> /Al<br>ITO/ <b>48(Tb)</b> /Ca              | 2200 (at 14 V)<br>6 (at 23 V)<br>226   | 63<br>63<br>64 |
| <b>49(Ln)</b>   | Ln(pmip) <sub>3</sub> (phen)               |           | ITO/TPD/ <b>49(Gd)</b> /BCP/Mg:Ag/Ag<br>ITO/TPD/ <b>49(Lu)</b> /BCP/Alq <sub>3</sub> /Mg:Ag/Ag         | 230 (at 17 V)<br>776 (at 17 V)         | 65<br>62       |

Table 1 (continued).

| Type of complex | Formula                         | Structure | OLED Device                                                                                | Maximum brightness /cd m <sup>-2</sup> | Ref.      |
|-----------------|---------------------------------|-----------|--------------------------------------------------------------------------------------------|----------------------------------------|-----------|
| 50(Ln)          | Ln(pmip) <sub>3</sub> (bipy)    |           | ITO/TPD/50(Lu)/BCP/Alq <sub>3</sub> /Mg:Ag/Ag                                              | 1010 (at 16 V)                         | 62        |
| 51(Ln)          | Ln(ebpmpp) <sub>3</sub> -(TPPO) |           | ITO/TPD/51(Tb)/Alq <sub>3</sub> /Mg:Ag/Ag<br>ITO/NPB/51(Tb)/BCP/Alq <sub>3</sub> /Mg:Ag/Ag | 20000 (at 20 V)<br>12000 (at 18 V)     | 66<br>66  |
| 52(Ln)          | Ln(pip) <sub>3</sub>            |           | ITO/TPD/52(Tb)/Alq <sub>3</sub> /Mg:Al                                                     | 20 (at 25 V)                           | 67        |
| 53(Ln)          | Lnq <sub>3</sub>                |           | ITO/TPD/53(Er)/Al<br>ITO/TPD/53(Nd)/Al<br>ITO/TPD/53(Yb)/Al                                | —                                      | 68–<br>71 |

<sup>a</sup> In this case, only two of six identical ligands are shown; <sup>b</sup> in the structural formula, the phen ligand is omitted for simplicity.

shell and partial or complete removal of degeneracy resulting in splitting of the energy levels (Fig. 2).<sup>76</sup>

It should be noted that emission can occur only from particular excited levels, which are indicated in the diagram presented in Fig. 2 by black semicircles. The schemes of electron transitions for selected lanthanide ions are shown in Fig. 3.

Some transitions can be made parity-allowed by admixing states of excited electron levels of the ligand to the states of the 4f<sup>n</sup>-electronic configuration.<sup>77</sup> As a consequence, the luminescence intensity of lanthanide ions sharply increases upon complexation with certain organic ligands. In these compounds, the light energy is absorbed primarily by the organic moiety of the complex, *i.e.*, the ligand serves as an 'antenna' (Fig. 4).<sup>78</sup>

The mechanism of electroluminescence of lanthanide compounds includes three steps. The first step involves electron–hole recombination, resulting in exciton generation and excitation of the ligand to the singlet (S<sub>1</sub>) and triplet (T<sub>1</sub>) levels. In the second step, the energy of the excited ligand is transferred (from the triplet level) to the emitting level of the metal ion. The latter step involves emission from the corresponding level of the metal atom. There-

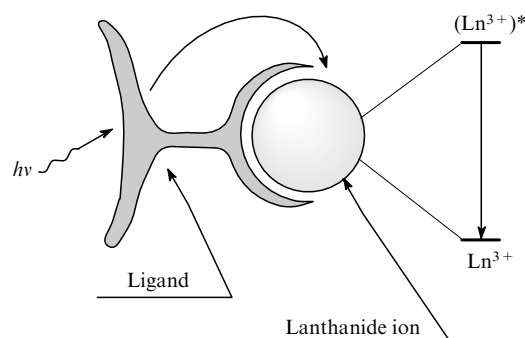


Figure 4. Scheme of energy transfers in lanthanide complexes.

fore, photoluminescence differs from electroluminescence only in the nature of excitation energy. It should be noted that, in the case of electroluminescence, the excitation of the T level of the ligand is not forbidden by quantum-mechanics. Since it is this level from which the energy transfer to metal occurs, the emitting level of the metal atom can be efficiently filled in the presence of an appropriate ligand. It is quite evident that the efficiency of energy transfer to the emitting levels of a lanthanide ion depends primarily on the nature of the ligand coordinated to this ion.<sup>4</sup> Of the rare-earth derivatives,  $\beta$ -diketonate, carboxylate, pyrazolone and hydroxyquinolate complexes are presently the most efficient electroluminescent materials for OLED devices.

### III. Light-emitting diodes based on lanthanide coordination compounds

#### 1. Light-emitting diodes based on rare-earth $\beta$ -diketonates

The use of lanthanide complexes in the design of electroluminescent cells was documented for the first time in 1990.<sup>12</sup> Kido *et al.*<sup>16</sup> described a two-layer OLED with a structure of ITO/TPD/1(Tb)/Al based on terbium acetylacetonate [1(Tb)] with a maximum brightness of 7 cd m<sup>-2</sup> at a current density of 0.4 mA cm<sup>-2</sup>. In this case, the electroluminescence spectrum was found to be identical to the photoluminescence spectrum. The maximum emission was observed at 544 nm, which cor-

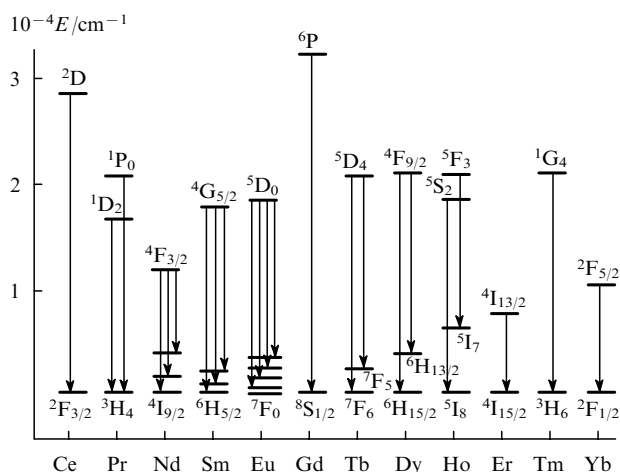


Figure 3. Diagrams of emission transitions in lanthanide ions.

responds to the  $^5D_4 \rightarrow ^7F_5$  transition of the  $Tb^{3+}$  ion. Shortly thereafter, the first europium OLED was constructed based on trifluoroacetylacetonate complex **5(Eu)**, which was molecularly dispersed in polymethylphenylsilane (PMPS) serving as a hole-transport layer.<sup>16</sup> The ITO/PMPS-**5(Eu)**/PBD/Mg/Ag device exhibited red emission characteristic of europium compounds with a maximum brightness of  $0.3 \text{ cd m}^{-2}$  at 18 V. Campos *et al.*<sup>79</sup> improved the luminescence characteristics of an analogous device based on complex **5(Eu)** with the use of a diamine hole-transport layer instead of polysilane, and a maximum brightness of  $\sim 10 \text{ cd m}^{-2}$  was achieved.

It should be noted that europium complexes proved to be the most promising luminescent materials for red emitters, because they generate monochromatic light with a wavelength of 614 nm, whereas known organic materials serving as emitters for the red spectral region give a broad band ( $\sim 100 \text{ nm}$ ) resulting in colour distortion. At the same time, the theoretically predicted high luminescence efficiency of lanthanide complexes remains so far unachievable under real conditions. Some authors relate this problem to poor transport properties of lanthanide complexes and believe that this problem can be solved by choosing organic ligands, which improve this property of materials.

Nakaya and co-workers<sup>34</sup> used compound **15(Eu)** for the construction of the two-layer device ITO/TPD/**15(Eu)**/AlLi with a maximum brightness of  $34 \text{ cd m}^{-2}$  at 12 V. A comparison of these data with the properties of complex **18(Eu)** ( $7 \text{ cd m}^{-2}$ ), which has been used earlier for this purpose, led these authors to conclude that compound **15(Eu)** has good charge-transport properties in the solid state. More recently, this research group<sup>35</sup> used complex **16(Eu)** as an emitting and electron-transport layer in a two-layer OLED device. The characteristics of this device ( $32.0 \text{ cd m}^{-2}$  at 9 V) were also attributed to the improved electron-transport properties due to the presence of the furyl fragment. Okada *et al.*<sup>36</sup> used 1,3-di(2-thionyl)propane-1,3-dione (dtp) as the  $\beta$ -diketonate ligand and 4,7-diphenyl-1,10-phenanthroline (bath) as the neutral ligand to prepare complex **17(Eu)**, and the latter was used for the construction of a three-layer OLED. The researchers observed bright red emission with a maximum brightness of  $450 \text{ cd m}^{-2}$  at 15 V. In the study,<sup>41</sup> the external efficiency of 3.5% and the maximum brightness of  $924 \text{ cd m}^{-2}$  at  $380 \text{ mA cm}^{-2}$  were achieved with the use of complex **25(Eu)** with mixed ligands.

Taking into account the good luminescent properties of azaindole, Wang *et al.*<sup>18</sup> synthesised terbium and yttrium complexes with the modified acetylacetonate ligands  $[\text{Ln}(\text{acac-azin})_3]_2$  [**7(Ln)**] and established their molecular structures by X-ray diffraction. The photoluminescence quantum yield of complex **7(Tb)** (11%) is lower than that of complex **1(Tb)** (19%). The low quantum yield is apparently associated with the fact that the triplet level of the ligand ( $22\,220 \text{ cm}^{-1}$ ) is only  $1720 \text{ cm}^{-1}$  higher than the  $^5D_4$  level of  $Tb^{3+}$  ( $20\,500 \text{ cm}^{-1}$ ) and it does not provide essential excitation of the metal cation. However, the authors of the cited study succeeded in achieving the efficiency of  $0.65 \text{ cd A}^{-1}$  at 13 V by choosing an appropriate composition of PVK and PBD.

Wang *et al.*<sup>15</sup> focussed their attention on the synthesis of  $\beta$ -diketonate ligands containing oxadiazole fragments. These fragments were chosen because oxadiazole derivatives are widely used as electron-transport and hole-blocking materials. The external efficiency of the OLED device ITO/PVK : PBD : **4(Tb)**/Al(pop)<sub>3</sub>/CsF/Al was  $\sim 1.1\%$  and  $0.6\%$  and the brightness was 100 and  $550 \text{ cd m}^{-2}$  at 15 and 20 V, respectively.

In the study,<sup>44</sup> the oxadiazole substituent was introduced into 2-(2-pyridyl)benzimidazole and the resulting compound was used as the neutral ligand in the europium complex  $\text{Eu}(\text{dbm})_3(\text{pybm-OXD})$  [**29(Eu)**]. A two-layer OLED device containing this compound [ITO/TPD/**29(Eu)**/LiF/Al] had an external quantum efficiency of 1.7% at 612 nm and a maximum brightness of  $322 \text{ cd m}^{-2}$  at 21 V. This study demonstrated that the introduction of the oxadiazole fragment into the lanthanide complex

improves the charge-transport properties of the complex and simplifies the structure of an electroluminescent cell.

Chinese researchers<sup>43,45</sup> combined the phenanthroline fragment possessing the electron-transport properties and the triphenylamine fragment with the hole-transport properties in a neutral ligand. The resulting europium complex **30(Eu)** was used for the construction of the single-layer OLED ITO/**30(Eu)**/MgAg/Ag with a maximum brightness of  $19 \text{ cd m}^{-2}$  at 13.5 V and the four-layer device ITO/TPD/**30(Eu)**/BCP/Alq<sub>3</sub>/MgAg/Ag with an external quantum efficiency of 0.85%, a light efficiency of  $1.44 \text{ lm W}^{-1}$  and a maximum brightness of  $1305 \text{ cd m}^{-2}$  at 16 V. With the aim of synthesising new highly efficient luminescent compounds, these authors<sup>46</sup> introduced the carbazole fragment into the neutral phenanthroline ligand. Devices based on compound **31(Eu)** exhibited excellent luminescent properties and had good stability. For example, the two-layer OLED ITO/TPD/**31(Eu)**/MgAg/Ag exhibited a maximum brightness of  $537 \text{ cd m}^{-2}$  at 13 V and an efficiency of  $0.089 \text{ lm W}^{-1}$ , the three-layer device ITO/TPD/**31(Eu)**/**14(Eu)**/MgAg/Ag exhibited a maximum brightness of  $1050 \text{ cd m}^{-2}$  at 16 V and an efficiency of  $0.50 \text{ lm W}^{-1}$ , and the four-layer device ITO/TPD/**31(Eu)**/BCP/Alq<sub>3</sub>/MgAg/Ag had the highest brightness of  $1460 \text{ cd m}^{-2}$  at 14 V and an efficiency of  $0.54 \text{ lm W}^{-1}$ .

In the study,<sup>43</sup> two new ligands, viz., 2-(2-pyridyl)benzimidazole (hpbm) and 2-(2-pyridyl)-1-ethylbenzimidazole (epbm), were used instead of phenanthroline. Europium complexes with these ligands, **27(Eu)** and **28(Eu)**, were used for the design of the OLED devices ITO/TPD/**27(Eu)**/Al, ITO/TPD/**28(Eu)**/Al and ITO/TPD/**28(Eu)**/Alq<sub>3</sub>/Al. The brightness of ITO/TPD/**27(Eu)**/Al ( $29 \text{ cd m}^{-2}$  at 11 V) is much higher than that of ITO/TPD/**28(Eu)**/Al ( $1.14 \text{ cd m}^{-2}$  at 23 V). The authors believed that compound **27(Eu)**, like most europium complexes, has poor transport properties. More recently, these authors used thenoyl trifluoroacetate (tta) as the central ligand<sup>47</sup> and found that the brightness of the OLED based on  $\text{Eu}(\text{tta})_3(\text{epbm})$  [**33(Eu)**] ( $36.6 \text{ cd m}^{-2}$ ) is much higher than that of the OLED based on  $\text{Eu}(\text{tta})_3(\text{hpbm})$  [**32(Eu)**] ( $< 7 \text{ cd m}^{-2}$ ).

In the study,<sup>48</sup> complex **34(Eu)** was synthesised with the use of substituted phenanthroline (dppz) as the central ligand, and the OLED ITO/TPD/**34(Eu)**:CBP/BCP/Alq<sub>3</sub> was constructed based on this complex; the external quantum efficiency of this device was 2.1% and the brightness was  $1670 \text{ cd m}^{-2}$ .

Presently, it is believed that ligands in complexes destined for the design of OLED devices should satisfy the following main requirements: (1) the triplet level of the ligand should match the emission level of metal; (2) the ligands should have the electron- and hole-transport properties to promote charge injection and exciton generation in the complex; (3) the complex should be easily deposited onto a support without the formation of aggregates and crystals and should be compatible with other components of the device.<sup>26</sup> It is evident that the position of the triplet level of the ligand relative to the corresponding level of metal is of considerable importance. However, in spite of numerous experimental and theoretical studies devoted to this problem, a theoretical model allowing the synthesis of the desired highly luminescent lanthanide complexes is lacking.

To simplify the task, comparative studies of related complexes are carried out with the aim of developing theoretical models. For example, Zheng *et al.*<sup>13</sup> investigated the photo- and electroluminescent properties of four terbium complexes, **1(Tb)**, **3(Tb)**, **8(Tb)** and **10(Tb)**. The comparative characteristics of OLED devices based on these complexes are given in Table 2.

It can be seen from this table that the introduction of fluorine atoms into the acetylacetonate ligand and additional coordination of the metal ion by the neutral phenanthroline ligand lead to an increase in the electroluminescence intensity. The emission bands of the ligand in the spectra of the complexes were not observed, which confirms high efficiency of excitation transfer from the levels of the ligand to the terbium ion in all four complexes. This led the authors to conclude<sup>13</sup> that the electroluminescence inten-

**Table 2.** Characteristics of the OLED devices ITO/PVK/PVK:Tb-complex:PBD/PBD/Al.<sup>13</sup>

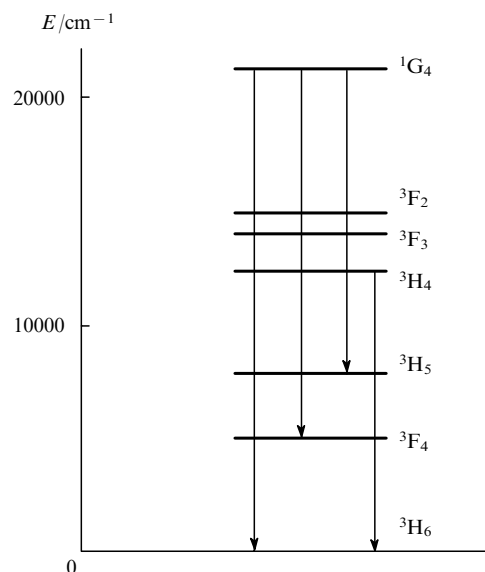
| Tb complex    | Luminescence yield $\eta$ (%) | Voltage /V | Maximum brightness /cd m <sup>-2</sup> |
|---------------|-------------------------------|------------|----------------------------------------|
| <b>10(Tb)</b> | 0.25                          | 8          | 58                                     |
| <b>8(Tb)</b>  | 0.16                          | 10         | 36                                     |
| <b>3(Tb)</b>  | 0.11                          | 11         | 25                                     |
| <b>1(Tb)</b>  | 0.08                          | 13         | 17                                     |

sity of lanthanide complexes is determined primarily by the ratio of the energy of the triplet level of the ligand to the energy of the emission level of lanthanide. Theoretical and experimental studies demonstrated that for the ligand-to-metal energy transfer to occur, the emission level of the metal must be somewhat lower than the triplet level  $T_1$  of the ligand, and the optimal difference  $\Delta E(T_1 - {}^5D_4)$  for terbium complexes should be  $2400 \pm 300$  cm<sup>-1</sup>. The triplet level of the fluorine-containing acetylacetonate ligand ( $22\,720$  cm<sup>-1</sup>) is lower than that of the acetylacetonate ligand ( $25\,310$  cm<sup>-1</sup>). Hence, the electroluminescence efficiency of complex **3(Tb)** with the Tb<sup>3+</sup> ion ( ${}^5D_4 = 20\,500$  cm<sup>-1</sup>) is higher than that of **1(Tb)** with the same ion.<sup>80–84</sup> The fact that the introduction of phenanthroline also increases luminescence was attributed to the intramolecular energy transfer from the  $\beta$ -diketonate ligand to phenanthroline (the triplet level of the  $\beta$ -diketonate ligand is much higher than that of phenanthroline), with the result that  $\Delta E(T_1 - {}^5D_4)$  approaches the optimal value.<sup>13</sup>

The intramolecular ligand-to-ligand energy transfer providing the necessary height of the triplet level of the ligand was observed also in samarium complex **12(Sm)**.<sup>26</sup> Lowering of the energy of the triplet level of the bfa ligands ( $T_1 = 21\,480$  cm<sup>-1</sup>) to  $21\,277$  cm<sup>-1</sup> (in the complex) due to the introduction of the phen ligand ( $T_1 = 21\,400$  cm<sup>-1</sup>) is accompanied by a decrease in the distance between the triplet level and the emission level of the metal ( ${}^4G_{5/2} = 18\,000$  cm<sup>-1</sup>) and provides bright emission of the samarium ion. It should be noted that the luminescence spectrum of samarium consists of three main peaks at 563, 598 and 643 nm corresponding to the  ${}^4G_{5/2} \rightarrow {}^6H_{5/2}$ ,  ${}^4G_{5/2} \rightarrow {}^6H_{7/2}$  and  ${}^4G_{5/2} \rightarrow {}^6H_{9/2}$  transitions, respectively, which is responsible for the orange colour of emission.<sup>50</sup> The two- and three-layer OLED devices ITO/MTCD/**36(Sm)**/Alq<sub>3</sub>/Al and ITO/MTCD/**36(Sm)**/Al were constructed on the basis of complex **36(Sm)**; however, the luminescence intensity of both devices appeared to be low ( $\sim 0.5$  cd m<sup>-2</sup>).<sup>2,50</sup>

The spectrum of thulium shows a narrow blue line at 480 nm assigned to the electron transition  ${}^1G_4 \rightarrow {}^3H_6$ .<sup>85</sup> This is presently the most desired colour of luminescence. However, data on the use of thulium compounds for the design of OLED devices are so far very scarce, probably because of the high price of this lanthanide. Li and co-workers<sup>20</sup> used complex **8(Tm)** for the construction of an OLED, but its characteristics unexpectedly appeared to be noticeably worse than those of the terbium analogue (the maximum brightness was as low as 6 cd m<sup>-2</sup> at 16 V). The authors of the cited study believed that this is associated with large  $\Delta E(T_1 - {}^1G_4)$  for the thulium complex (the triplet level of the acetylacetonate ligand is  $25\,500$  cm<sup>-1</sup>, the  ${}^1G_4$  level of the Tm<sup>3+</sup> ion is  $21\,196$  cm<sup>-1</sup>). In the study,<sup>86</sup> the  ${}^1D_2$  level was considered as the emission level of the Tm<sup>3+</sup> ion, and the absence of luminescence in complexes with the terphenyl ligands (the energy of the  $T_1$  level in these ligands is  $\sim 23\,500$  cm<sup>-1</sup>) was attributed to the high energy of the  ${}^1D_2$  level ( $\sim 27\,800$  cm<sup>-1</sup>). However, an investigation of the photoluminescent properties of thulium  $\beta$ -diketonate complexes<sup>85</sup> confirmed emission in thulium from the  ${}^1G_4$  ( $21\,275$  cm<sup>-1</sup>) and  ${}^3H_4$  ( $12\,500$  cm<sup>-1</sup>) levels:  ${}^1G_4 \rightarrow {}^3H_6$  (475 nm) (this transition has the maximum intensity),  ${}^1G_4 \rightarrow {}^3F_4$  (650 nm),  ${}^1G_4 \rightarrow {}^3H_5$  (780 nm) and  ${}^3H_4 \rightarrow {}^3H_6$  (795 nm) (Fig. 5).

It was found<sup>30</sup> that the replacement of the acac ligand with the dbm ligand gives rise to electroluminescence in the ITO/TPD/

**Figure 5.** Diagrams of emission transitions in the Tm<sup>3+</sup> ion.<sup>85</sup>

**13(Tm)**/Mg:Ag and ITO/TPD/**14(Tm)**/Mg:Ag devices in the near-IR region. However, the emission intensity appeared to be much lower than that in analogous erbium complexes **13(Er)** and **14(Er)**.

Holmium complex **14(Ho)** in an analogous OLED device with a structure of ITO/TPD/**14(Ho)**/Mg:Ag shows photo- and electroluminescence in the visible and near-IR regions.<sup>33</sup> Due to the presence of an intense band at a wavelength of 1500 nm, these complexes hold promise as materials for optical communications devices, for which the 1.3–1.5  $\mu$ m region (a frequency window of modern light pipes) is of great importance.

Dysprosium tris(acetylacetonate) complex **8(Dy)** was used as an emitter for the construction of a white-emitting OLED cell.<sup>21</sup> The Dy<sup>3+</sup> cation has two intense emission bands in the visible region, blue ( $\sim 480$  nm) and yellow ( $\sim 580$  nm), corresponding to the  ${}^4F_{9/2} \rightarrow {}^6H_{13/2}$  and  ${}^4F_{9/2} \rightarrow {}^6H_{15/2}$  transitions. However, the drawbacks of this device are low resistance of the complex to voltage and weak luminescence (lower than  $20$  cd m<sup>-2</sup>) associated, apparently, with inefficient energy transfer from the triplet level of the ligands to the dysprosium ion.

However, analysis of the spectra of numerous substituted europium  $\beta$ -diketonate complexes showed that the change in the luminescence intensity cannot be attributed solely to the difference in the energy of the triplet levels of the ligands.<sup>87</sup> In the cited study, the electron system of the  $\beta$ -diketonate ligand was changed by introducing substituents possessing different donor–acceptor properties and steric characteristics, the relative arrangement of the substituents in the ligands being varied and particular linking groups, which block energy transfer within the ligands, being constructed. These experiments demonstrated that an increase in the donating ability of the  $\beta$ -diketonate ligand, weakening of the Eu–N bonds, strengthening of the Eu–O bonds and the introduction of the methylene or oxymethylene bridges separating the  $\pi$ -electron system of the ligand from the Eu<sup>3+</sup> ion lead to a decrease in the efficiency of the ligand-to-metal excitation energy transfer and, as a consequence, to a decrease in the luminescence intensity of europium.<sup>87,88</sup>

Bazan and co-workers<sup>25</sup> found that, in spite of the different nature of the substituents, the triplet levels of the tta, dbm, flta, flpa and flha ligands present in complexes **5(Eu)**, **2(Eu)**, **21(Eu)**, **22(Eu)** and **23(Eu)** are located in close proximity (in the region of  $20\,500$  cm<sup>-1</sup>). Hence, the corresponding  $\beta$ -diketonates should have similar efficiency of energy transfer from these ligands to the europium ion. However, the luminescence intensities of these complexes and cells constructed on their basis appeared to be

different. The best result was obtained for the ITO/TPD/**24(Eu)**:AZM-Hex/Mg device with a maximum brightness of  $10 \text{ cd m}^{-2}$ . It is expected that an increase in the purity of the starting compounds and optimisation of the structure of the device would allow an increase in the luminescence brightness.

Recently, Chinese researchers have achieved remarkable results by replacing the flha ligand in complexes **23(Eu)** and **23(Sm)** with the hfnh ligand.<sup>40</sup> New complexes **20(Eu)** and **20(Sm)** exhibited electroluminescence in the OLED devices ITO/TPD/**20(Eu)**:CBP/BCP/Alq<sub>3</sub>/LiF/Al and ITO/TPD/**20(Sm)**:CBP/BCP/Alq<sub>3</sub>/LiF/Al with maximum brightnesses of 967 and  $42 \text{ cd m}^{-2}$ , respectively.

It should be noted that a search for new organic ligands for lanthanide complexes destined for the construction of OLED devices was traditionally limited to oxygen- and nitrogen-containing compounds. However, the synthesis of terbium complex **52(Tb)** with the imidodiphosphinate ligands has been recently documented.<sup>67</sup> This compound showed photoluminescence with a quantum yield of 14%, the maximum brightness of electroluminescence in the OLED device based on this compound (ITO/TPD/**52(Tb)**/Alq<sub>3</sub>/Mg:Al) was  $20 \text{ cd m}^{-2}$  at 25 V, and the external efficiency was  $0.7 \text{ cd A}^{-1}$ .

The Yb<sup>3+</sup>, Nd<sup>3+</sup>, Pr<sup>3+</sup> and Er<sup>3+</sup> ions are known to have emission bands in the near-IR region, *i.e.*, in the region of communications frequencies. However, complexes of these metals are of limited use as materials for OLED devices because of a low luminescence intensity. For example, the maximum quantum yield of neodymium, praseodymium and erbium acetylacetonate complexes is as low as  $2.8 \times 10^{-2}\%$ .<sup>89</sup>

In attempting to find new luminescent materials, Voloshin *et al.*<sup>52</sup> synthesised neodymium and ytterbium thiodiketonate complexes **37(Nd)** and **37(Yb)**. However, the luminescent properties of these complexes appeared to be substantially worse than those of oxygen-containing analogues **36(Nd)** and **36(Yb)**, which was attributed to a substantially lower position of the triplet level of the sulfur-containing ligand (slightly higher than  $12\,000 \text{ cm}^{-1}$ ). These authors studied also Pr<sup>3+</sup>  $\beta$ -diketonates and carboxylates<sup>90</sup> and demonstrated that emission in praseodymium complexes occurs not only in the IR region but also in the visible region depending on the energy of the triplet level of the ligand. However, the quantum yield is also very low (at most 0.2%).

The most efficient energy transfer from the triplet level of the ligand to the metal ion in fluorinated neodymium  $\beta$ -diketonates was observed in a compound containing the pentafluorophenyl substituents, which is characterised by the lowest triplet level of the ligand ( $\Delta E \approx 1400 \text{ cm}^{-1}$ ) and the largest overlap between the phosphorescence spectrum of the ligand and the absorption spectrum of Nd<sup>3+</sup> in the 400–650 nm region.<sup>91</sup> An increase in the luminescence intensity was observed in neodymium complexes with asymmetric  $\beta$ -diketonate ligands, in which all C–H bonds are replaced with C–F or C–D bonds.<sup>92</sup> However, this increase is more likely to be attributable to weakening of luminescence quenching rather than to a change in the position of the triplet level.

In actuality, quenching processes play an essential role not only for lanthanides exhibiting luminescence in the near-IR region but also for all rare-earth metals. Hence, when searching for highly luminescent complexes for OLED devices, it is necessary to take into account the possibility of such processes occurring. For example, OH oscillators in coordinated water molecules were found to be the most efficient quenchers both in the solid state and in solution.<sup>93–95</sup> Other oscillators (NH, CH and C=O) are less active. The degree of quenching by water molecules is inversely proportional to the energy gap between the emission level and the ground state, and each oscillator independently quenches the excited state. The energy gaps for Yb<sup>3+</sup>, Eu<sup>3+</sup>, Tb<sup>3+</sup>, Sm<sup>3+</sup> and Dy<sup>3+</sup> are approximately equal to 10 200, 12 300, 14 200, 7400 and  $7850 \text{ cm}^{-1}$  respectively.<sup>86,96</sup> Consequently, the emitting states of ytterbium and europium correspond to the third vibrational overtone of an OH oscillator ( $\nu_{\text{OH}} \approx 3300\text{--}3500 \text{ cm}^{-1}$ ), whereas

the emitting state for terbium corresponds to the fourth harmonics. Hence, the efficiency of quenching by coordinated water molecules is much lower for the terbium ion. It is necessary to take into account the distance to the europium and terbium ions in the case of CH oscillators ( $\nu_{\text{CH}} \approx 3050 \text{ cm}^{-1}$  for aromatic and  $\nu_{\text{CH}} \approx 2950 \text{ cm}^{-1}$  for aliphatic). For example, quenching does not occur in complexes in which this distance is shorter than  $3.4 \text{ \AA}$ .<sup>86</sup> Luminescence is not observed in Ho<sup>3+</sup> complexes containing C–H bonds, because the energy transition  $^5\text{S}_2 \rightarrow ^5\text{F}_5$  [ $\Delta E(\text{Ho}^{3+}) \approx 3000 \text{ cm}^{-1}$ ] resonates with the CH vibrational mode ( $\nu_{\text{CH}} \approx 2900\text{--}3100 \text{ cm}^{-1}$ ). Deuteration of the ligand is inefficient in the case of Pr<sup>3+</sup> [ $\Delta E(\text{Pr}^{3+}) \approx 4100 \text{ cm}^{-1}$ ] and Nd<sup>3+</sup> [ $\Delta E(\text{Nd}^{3+}) \approx 5300 \text{ cm}^{-1}$ ], because the energy gaps in neodymium and praseodymium correspond to the first CD vibrational overtone.<sup>86</sup> The inductive resonance mechanism of radiationless transitions between the electronic levels of lanthanide ions in the condensed phase has been considered in detail in publications by Ermolaev and co-workers.<sup>97–99</sup>

## 2. Light-emitting diodes based on mixed $\beta$ -diketonate complexes

In recent years, along with a selection of neutral ligands in complex compounds, a new line of research on the introduction of the second metal ion into complex molecules has assumed increasing importance.<sup>19,100</sup>

Li and co-workers<sup>101</sup> were the first to use the mixed Eu<sub>x</sub>Tb<sub>1–x</sub>(acac)<sub>3</sub>(phen) complexes **8(Eu,Tb)** as an emitting layer. However, no data in support of the composition of this compound were presented. The device was reported to generate white emission resulting from mixing of the green emission of Tb<sup>3+</sup> (550 nm), red emission of Eu<sup>3+</sup> (616 nm) and blue emission of the NPB compound (450 nm). It was noted that the device is simple, but the luminescence characteristics were not published. More recently, these authors<sup>19</sup> considered the emission mechanism of complex **8(Eu,Tb)**. Interestingly, the maximum brightness of the composite ITO/PVK/**8(Tb)**/Al is  $210 \text{ cd m}^{-2}$ , whereas the maximum brightness of an analogous device with a europium complex, ITO/PVK/**8(Eu)**/Al, is as low as a few units of  $\text{cd m}^{-2}$ . In the luminescence spectrum of a device containing complex **8(Eu,Tb)** as the emitting layer, the red peak (615 nm) belonging to Eu<sup>3+</sup> is much stronger than the green peak (545 nm) belonging to Tb<sup>3+</sup>. The intensity of red emission in the mixed complex is 10 times higher than that of the mononuclear europium complex. The probable energy transfer process is shown in Fig. 6.

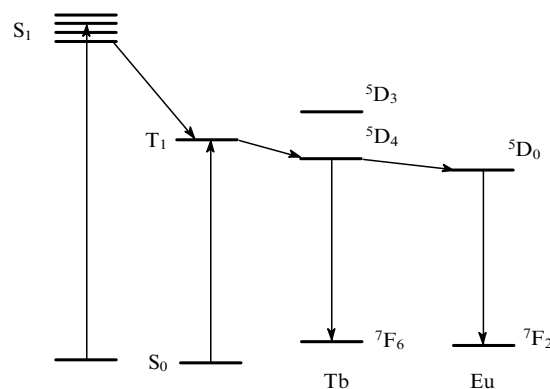


Figure 6. Energy diagram of dinuclear europium–terbium complexes.<sup>19</sup>

As can be seen from Fig. 6, several radiationless  $\text{S}_1 \rightarrow \text{T}_1$  ( $\text{Tb}^{3+} \rightarrow \text{Eu}^{3+}$ ) transitions are possible. As a result, the energy can be predominantly released through the  $^5\text{D}_0 \rightarrow ^7\text{F}_2$  emission of the Eu<sup>3+</sup> ion. Hence, the red emission in the mixed compound is an order of magnitude more bright than that in the compound containing only europium.

An increase in the emission brightness from 32 to 99  $\text{cd m}^{-2}$  on going from a mononuclear to dinuclear emitter was observed also for the OLED devices ITO/TPD/**18(Eu)**/Alq<sub>3</sub>/Mg:Ag and ITO/TPD/**18(Eu,Y)**/Alq<sub>3</sub>/Mg:Ag. It was hypothesised that the presence of the  $\text{Y}^{3+}$  ion promotes energy transfer from the triplet level of the ligand to the europium ion, resulting in an increase in the emission intensity.<sup>39</sup>

An alternative approach, which is also based on the use of several lanthanides in one OLED device, was described in the study.<sup>23</sup> With the aim of designing a white-emitting diode, a multilayer cell containing complex **9(Tb)** as the green (548 nm) emitting layer, complex **18(Eu)** as the red emitting layer (612 nm), the compound TPD as simultaneously the hole-transport and emitting (blue, 405 nm) layer and Alq<sub>3</sub> as the electron-transport layer was constructed. Actually, the device exhibited white emission, the emission brightness being 95  $\text{cd m}^{-2}$ .

### 3. Light-emitting diodes based on rare-earth carboxylates

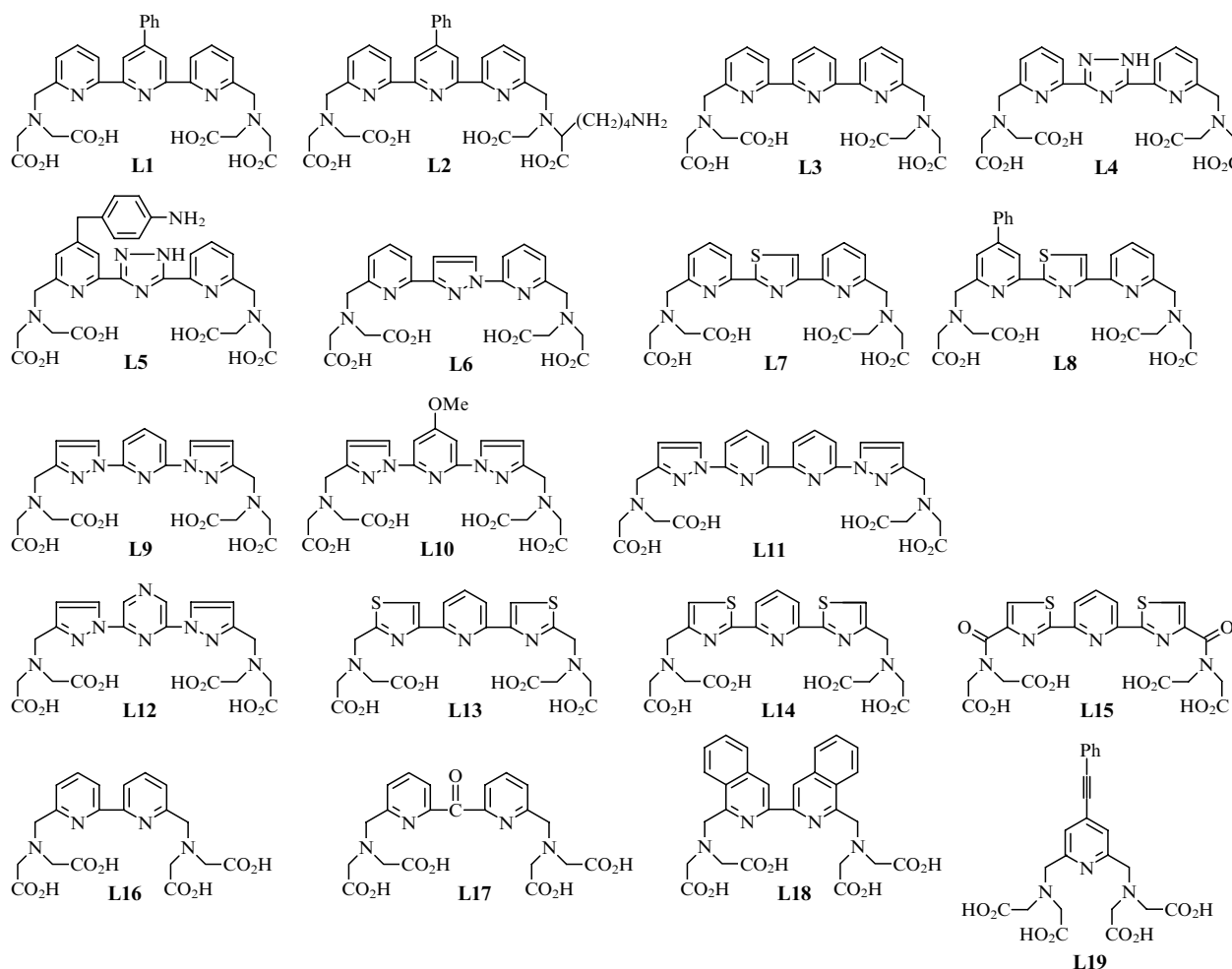
As mentioned above, most studies on luminescent lanthanide complexes with organic ligands dealt with  $\beta$ -diketonate complexes because they are readily accessible, stable in air and show rather high emission activity. However, a considerable drawback of these compounds is their low photo and thermal stability.<sup>53</sup> In this respect, another class of rare-earth complexes, *viz.*, lanthanide carboxylates, have advantages. The latter not only have good ultraviolet absorption properties but also possess luminescence and thermal stability, which is better compared to the corresponding characteristics of  $\beta$ -diketonates.

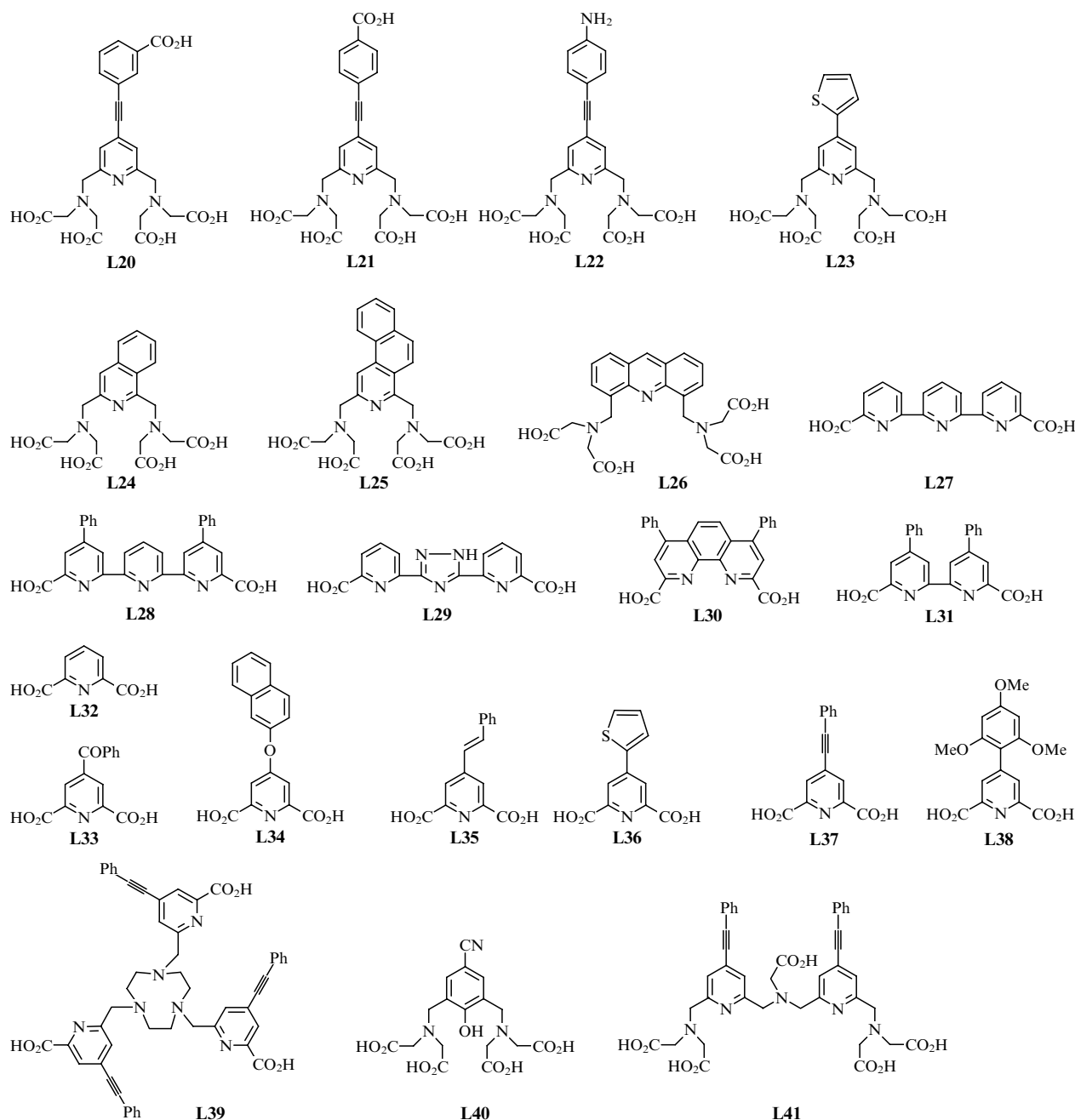
It should be noted that lanthanide carboxylates are traditionally extensively studied by spectroscopic methods.<sup>102, 103</sup> In the review by Vicentini *et al.*,<sup>104</sup> the relationship between the molecular structure and emission spectra of metal ions was demon-

strated with the use of numerous europium complexes (primarily, with carboxylates). The emission spectra were found to depend on the coordination number and symmetry. For example, the presence of two peaks belonging to the  $^5\text{D}_0 \rightarrow ^7\text{F}_0$  transition and a large number of peaks belonging to the  $^5\text{D}_0 \rightarrow ^7\text{F}_{1,2}$  transition are indicative of two different states of the europium ion. It was hypothesised that compounds characterised by broadened and poorly resolved  $^5\text{D}_0 \rightarrow ^7\text{F}_{1,2}$  transition bands have a polymeric nature. However, it was noted that a deep insight into the relationship between the structure and the luminescent properties requires that the structural data for complexes studied by spectroscopic methods be substantially extended.

Lanthanide carboxylates were used for the development of the concept of modeling of highly luminescent lanthanide systems. Latva *et al.*<sup>105</sup> studied more than 40 compounds with various carboxylate ligands **L1**–**L41** and confirmed the already known principle that the synthesis of luminescent europium and terbium compounds should be performed with the use of ligands having a high absorption coefficient and an efficient intrasystem transition from the singlet to triplet level. The efficiency of ligand-to-metal energy transfer and the luminescence quantum yield of  $\text{Ln}^{3+}$  depend on numerous factors, among which are the energy of the lower triplet level of the ligand (which plays the major role), the distance between the donor and acceptor in the luminophore molecule, quenching mechanisms, *etc.*

A range of compounds under study was chosen in such a way that the distance between the donor and acceptor remained virtually constant, the energy of the triplet level of the ligand being varied from 18 600 to 27 000  $\text{cm}^{-1}$ . It was found for the first time that the triplet level of the ligand in the complex should be not only somewhat higher than the resonance level of the ion but also somewhat different, each lanthanide being characterised by its





own optimum  $\Delta E$ . In the publication,<sup>105</sup> it was concluded that the difference between the triplet level of the ligand and the resonance level of terbium in terbium compounds should be no smaller than  $1850\text{ cm}^{-1}$ . However, the exact energy gap for europium compounds remains unknown. The dependence of the quantum yield of terbium and europium compounds on the position of the triplet level of the ligand is shown in Fig. 7.

The following dependence (the so-called Latva rule) was revealed: the optimum gap widths for  $\text{Eu}^{3+}$  and  $\text{Tb}^{3+}$  are  $2500 < \Delta E(^3\pi\pi^* - ^5D_0) < 3500$  and  $2500 < \Delta E(^3\pi\pi^* - ^5D_4) < 4000\text{ cm}^{-1}$ , respectively.<sup>105</sup>

In addition, investigation of carboxylate complexes<sup>106</sup> demonstrated that the intrasystem transfer is efficient when the difference between the singlet and triplet levels of the ligand  $\Delta E(^1\pi\pi^* - ^3\pi\pi^*)$  is  $\sim 5000\text{ cm}^{-1}$ . For example, the luminescence quantum yields for europium and terbium complexes with the 5'-methyl-2,2'-bipyridyl ligands containing the carboxyl or phosphonium substituent at position 6 do not satisfy the Latva rule. The ratio of the quantum yields opposite to the above rule was

attributed to the fact that  $\Delta E(^1\pi\pi^* - ^3\pi\pi^*)$  for a phosphonium-containing ligand ( $6750\text{ cm}^{-1}$ ) is closer to the ideal value ( $5000\text{ cm}^{-1}$ ) compared to the carboxyl-containing analogue ( $7100\text{ cm}^{-1}$ ).

The introduction of the neutral coordinated phenanthroline ligand into lanthanide carboxylates was found<sup>107, 108</sup> to increase luminescence. Presumably, a new ligand-to-ligand transition occurs if the level of the neutral ligand is lower than the triplet level of the main ligand and, as a consequence, the energy transfer from phenanthroline to the lanthanide ion increases. Tsaryuk *et al.*<sup>109</sup> studied photoluminescence of europium acetates  $\text{Eu}(\text{OAc})_3(\text{phen-R})$ , where phen-R is 3,4,7,8-tetramethyl-, 5-methyl-, 5-phenyl-, 4,7-diphenyl- or 5-nitrophenanthroline, and found that the nature of phenanthroline has no effect on the luminescent properties of the complexes.

An alternative approach to the design of highly luminescent lanthanide carboxylates was developed by Selvin and co-workers.<sup>110–114</sup> This method is based on the use of well-known organic laser dyes, which enhance emission in complexes, as substituents



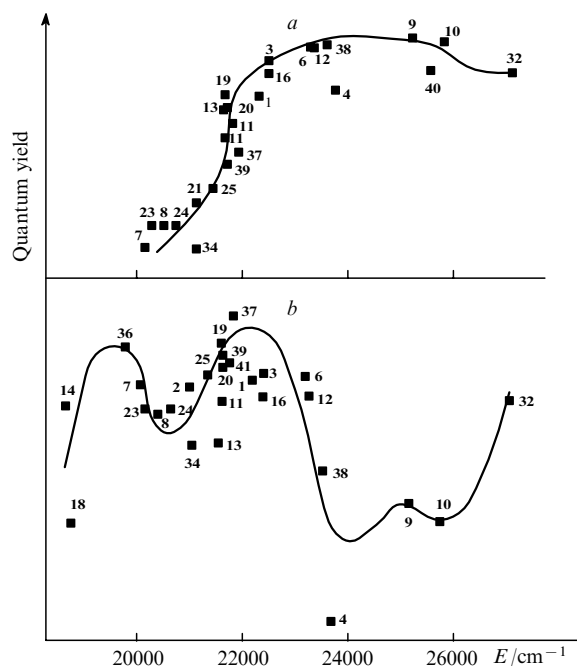


**Figure 7.** Plots of the quantum yields of terbium (a) and europium (b) carboxylate complexes vs. the energy of the triplet level of the ligand.<sup>105</sup> (The letter L in the notations of the ligands is omitted for simplicity.)

in the carboxylate ligand. However, this modification of the carboxylate ligand appeared to be inefficient.

In spite of considerable progress in theoretical studies concerned with luminescence of lanthanide carboxylates, publications on the use of these compounds in electroluminescent devices are few in number.

Edwards *et al.*<sup>54</sup> synthesised europium and terbium benzoylbenzoate complexes, which gave rather high photoluminescence quantum yields: **39(Tb)**, 4%; **40(Eu)**, 16%; and **40(Tb)**, 27%. However, electroluminescence was not observed in compound **40(Eu)**, and the maximum brightnesses of OLED devices based on compounds **39(Tb)** and **40(Tb)** are as low as 7 and 0.7 cd m<sup>-2</sup>, respectively.

The OLED devices with structures of ITO/PVK/PVB:PBD:**38(Tb)**/PBD/Alq<sub>3</sub>/Al and ITO/PVK/PVB:PBD:**38(Tb)**/PBD/Al were designed on the basis of terbium acetylsalicylate **38(Tb)**.<sup>53</sup> The electroluminescence spectrum of the terbium ion was not observed for the former device, whereas the latter showed strong green emission characteristic of Tb<sup>3+</sup> with a maximum brightness of 4.0 cd m<sup>-2</sup> at 22 V.

Electroluminescence typical of the terbium ion (545 nm) was observed in the OLED cell ITO/PEDOT/PVK/**41(Tb)**/Al based on terbium acetylsalicylate containing neutral triphenylphosphine oxide.<sup>55</sup> Bright green electroluminescence of terbium at 547.5 nm was observed also in the three-layer OLED device ITO/PVK:**42(Tb)**/Al.<sup>56</sup>

A drawback of carboxylate derivatives of lanthanides as luminophores for OLED devices is their low solubility. To increase solubility, oligomeric hydrocarbon substituents are introduced into the organic moiety of complexes. For example, Chinese researchers<sup>58</sup> synthesised readily soluble terbium hexadecylphthalate complex **44(Tb)** and designed the OLED device ITO/PPV/PVK:**44(Tb)**:PBD/Alq<sub>3</sub>/Al on the basis of this complex with a maximum brightness of 74 cd m<sup>-2</sup> at 18 V. In the discussion, these authors noted that, according to the Latva rule, luminescence of the Tb<sup>3+</sup> ion was observed at the difference T<sub>1</sub>(22 951 cm<sup>-1</sup>) – <sup>5</sup>D<sub>4</sub>(20 500 cm<sup>-1</sup>) = 2331 cm<sup>-1</sup>. The position of the triplet level of the ligand was determined using an analogous gadolinium complex.

More recently, terbium monododecylphthalate complex **43(Tb)** containing a shorter alkyl chain was synthesised.<sup>57</sup> The OLED device ITO/PVK/PVK:PBD:**43(Tb)**/Alq<sub>3</sub>/Al also showed green emission with a maximum brightness of 16 cd m<sup>-2</sup> at 24 V.

In the study,<sup>59</sup> terbium monotetradecylphthalate phenanthroline complex **45(Tb)** was used to design the OLED device ITO/PPV/PVK:**45(Tb)**:PBD/Alq<sub>3</sub>/Al with a maximum brightness of 152 cd m<sup>-2</sup> at 24 V and an external quantum efficiency of 0.017%. The electroluminescence spectrum of the cell was identical to the photoluminescence spectrum in which the most efficient transition is observed from <sup>5</sup>D<sub>4</sub> to <sup>7</sup>F<sub>5</sub> at 545 nm with a linewidth of at least 10 nm.

Zheng *et al.*<sup>60</sup> synthesised a new carboxylate ligand, *o*-amino-4-cetylbenzoate, and used it to prepare terbium complex **46(Tb)**. The OLED device ITO/PPV/PVK:**46(Tb)**:PBD/Alq<sub>3</sub>/Al showed characteristic emission of the terbium ion with a maximum brightness of 35 cd m<sup>-2</sup> at 20 V, the characteristics of the device ITO/PVK:**46(Tb)**:PBD/Al being worse (the maximum brightness was only 18 cd m<sup>-2</sup>).

#### 4. Light-emitting diodes based on rare-earth complexes containing pyrazolone ligands

In recent years, a new class of compounds, *viz.*, lanthanide complexes with pyrazolone ligands coordinated to the metal ion through the chelate β-diketonate group (Table 1, compounds **47–51**), has attracted the attention of researchers concerned with the design of materials for image converters.<sup>63</sup> The hetero-ligand complex Eu(tta)<sub>2</sub>(pmbbp)(phen) [**35(Eu)**] synthesised by Tsutsui and co-workers<sup>49</sup> is one of the first compounds belonging to this class. The light-emitting diode ITO/TPD/**35(Eu)**/Alq<sub>3</sub>/Mg:Al prepared on the basis of the above complex generated emission at a wavelength of 613 nm with a brightness of 16 cd m<sup>-2</sup> at 12.5 V, which is twice as good as for compound **18(Eu)**. By contrast, the Eu(pmabbp)<sub>3</sub>(phen) complex does not show luminescence at all because of the low position of the triplet level of the ligand. It was expected that luminescence in mixed-ligand complex **35(Eu)** would be low due to energy transfer from the thiophenediketonate ligand to the pyrazolonediketonate one. The observed increase in luminescence was attributed to the improvement of the charge-transport properties of the complex.

Huang and co-workers<sup>61</sup> found that compound **47(Tb)** also possesses good electron-transport properties. The diode ITO/TPD/**47(Tb)**/Alq<sub>3</sub>/Al designed on the basis of this complex has a maximum brightness up to 920 cd m<sup>-2</sup> at 18 V and a luminescence efficiency of 0.51 lm W<sup>-1</sup> at a current density of 0.70 mA cm<sup>-2</sup>.

In the study,<sup>63</sup> a brightness of 2200 cd m<sup>-2</sup> at 14 V was achieved in the OLED device ITO/MTDATA/TPD/**48(Tb)**/TAZ/Al designed with the use of new terbium pyrazolone complex **48(Tb)**. The maximum efficiency of the device was 2.6 lm W<sup>-1</sup> at a brightness of 25 cd m<sup>-2</sup>. Interestingly, the maximum brightness of the single-layer cell ITO/**48(Tb)**/Al was only 6 cd m<sup>-2</sup> at 23 V. The use of a potassium cathode made it possible to increase the maximum brightness and the efficiency to 226 cd m<sup>-2</sup> and 0.67 cd A<sup>-1</sup>, respectively.<sup>64</sup> However, the maximum brightness of 2200 cd m<sup>-2</sup> was achieved with the use of an appropriate combination of electron- and hole-transport layers. This result shows once again that the efficiency of devices substantially depends on their composition.

Complex **49(Gd)** was used<sup>65</sup> as the electron-transport and emission layer. The observed green emission at 535 nm characterises the pyrazolone complex as ligand-emitting. The maximum brightness of an OLED device designed on the basis of this complex is 230 cd m<sup>-2</sup> at 17 V. Another example of the use of lanthanide complexes as ligand-emitting rather than traditional metal-emitting compounds was given in the study,<sup>62</sup> where the synthesis of three lutetium pyrazolone complexes, **47(Lu)**, **49(Lu)** and **50(Lu)**, was documented. Complex **47(Lu)** was studied by X-ray diffraction. The results of this study confirmed the fact that

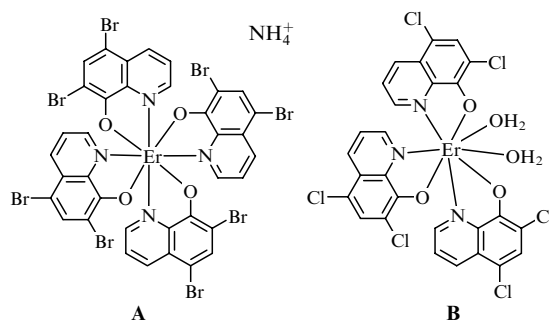
the nature of the neutral ligand may strongly affect the luminescence intensity. The photoluminescence spectra of all complexes are similar. However, the intensity for complex **47(Lu)** appeared to be 100 times higher. At the same time, the brightness of electroluminescence of the OLED device ITO/TPD/**47(Lu)**/BCP/Alq<sub>3</sub>/Mg:Ag/Ag constructed with the use of this complex was at most 119 cd m<sup>-2</sup> at 19 V, whereas a brightness of 1010 cd m<sup>-2</sup> at 16 V was achieved in the ITO/TPD/**50(Lu)**/BCP/Alq<sub>3</sub>/Mg:Ag/Ag device designed on the basis of a bipyridyl complex, whose photoluminescence characteristics are worse, and the brightness of the ITO/TPD/**49(Lu)**/BCP/Alq<sub>3</sub>/Mg:Ag/Ag device designed with the use of a phenanthroline complex was 776 cd m<sup>-2</sup> at 17 V. Triphenylphosphine oxide complex **47(Lu)** was found to have good transport properties, whereas the bipyridyl [**50(Lu)**] and phenanthroline [**49(Lu)**] complexes easily form exciplexes with TPD having high emission brightness. These data show that not only highly photoluminescent complexes but also compounds, which are weakly photoluminescent but form exciplexes with high electroluminescence efficiency, can be used as emitters for OLEDs. The authors believed that the function of a neutral ligand is to provide energy exchange between the neutral and valence-bound ligands. In the bipyridyl [**50(Lu)**, 280 nm] and phenanthroline [**49(Lu)**, 265 nm] complexes, the luminescence decreases as a result of energy transfer from the pyrazolone ligand to the neutral ligand, whereas this transfer does not occur in TPPO-containing complex **47(Lu)**.<sup>115</sup> It should be noted that the ITO/TPD/**47(Tb)**/Alq<sub>3</sub>/Al device has the better luminescent properties with a maximum brightness of 2680 cd m<sup>-2</sup>. These data suggest that the main role of the neutral ligands is to change the transport properties of materials. More recently, Huang *et al.*<sup>116</sup> successfully used compound **47(Tb)** as an electron-transport layer instead of Alq<sub>3</sub>, which also confirmed the excellent electron-transport properties of this compound.<sup>66</sup> In complex **51(Tb)**, the number of coordinated triphenylphosphine oxide groups was decreased due to the steric effect of the new pyrazolone ligand, which provides a balance between the hole- and electron-transport properties of the complex. However, the brightness of a single-layer device based on this compound is as low as 46 cd m<sup>-2</sup>. The use of additional hole- (TPD) and electron-transport (Alq<sub>3</sub>) layers made it possible to increase the emission brightness of the diode ITO/TPD/**51(Tb)**/Alq<sub>3</sub>/Mg:Ag/Ag to 20 000 cd m<sup>-2</sup> at 20 V, and the efficiency was increased to 3.24 lm W<sup>-1</sup>. A further optimisation of the device [ITO/NPB/**51(Tb)**/BCP/Alq<sub>3</sub>/Mg:Ag/Ag] resulted in an increase in the efficiency to 11.4 lm W<sup>-1</sup> at 7 V and the maximum brightness to 12 000 cd m<sup>-2</sup> at 18 V.

### 5. Light-emitting diodes based on rare-earth complexes containing quinoline derivatives as ligands

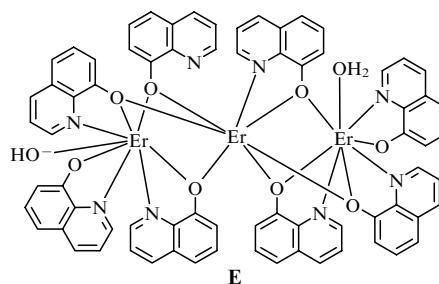
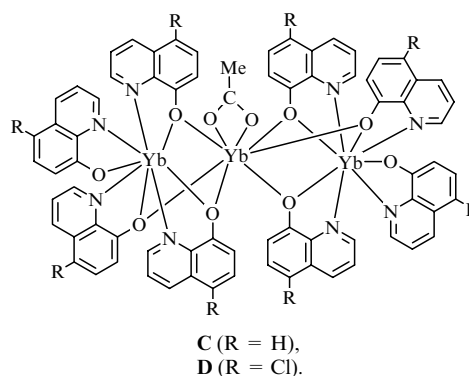
In spite of the fact that the first brief communication<sup>117</sup> on the design of a single-layer light-emitting diode with the use of neodymium 8-hydroxyquinolate was published almost 10 years ago, 8-hydroxyquinoline derivatives of lanthanides have attracted considerable attention only in 1999 after a series of publications on infrared emission in an erbium 8-hydroxyquinolate-based OLED device, in which the erbium compound was used as the emission and electron-transport material.<sup>2,3</sup> The electroluminescence at a wavelength of 1.53  $\mu$ m associated with the <sup>4</sup>I<sub>13/2</sub> → <sup>4</sup>I<sub>15/2</sub> transition was observed in the ITO/TPD/**53(Er)**/Al device containing erbium 8-hydroxyquinolate.<sup>68,69</sup> Analogous diodes based on Nd<sup>3+</sup> complexes show electroluminescence at 0.9, 1.06 and 1.32  $\mu$ m (Nd<sup>3+</sup>),<sup>70</sup> whose highest peak (1.06  $\mu$ m) corresponds to the <sup>4</sup>F<sub>3/2</sub> → <sup>4</sup>F<sub>11/2</sub> transition. The luminescence of a diode containing ytterbium 8-hydroxyquinolate at 0.98 nm is associated with the interatomic <sup>2</sup>F<sub>5/2</sub> → <sup>2</sup>F<sub>7/2</sub> transition.<sup>71</sup> Investigation of the kinetics of electroluminescence of the Erq<sub>3</sub> complex revealed two different times (0.23 and 2.2 ms). In the study,<sup>118</sup> this was attributed to the occurrence of different intraatomic transitions in the erbium ion.

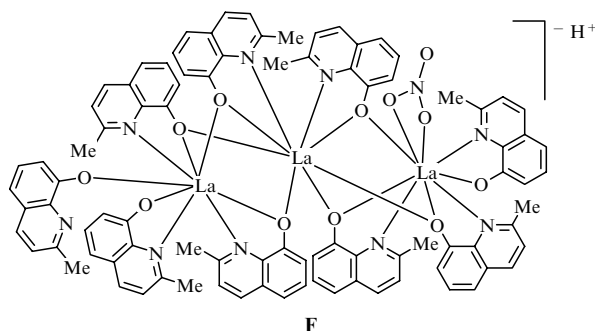
It was noted that the electroluminescence in devices based on hydroxyquinoline derivatives of lanthanides is substantially weaker than the photoluminescence of the same complexes. Additional studies by time-resolved photoluminescence<sup>119</sup> demonstrated that the luminescence intensity is substantially influenced by deactivation processes, which depend on the nature of the solvent and ligands. It was estimated<sup>119</sup> that the luminescence efficiency of erbium 8-hydroxyquinolate can vary in the range of 0.002%–0.03%.

It should be noted that rare-earth 8-hydroxyquinolates, which were used for the construction of the above-mentioned OLED devices, were not structurally investigated. It was believed that all these compounds are structurally similar to the well-known aluminium analogue Alq<sub>3</sub>. This assumption was indirectly confirmed by investigation of thin films of erbium and ytterbium 8-hydroxyquinolates by X-ray photoemission spectroscopy.<sup>120</sup> However, recent X-ray diffraction studies demonstrated that rare-earth 8-hydroxyquinolates have various structures, which are sharply different from that of the aluminium compound. It was found that none of lanthanide complexes corresponds to the formula Lnq<sub>3</sub>.<sup>121</sup> Compound **A**, which is most compositionally similar to Lnq<sub>3</sub>, contains, in addition to the metal atom and three 8-hydroxyquinolate ligands, an ammonium cation. In complex **B**, the metal ion is coordinated by two water molecules.



All other known lanthanide quinolates are trinuclear clusters containing Ln<sup>3+</sup> cations coordinated by the 8-hydroxyquinolate anions.





In complexes **C** and **D**, the central atom in the Ln–Ln–Ln group is coordinated by the acetate anion, whereas one of the terminal erbium atoms in compound **E** is coordinated by both the quinolate ligands and the hydroxy group. Compound **F**<sup>122</sup> studied by X-ray diffraction and <sup>1</sup>H NMR spectroscopy is of particular interest. In the molecules of the latter, one of the 8-hydroxyquinolate ligands is coordinated in a monodentate fashion, which is unusual for such complexes, and contains the N–H group.

Electroluminescence of the above-mentioned complexes, as well as of the recently prepared quinolates containing no water and acidic residues, was not studied.<sup>122</sup> However, their photoluminescence spectra confirm the above-mentioned quenching with coordinated water molecules, organic solvent molecules or acidic residues.

#### IV. Optimisation of lanthanide-containing light-emitting diodes

In the design of highly efficient lanthanide-based OLED devices, not only a high luminescence intensity of these complexes but also optimisation of the construction of a light-emitting element, *i.e.*, the use of an optimal combination of materials of electrodes and electron-transport, hole-transport and emitter layers, is of great importance. For example, the maximum brightness of compound **13(Eu)** in a single-layer OLED device is as low as 0.3 cd m<sup>−2</sup>, whereas the maximum brightness of the ITO/TPD/**13(Eu)**:PBD/Alq<sub>3</sub>/Mg:Ag device, which was prepared<sup>27</sup> by introducing this compound into a layer of 1,3,4-oxadiazole (PBD) possessing good electron-transport properties, is 460 cd m<sup>−2</sup>. Presumably, a substantial increase in the maximum brightness is associated with primary excitation of oxadiazole due to charge recombination. The excitation energy is transferred to the ligand and then to lanthanide. Li *et al.*<sup>123</sup> noted that an OLED device, which was constructed with the use of PVK as the hole-transport layer and complex **8(Tb)** as the emission layer, showed bright luminescence with a maximum brightness of 210 cd m<sup>−2</sup>, whereas pure green emission of the Tb<sup>3+</sup> cation at 545 nm was not observed in a device constructed with the use of TPD as the hole-transport layer.

Doping of the TPD layer with complex **14(Eu)** led to an increase in the brightness of the two-layer device ITO/TPD/**14(Eu)**/Mg:Ag from 150 to 820 cd m<sup>−2</sup>; the external quantum efficiency was 1%.<sup>31</sup> Simultaneously, the emission time was increased from 18 to 200 h and the colour purity was considerably improved. The authors believed that compound **14(Eu)** possesses excellent electron-transport properties.

Study of the electroluminescent properties of europium complex **13(Eu)** showed<sup>29</sup> that the two-layer device ITO/TPD/**13(Eu)**/Mg:Ag/Ag based on this complex has a narrow emission peak at 613 nm; however, the maximum brightness is low (3.7 cd m<sup>−2</sup> at 17 V). The poor performance was attributed to the insufficiently good electron-transport properties of the complex. The introduction of Alq<sub>3</sub> as an additional electron-transport layer into a device resulted in yellow emission due to simultaneous emission of Alq<sub>3</sub> and **13(Eu)**. With the aim of improving the electroluminescent device, a BCP layer was added as a hole-blocking layer. The resulting ITO/TPD/**13(Eu)**/BCP/Alq<sub>3</sub>/Mg:Ag/Ag diode showed

pure red emission (615 nm) with a maximum brightness of 42 cd m<sup>−2</sup> at 16 V. Luminescence of Alq<sub>3</sub> was found to be absent in this device due to the presence of the BCP layer, which blocks hole injection, with the result that electron–hole recombination occurs only within the layer composed of the europium compound.

Forrest and co-workers<sup>37</sup> studied electroluminescence of complex **18(Eu)** doped into a CBP layer with a wide energy gap, which is responsible for bipolar charge transfer. In the cited study, a maximum external quantum efficiency of 1.4% was achieved for a ‘guest–host’ system at a low current density. An increase in the density from 1 to 100 mA cm<sup>−2</sup> led to a substantial decrease in the efficiency due to triplet–triplet annihilation. The OLED devices ITO/TPD/**18(Eu)**:CBP/BCP/Alq<sub>3</sub>/MgAg, which differ in the concentration of **18(Eu)** (1%, 2% and 100%), possess different characteristics. The device containing 100% of the europium complex as an emitter exhibited the poorest performance (the maximum brightness was 32 cd m<sup>−2</sup>), whereas the device containing 1% of the europium complex had the best performance (the maximum brightness was 500 cd m<sup>−2</sup> at 100 mA cm<sup>−2</sup>).

The light-emitting diode based on compound **26(Eu)**, ITO/TPD/**26(Eu)**/BCP/Alq<sub>3</sub>/Mg:Ag or Al:Li, exhibited pure red emission with a maximum brightness of 320 cd m<sup>−2</sup> at 14.5 V, whereas the OLED device ITO/TPD/**26(Eu)**/Alq<sub>3</sub>/Mg:Ag, which does not include a BCP layer serving as a hole-blocking material, showed only yellow emission with a brightness of 420 cd m<sup>−2</sup> (see Refs 42, 124).

The introduction of complex **13(Eu)** (20%) into a matrix possessing the hole-transport properties led to an increase in the brightness of the OLED device ITO/CuPc/**13(Eu)**:NPD/BCP/Alq<sub>3</sub>/LiF/Al to 200 cd m<sup>−2</sup> (see Ref. 125).

In the study,<sup>126</sup> it was demonstrated that doping of complex **13(Eu)** into phosphorescent layers of dimethoxybenzophenone or triphenylacetophenone also led to a slight increase in electroluminescence.

According to the results of the investigation,<sup>32</sup> compound **14(Eu)**, unlike phenanthroline complex **13(Eu)**, possesses excellent electron-injection, transport and luminescent properties. This compound combined with PVK in the ITO/PVK/**14(Eu)**/Mg:Ag diode exhibits pure monochromatic red emission with a brightness 400 cd m<sup>−2</sup> at 15 V. The replacement of PVK with NPB (ITO/NPB/**14(Eu)**/Mg:Ag) leads to a substantial change in the emission colour: a broad band at 483 nm appears in addition to the narrow emission band of Eu<sup>3+</sup> at 615 nm with the result that the colour of the device becomes white with a maximum brightness of 550 cd m<sup>−2</sup> at 9 V. The authors of the study<sup>32</sup> believed that the presence of electroluminescence at a low operating voltage (~2 V) is proof of the excellent electron-injection and electron-transport properties of complex **14(Eu)**. Since the broad band at 483 nm cannot be assigned to the NPB compound, which has its own luminescence band at 440 nm, this band is, apparently, caused by emission of an exciplex, that appears between the layers of NPB and compound **14(Eu)**.

After introduction of complex **18(Eu)** into hole-transport PVK, the OLED device gives a maximum brightness of 30 cd m<sup>−2</sup>. The addition of the same complex to electron-transport PBD leads to an increase in the brightness of 417 cd m<sup>−2</sup>.<sup>127</sup> The maximum luminescence intensity of the single-layer OLED device ITO/**18(Eu)**:PVK/Mg:In was observed at a concentration of 0.12 mol.% of **18(Eu)** in PVK.<sup>128</sup> The use of another electron-transport material (PBD) as a matrix for compound **18(Eu)** made it possible to construct the OLED ITO/TPD/**18(Eu)**:PBD/PBD/Mg with a maximum brightness of 320 cd m<sup>−2</sup> and an external quantum efficiency of 1%.<sup>38</sup> The maximum brightness of 137 cd m<sup>−2</sup> was observed,<sup>129</sup> when complex **18(Eu)** was used as a dopant (5%) to the azomethine zinc complex in the emitter layer.

Wong and co-workers<sup>130, 131</sup> studied electroluminescence of europium and samarium complexes **36(Eu)** and **36(Sm)**. The observed luminescence of samarium complexes compared to that of europium complexes was too low. Hence, single-, two and

three-layer OLED devices were constructed with the use of europium complexes. A single-layer device exhibited very low quantum efficiency. A two-layer device was much more efficient due to the presence of TPD as the HTL layer. The introduction of the third ETL layer ( $\text{Alq}_3$ ) did not lead to substantial changes. In another study,<sup>51</sup> a maximum brightness of  $10 \text{ cd m}^{-2}$  at an operating voltage of 18 V was achieved by constructing an analogous OLED device consisting of compound **36(Eu)**, TPD and  $\text{Alq}_3$ .

An orange-emitting OLED device with a maximum brightness of  $135 \text{ cd m}^{-2}$  has been recently constructed<sup>26</sup> with the use of complex **12(Sm)** in combination with PVK and PBD.

Dispersion of compound **8(Er)** into a polymeric PVK matrix afforded the OLED device ITO/PVK: **8(Er)**/Al:Li/Ag with infra-red electroluminescence at  $1.54 \mu\text{m}$ .<sup>22</sup> Li and co-workers<sup>132</sup> studied interactions between PVK and various Tb and Eu complexes and found that efficient energy transfer processes occur between PVK and lanthanide complexes.

The above data show that energy transfer processes from a matrix to a compound should be taken into account when rare-earth compounds are used as dopants. It is generally agreed<sup>14</sup> that the energy, which is generated in OLED devices containing lanthanide  $\beta$ -diketonates as dopants upon charge recombination, is transferred from the matrix to the singlet excited state of the ligand, from which it is transferred to the triplet level of the ligand as a result of intersystem crossing, and is finally transferred to the metal ion. In this connection, two main problems should be taken into account in the design of devices: (1) the efficiency of energy transfer from the matrix to lanthanide  $\beta$ -diketonates; (2) the efficiency of energy transfer from the triplet level of the ligand to the metal ion.

In the study,<sup>125</sup> three main mechanisms of excitation of lanthanide complexes in a matrix were proposed.

1. A complex is excited as a result of energy transfer from the matrix to the complex. In this case, the Frenkel exciton should be formed within the emitter layer, in which the resonance transfer of the electronic excitation energy to the complex molecule occurs. If the energy transfer occurs by the Forster mechanism (a dipole mechanism), the spectral overlap between emission bands of the matrix and absorption bands of the complex should take place. If the energy transfer is based on exchange interactions according to the Dexter mechanism (an exchange mechanism), the correspondence between the energy levels and interactions of the involved orbitals are of importance.

2. A complex becomes excited as a result of charge transfer from the matrix, *i.e.*, electrons and holes, which are separately transported to the complex molecule, recombine with the result that the energy is released, and the latter is transferred to the metal ion serving as an emission centre. This requires particular properties of the complex providing simultaneous electron and hole capture.

3. If the emission layer consists only of complex molecules, the latter, as in the previous case, are excited due to recombination of the opposite charges on the complex molecules. Excitation of the complex is most efficient if the charge injection (electron and hole injection) in a layer is balanced and the charges are present at a high concentration and are highly labile. The charge balance can be controlled by introducing an additional charge-blocking layer.

Bazan and co-workers<sup>25</sup> demonstrated that the correspondence between the absorption spectra of the matrix and the dopant is of importance for the design of 'guest-host' systems. For example, the electroluminescence efficiency in a polycyanophenylene (CN-PPP) matrix decreases in a series **19(Eu)** (1.1%) > **13(Eu)** (0.7%) > **11(Eu)** (0.1%) > **8(Eu)** (0.03%), which corresponds to absorption spectra of europium complexes and emission spectra of CN-PPP (Fig. 8).

It was hypothesised<sup>133</sup> that complexes with higher emission energy compared to the absorption energy of the dopant should be used as a matrix for the design of devices with europium-based

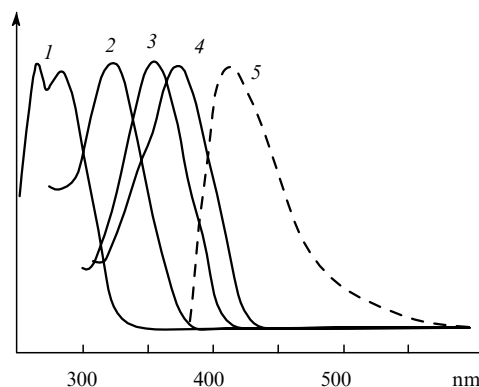


**Figure 8.** Absorption spectra of the europium  $\beta$ -diketonate complexes  $\text{EuR}_3(\text{phen})$  (1–4) and the emission spectrum of polycyanophenylene (5).<sup>25</sup>

R = acac (1), mppy (2), dbm (3), and dnm (4).

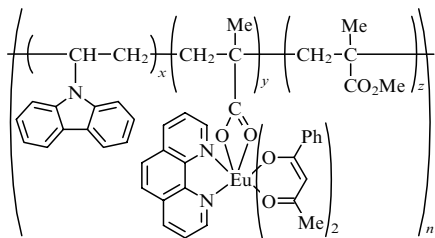
pure red emission. Compound **19(Eu)** was found to be the dopant of choice for TPD used as the matrix.<sup>133</sup>

Li and co-workers<sup>134</sup> found that the hole injection in a layer formed from lanthanide complexes leads to luminescence quenching and is responsible for decomposition of the compound, and these authors suggested an alternative approach to the problem based on interactions between the layers.<sup>31</sup> They constructed several types of OLED devices containing different layers between which europium complex **14(Eu)** was placed. The ITO/TPD/**14(Eu)**/TPD/ $\text{Alq}_3$ /Ag:Mg device differs from the ITO/**14(Gd)**/**14(Eu)**/**14(Gd)**/Ag:Mg device in that the europium complex is enclosed between the layers of a hole-transport material (TPD) in the former device and between the layers of an electron-transport material [**14(Gd)**] in the latter device. In the ITO/**14(Eu)**/Ag:Mg device containing no separating layers, electroluminescence was not observed due apparently to the fact that hole injection in the europium complex from the ITO anode is hindered. In yet another device, ITO/TPD/**14(Eu)**/Ag:Mg, hole injection occurs from the TPD layer, resulting in red emission. However, the emission time of the latter device is short compared to the other devices. The best results were achieved with the use of the second light-emitting diode with an external quantum efficiency of 4.6% at a current density of  $0.01 \text{ mA cm}^{-2}$  and a maximum brightness of  $\sim 100 \text{ cd m}^{-2}$ . Based on these results, the authors concluded that the first device contains an excess of holes, the third device contains an excess of electrons, whereas the concentrations of holes and electrons are balanced in the second device.

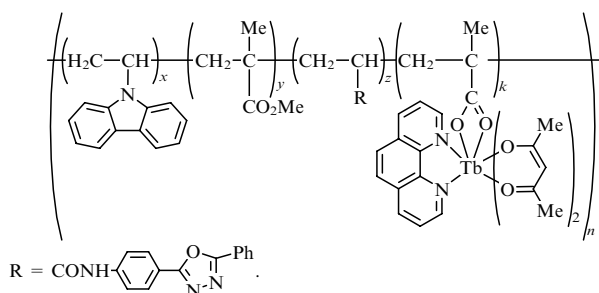
The same authors<sup>28</sup> studied the electron-transport properties of yttrium, lanthanum and gadolinium (their ions show no emission)  $\beta$ -diketonates using complexes **8(Ln)** as an example. These chelates were used as an additional layer in OLED devices. These complexes were found to have good electron-transport properties. The introduction of compound **8(Gd)** as an additional layer into the electroluminescent devices ITO/**13(Eu)**/ $\text{Alq}_3$ /**8(Gd)**/ $\text{Alq}_3$ /Al and ITO/TPD/**13(Eu)**/ $\text{Alq}_3$ /**8(Gd)**/ $\text{Alq}_3$ /Al increases the quantum efficiency of both devices (for the latter device, the efficiency was increased by a factor of almost two, from 0.6% to 1.0%) and changes the colour of emission from red (characteristic of Eu) to yellow.<sup>135</sup>

Low-molecular-weight lanthanide complexes are widely used for the construction of OLED devices. However, many such complexes are non-technological because film deposition is often accompanied by undesired crystallisation or aggregation. To solve this problem, attempts were made to synthesise high-molecular-weight lanthanide complexes. However, the simplest procedure is apparently based on the introduction of low-molecular-weight europium, terbium and thulium compounds into polymeric matrices, *i.e.*, the design of the above-mentioned 'host-guest' systems with all their drawbacks and advantages.<sup>1, 136–142</sup>

Another solution of this problem is to synthesise polymers containing chemically bound lanthanide ions. An example is a carbon-chain polymer containing europium  $\beta$ -diketonate in side fragments.<sup>143</sup>



The luminescence efficiency of an OLED device constructed on the basis of this polymer is  $2.87 \times 10^{-4} \text{ lm W}^{-1}$ , and its brightness is  $0.228 \text{ cd m}^{-2}$  at 29 V. More recently, with the aim of improving the luminescent properties and constructing a single-layer OLED device, oxadiazole fragments were additionally introduced<sup>144</sup> into a copolymer, resulting in the presence of an emission, electron-transport and hole-transport layers in the same layer and, moreover, in the same polymeric matrix.



The resulting single-layer OLED device shows monochromatic green emission at 545 nm. However, the authors mentioned that the brightness of this device is unsatisfactory. A device constructed with the use of a polymeric matrix containing simultaneously europium and terbium shows white emission.<sup>145</sup>

One of the main procedures for the design of OLED devices involves deposition of the corresponding layers of working materials onto an ITO layer. This technological step has a strong effect on the characteristics of light-emitting diodes. The following two main methods are used for layer deposition: sublimation or spraying of a material and the preparation of films from solutions by evaporation of the solvent in a centrifugal field (spin-coating) or under standard conditions. This, as applied to rare-earth compounds, imposes the following additional requirements: rather high thermal stability and good solubility of the compound in an organic solvent suitable for the above operations. The surface quality of thin films of terbium carboxylate complexes prepared from various solvents was studied<sup>146</sup> by scanning atomic force microscopy and optical near-field microscopy. A device prepared from THF was found to have the best performance.

For lanthanide  $\beta$ -diketonate complexes, poor solubility is often a considerable obstacle. Complexes **6(NaEu)**, **6(LiEu)** and **6(KEu)** are readily soluble in chloroform, ethanol, acetonitrile and acetone,<sup>17</sup> their photoluminescence spectra are analogous to those of the  $\text{Eu}^{3+}$  ion, but the fluorescence intensity strongly depends on the nature of the solvent. It was attributed to the fact that high dielectric constants and the coordination ability lead to better solvation of alkali metal ions, which prevents undesired aggregation of europium species. These compounds were used to construct single-, two- and three-layer OLED devices with a maximum brightness of  $36.7 \text{ cd m}^{-2}$  at 26 V, which is substantially higher than that for the above-described devices based on compound **5(Eu)**.

## V. Conclusion

The data considered in the present review show that there are real prospects for the use of lanthanide complexes in organic light-emitting devices. The most substantial results were achieved in the design of OLED devices based on pyrazolonate complexes (Fig. 9).

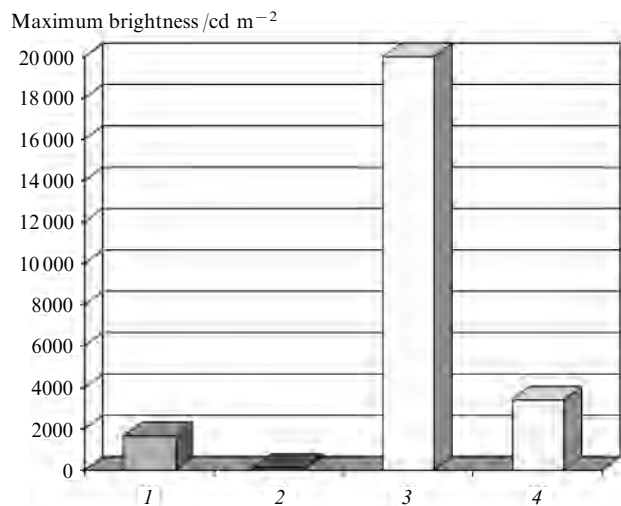


**Figure 9.** Relative brightnesses of the most efficient OLED based on lanthanide  $\beta$ -diketonates (1),<sup>48</sup> carboxylates (2)<sup>59</sup> and pyrazolonates (3)<sup>66</sup> and Alq<sub>3</sub> (4).<sup>147</sup>

As mentioned above, the OLED device constructed with the use of the purely organic compound rubrene still provides record brightness (higher than  $200\,000 \text{ cd m}^{-2}$ ).<sup>73</sup> The brightness of a diode constructed with the use of tris(2-phenylpyridine) iridium is somewhat lower ( $100\,000 \text{ cd m}^{-2}$ ).<sup>74</sup> The characteristics of lanthanide-based OLED devices are noticeably worse. However, the latter devices have the following undeniable advantages: generation of 'pure'-coloured emission and a much lower price compared to the iridium device. In addition, there is good reason to hope that the emission brightness, efficiency, quantum yield and other characteristics of diodes containing organic lanthanide complexes will be sharply improved by choosing an optimum ligand environment.

Analysis of the published data shows that the compositions of lanthanide-containing OLED devices cannot be considered as completely optimised. Elucidation of the factors of interactions between organic matrices and lanthanide compounds is one of the most important problems. A more complete theoretical description of the mechanisms of intramolecular energy transfer is required. An extension of the range of ligands used in these complexes is of considerable significance. This will allow one to synthesise new highly luminescent complexes. Studies of the dependence of the luminescent properties on the nature of the chemical bonds between metals and ligands, the structures of the latter and organisation of the complexes are also of importance. Evidently, a combination of fundamental and applied investigations will provide interesting results and assist in constructing highly efficient OLED devices.

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# Oxidative conversion of methane

V S Arutyunov, O V Krylov

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**Abstract.** The data on various aspects of oxidative conversion of methane published in 1998–2004 are considered. The bibliography includes 295 references.

## I. Introduction

The advent of the 21st century brought about radical changes in the views on the future prospects of the world power engineering and the role of various sources of hydrocarbon raw materials. It has become evident that the oil era is not everlasting and its decline is not far off.<sup>1</sup> It is small-power energetics that make use of alternative renewable energy sources, solar energy in particular. The power flux densities are still so low that they cannot, in principle, meet the rapidly growing demands of the world economy despite the declaratory statements on the developments in this field. Renewable bioresources are obviously inadequate to satisfy the demands of the population inhabiting our planet for food or to solve the problems of the world energetics. As for thermonuclear energy, it has virtually not been called into being yet and according to the most optimistic prognoses will hardly become a reality before the end of this century. Atomic energy introduces well-known problems and causes alarm in view of environmental safety, but will hardly have a reasonable alternative within the next few decades. This all means that, till the end of this century, mankind will have to rely mainly upon fossil fuel, viz., carbon and natural gas. In this context, their efficient exploitation and development of novel resource-saving and environmentally friendly technologies are of paramount importance. Considerable efforts should be given to further improvement of chemical processes for the conversion of gaseous and solid hydrocarbon raw material into more convenient types of energy carriers and promising chemical products.

Today, the crucial role of natural gas and gas-chemical processes in the economy of the 21st century and the fact that they will gradually replace the existing oil stock and petrochemical technologies are not in doubt. The recent 7th Natural Gas Conversion Symposium (NGCS7), the largest international meeting devoted to the problems of reforming of natural gas and light

hydrocarbons,<sup>2,3</sup> has demonstrated a real breakthrough in the technology and commercialisation of chemical conversion of natural gas. In the three years elapsed from the previous Symposium, the leading world companies have brought into operation several large-scale pilot plants and started the realisation of several jumbo projects. The overall output of liquid products is expected to amount to  $2 \times 10^6$  barrels per day with an overall gas consumption of about  $166 \times 10^9$  m<sup>3</sup> per year. There are more than 20 large oil and gas producers all over the world continuously patenting their developments; the total number of patents in different aspects of 'gas-to-liquid' (GTL) technologies has reached 8000.<sup>4</sup> Several hundred reports on the use of catalysis in natural gas reforming presented at the 13th International Congress on Catalysis are evidence of high scientific activity in this field.

The main recent trend has become the intention of leading chemical companies to broaden the range of natural gas conversion products other than motor fuels. For example, the market of such products can be expanded owing to the greater manufacture of polymers, which has been implemented by several companies.

The world capital of gas-chemical technologies is now moving to Qatar. Recently, the state-owned company Qatar Petroleum completed agreements with the largest oil-and-gas producing and developing companies (Sasol, Chevron, ConocoPhillips, Shell, ExxonMobil, etc.) to the total sum of USD  $\sim 23 \times 10^9$ , which corresponds to daily liquid product output of  $\sim 700\,000$  barrels. This means that the total investment in the infrastructure of the gas industry of this small country will amount to USD  $\sim 60 \times 10^9$ . Considerable activity in the establishment of new gas-chemical enterprises is shown by Iran and other Middle Eastern countries as well as by Nigeria, Australia, Trinidad, etc. Unfortunately, Russian gas- and oil-producing companies still continue to direct their exclusive efforts to the export of raw materials despite the fact that for Russia, the world leader in the resources and production of natural gas, its reforming is of strategic importance. So far, not a single oil- or gas producing company or a representative of a state-owned or academic institution within Russia has shown interest in the work of the NGCS7. However, Russian scientists will hardly be able to carry out research at a really high level in this technologically complicated area that requires expensive modern equipment without financial support from large companies.

The specific nature of the domestic gas industry determines the need for financial support of fundamental research. The bulk of Russian natural gas is extracted from the gas fields of Urengoi and Yamburg, regions that are difficult of access, with inclement climate where the use of the existing foreign technologies is unprofitable or impracticable. In addition, Russia possesses substantial reserves in the form of nearly 600 marginal or low-

V S Arutyunov, O V Krylov N N Semenov Institute of Chemical Physics, Russian Academy of Sciences, ul. Kosygina 4, 119991 Moscow, Russian Federation. Fax (7-495) 651 21 91, tel. (7-495) 939 72 87, e-mail: arutyunov@center.chph.ras.ru (V S Arutyunov), tel. (7-495) 939 71 68 (O V Krylov)

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pressure gas fields that are hitherto unexplored due to the lack of efficient technologies for their transportation or reforming.

The results of investigations carried out by Foster Wheeler Energy Ltd. by request of Sasol<sup>5</sup> and those reported at the NGCS6<sup>6</sup> suggest that an enterprise on natural gas oxidative conversion and Fischer—Tropsch synthesis with a productive capacity of 30 000 barrels per day (1 400 000 tons per year) located in seaside regions in order to ensure easy sea transportation of the final products, costs capital outlays per unit of USD 25 000 per barrel of the daily product, *i.e.*, about USD 530 per ton per year. According to technical-and-economic assessments,<sup>7</sup> the investment cost for the construction of a gas-converting plant in the vicinity of the gas fields of the Yamal Peninsula exceeds USD  $4 \times 10^9$  with a provisional pay-back period of  $\sim 20$  years, which makes such projects unacceptable *a priori*.

All of the current chemical productions and works-in-project (WIP) are based on the preliminary conversion of natural gas, which contains methane as the main component, into synthesis gas which represents a mixture of carbon monoxide and hydrogen. This technologically complicated energy-consuming process takes up from 50% to 75% of the total cost of the basic chemical products prepared from natural gas (ammonia, methanol, GTL-products, *etc.*), which is the reason for their high prime cost and high capital intensity. Even an insignificant reduction of the cost of synthesis gas significantly reduces the production costs of the final products. Therefore, the main goal of the studies on methane reforming is both the reduction of the cost price of the synthesis gas, which can also be achieved with the use of oxidative conversion, and development of new in principle approaches to oxidative conversion of methane irrelevant to the production of synthesis gas.

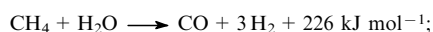
The number of publications devoted to different aspects of oxidative conversion of methane is increasing annually. However, in this review only the investigations carried out in the past 6–7 years are reviewed, since the literature data on this subject published before 1998 were considered in detail in the monograph<sup>8</sup> and earlier papers.

## II. Oxidative conversion of methane into synthesis gas and hydrogen

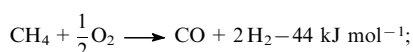
Recently, the interest in hydrogen fuels has increased substantially, particularly with regard to its possible utilisation in vehicles.<sup>9</sup> Although about 97% of motor fuels are currently oil reforming products, it is expected that by the end of the next decade hydrogen will be extensively used as a fuel for the most popular production cars. Hydrogen will be used as an additive to organic fuels, as a fuel itself for internal combustion engines and as a power supply for fuel cells. The main hydrogen source is synthesis gas ( $\text{CO} + \text{H}_2$ ).

There exist three methods for preparing synthesis gas:

- 1) steam reforming of methane (SRM)



- 2) partial oxidation of methane (POM)



- 3) carbon-dioxide ('dry') reforming of methane (CDR).



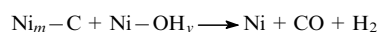
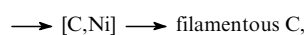
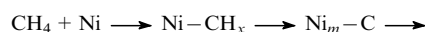
Only the first of these reactions is widely employed in the large-scale production of nearly 95% of synthesis gas. A Shell plant in Bintoulou (Malaysia) that makes use of non-catalytic POM is an exception. Different modifications are reported that represent combinations of the above reactions. Irrespective of the process used to prepare synthesis gas, further elucidation of the reaction mechanism, the choice of effective and stable catalysts and efficient technological design still remain the topical tasks.

## 1. Steam reforming of methane

Since the introduction, in 1966, of SRM over nickel catalysts into industrial practice, a systematic solution of a wide range of problems related to sulfur poisoning of catalysts, coke formation and reduction of reactor size has begun. The SPARG technology developed by Haldor Topsoe Ltd. allowed solution of the problem of sulfur poisoning by reducing the overall catalyst activity and using a preconverter. Supported nickel and cobalt catalysts promoted by basic oxides possessed the highest activities. At present, the activity of a catalyst is not a limiting factor in SRM and the main efforts are focused on improving heat- and mass-exchange, optimisation of the process and minimisation of the reactor size.

The theoretical aspects of SRM were considered by Rostrup-Nielsen *et al.*<sup>10–12</sup> Steam reforming is accompanied by carbonisation of nickel catalysts, since carbon fibres appear upon decomposition of methane; their growth results in destruction of the catalyst, prevents interaction of the gas flow with the surface and impairs heat exchange.

A simplified scheme of this process was developed based on the concept of ensembles on surfaces of metals.<sup>13</sup>



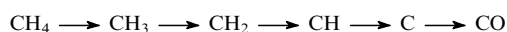
( $m > n$ ).

The state and reactivity of the surface carbon are the key problems in the mechanism of SRM. The adsorbed carbon atoms do not react with gas molecules and are dissolved in Ni to generate carbon filaments that block the catalyst surface. A carbon-free mode is reached where the concentration of dissolved carbon  $[\text{C}, \text{Ni}]$  is below the equilibrium concentration of carbon. This ratio can be achieved by increasing the steam-to-carbon ratio and, correspondingly, adsorption of water vapour and the rate of the surface reaction with a simultaneous decrease in the rate and degree of activation and dissociation of  $\text{CH}_4$ .

The Topsoe company is the world leader in both the development of technologies for the production of synthesis gas and the use of the newest physical methods for the study of the reaction mechanism. Electron microscopic *in situ* studies on a specially designed instrument with the atomic resolution<sup>14</sup> enabled detailed investigations into the mechanism of methane activation over Ni.  $\text{CH}_4$  molecules interact with the steps of Ni nanocrystals to form graphite-like clusters, which were further transformed into multi-layered carbon nanotubes. Growth of the nanotube occurs in parallel with the rearrangement of the nickel particles which changes their shapes and sizes. After complete encapsulation of Ni, the growth of the nanotube stops and the catalyst is poisoned. Synthesis gas is formed in the reaction of the  $\text{CH}_x$  groups with the OH groups formed upon  $\text{H}_2\text{O}$  adsorption. A scheme was proposed that explained the promoting effect of  $\text{MgO}$ ,  $\text{La}_2\text{O}_3$ ,  $\text{Ce}_2\text{O}_3$  and alkalis favouring adsorption of water. Total adsorption of  $\text{H}_2\text{O}$  over  $\text{Ni}/\text{Al}_2\text{O}_3$  or  $\text{Ni}/\text{MgAl}_2\text{O}_4$  exceeded that over  $\text{Ni}/\text{MgO}$  where a larger amount of the OH groups is formed as followed from the data on the isotope exchange with  $\text{D}_2\text{O}$ .<sup>14</sup> This accounts for the little coke formation over  $\text{MgO}$ . In this case, the amount of the OH groups increased despite a decrease in the dissociation rate of  $\text{CH}_4$  by more than an order of magnitude. Over Co, the value of  $x$  in the  $\text{CH}_x$  groups was larger than over Ni, and over  $\text{Ni}/\text{MgO}$  it was larger than over  $\text{Ni}/\text{SiO}_2$ .

The mechanism of SRM was studied at the level of elementary reactions<sup>15</sup> using Ni single crystals as surface catalysts. The data obtained were consistent with the results of quantum-chemical calculations obtained by the DFT (Density Functional Theory) method. A comparison of reactions occurring on the plain surface of  $\text{Ni}(111)$  single crystal and on the step-like surface of  $\text{Ni}(211)$

revealed that in the latter case the values of the activation energies in all the stages of the sequence:



were smaller than on the plain surface, although the corresponding values for different stages of this sequence were different. The SRM reaction was structure-sensitive: the facet of Ni(111) was catalytically active in SRM, but was inactive in carbon deposition. In contrast, both the catalytic reaction and carbon deposition occurred on the facet of Ni(211). On the whole, the presence of steps and other structural defects is unfavourable for SRM.

It was found that the degree of methane conversion was low at low metal-to-carbon binding energies.<sup>16</sup> The optimum energies of the M–C and metal-to-hydrogen (M–H) bonds are equal to 160–169 and 64–67 kcal mol<sup>−1</sup>, respectively, which have been recommended as criteria for the selection of promoters for Ni catalysts.

#### a. Catalysts

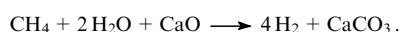
As usual, supported nickel catalysts are mainly employed in SRM. The improvements applied largely to the shape of the pellets. Some newly developed catalysts have the shape of complex rings with multiple holes. Heat transfer on the walls of the reactor tubes is often a limiting factor in SRM, therefore, application of a thin layer of a catalyst directly onto the reactor walls is beneficial.

A highly active catalyst for SRM at a low H<sub>2</sub>O : CH<sub>4</sub> ratio was prepared from perovskite LaNi<sub>x</sub>Fe<sub>1−x</sub>O<sub>3</sub> (0 < x < 1).<sup>17</sup> At 800 °C, the selectivity towards CO reached 96%. In the majority of catalytically active systems (0.2 < x < 0.4), perovskite LaFeO<sub>3</sub> and finely dispersed Ni particles are formed under the conditions of SRM. Carbon deposition was the lowest over catalysts with this composition.

CaAl<sub>2</sub>O<sub>4</sub> was found to be a good support for Ni and Rh catalysts.<sup>18</sup> The equilibrium conversion over Ni/CaAl<sub>2</sub>O<sub>4</sub> and Rh/CaAl<sub>2</sub>O<sub>4</sub> was reached at 400 °C and 480 °C, respectively, the volumetric gas flow rate being 10-fold larger than in conventional industrial reactors.

#### b. Kinetics and mechanism

Removal of hydrogen or CO from the reaction zone favours a shift of the equilibrium in SRM to the right and thus favours the increase in the yields of the target products. Metal membranes can be used to remove hydrogen,<sup>19,20</sup> which also reduces the risk of poisoning of the catalyst with hydrogen sulfide present in methane. Removal of CO<sub>2</sub> from the reaction zone can be carried out by binding it with an adsorbent, *e.g.*, CaO.<sup>21</sup>



In this case, regeneration of the adsorbent, *i.e.*, decomposition of CaCO<sub>3</sub>, is required. A gas containing more than 95% of dry H<sub>2</sub> can be prepared in one step. After 25 cycles, the activity of the adsorbent decreased insignificantly.

Extensive studies into SRM are currently underway at the Institute of Catalysis of the Siberian Branch of the RAS. It was found<sup>22</sup> that the reaction rate decreased with the increase in the amount of the catalyst (Ru/Al<sub>2</sub>O<sub>3</sub> or Ni/Al<sub>2</sub>O<sub>3</sub>), which is believed to support a hypothesis on a homogeneous–heterogeneous mechanism of this reaction. The maximum activity of Ni/Al<sub>2</sub>O<sub>3</sub> corresponds to the activity of a wire of metallic nickel. At higher content of the catalyst, the reaction is purely heterogeneous (800 °C). The introduction of hydrogen decreases the activation energy and increases the rate of carbon formation.

The application of a thick layer of a catalyst (Ni/Al<sub>2</sub>O<sub>3</sub>/Al) onto the surface of a tubular reactor for SRM facilitates heat exchange on the tube walls.<sup>23</sup> A tubular heat-exchange reactor for SRM has been considered<sup>24</sup> where deep oxidation of methane took place on the outer surface coated with Ni–Cr-foam over perovskite, while steam reforming occurred on the inner surface of the Ni-foam catalyst. A combination of exothermic and endo-

thermic reactions separated by the reactor wall enables a design of a virtually thermoneutral reactor.

The kinetics of SRM over a Ni/α-Al<sub>2</sub>O<sub>3</sub> catalyst were studied.<sup>20</sup> The reaction rate was proportional to the partial pressure of hydrogen *p*<sub>H<sub>2</sub></sub>. The surface interaction CH<sub>4</sub><sub>ads</sub> + H<sub>2</sub>O<sub>ads</sub> is the limiting step of this reaction, which occurs according to the Langmuir–Hinshelwood mechanism. As noted previously,<sup>20</sup> the first study<sup>25</sup> devoted to the steam reforming of CO had been published nine years before the frequently cited paper.<sup>26</sup>

#### c. Technological features

The start-up of a BP large pilot plant in Alaska constructed according to an original technology was a prominent event in the history of SRM technologies. Its daily capacity is 300 barrels of liquid GTL products at a production cost of USD 86 × 10<sup>6</sup>. The SRM process enables the reduction of the prime cost of synthesis gas by excluding expensive oxygen. It was claimed<sup>2</sup> that it was possible to design a much more compact SRM apparatus with the mass smaller by 75% than that of analogous units.

Microchannel Process Technology (MPT) developed by Velocys Inc. is a novel promising approach to the study of SRM, since it substantially intensifies heat and mass exchange. A typical MPT reactor consists of stacks of closely spaced thin plates that form microchannels with diameter < 1 mm. The stacks where heat carrier is circulating or fuel is combusted alternate with those where reforming of natural gas occurs, which is accompanied by absorption of heat. A nearly 100-fold increase in the heat exchange intensity in comparison with conventional SRM processes made it possible to reduce significantly the overall dimensions of the equipment and to diminish the residence time. The latter circumstance is especially important for steam reforming, since soot formation takes much more time than the reforming itself. Very fast (< 10 ms) attainment of equilibrium concentrations in MPT reactors makes it possible to avoid soot formation, to increase the productivity and to reduce production costs. The trials conducted for several months demonstrated the durability of the MPT reformer. With this design, higher capacity is achieved by merely multiplying the number of stacks; no scaling-up is required. The operation principle of the MPT reactor is applicable to the subsequent steps of reprocessing of synthesis gas, *viz.*, the Fischer–Tropsch synthesis or synthesis of methanol.<sup>27</sup>

Despite the intensive search for alternative methods for methane conversion into synthesis gas and the appearance and ever increasing number of production technologies based on them, the SRM reaction is still the main industrial method for the production of synthesis gas. Although this reaction is highly endothermic, it is considered to be a candidate of choice as a hydrogen source in hydrogen technology. Steam reforming of methane is a high-tech process ensuring lower prime cost of H<sub>2</sub> in comparison with its production from biomass or using nuclear, solar and electric energy or wind power.

## 2. Partial oxidation of methane (POM)

Despite the indisputable achievements in the practical application of SRM, partial oxidation and combined steam-oxygen reforming of methane are the most popular trends of research. In addition to minimisation of power input, these methods allow production of synthesis gas with the composition (H<sub>2</sub>:CO = 2:1), which is especially favourable for the Fischer–Tropsch synthesis and synthesis of methanol. The main problems include the necessity of using expensive oxygen, high explosion hazard and local overheating. Besides, the large size of POM reactors is a considerable obstacle to their commercialisation. Continuous search for novel technologies for oxidative conversion of methane into synthesis gas is underway.

A gas-phase method for the oxidation of methane to synthesis gas is being developed in Russia. This approach is based on the use of modified diesel or compression engines that also serve as the chemical reactors.<sup>28,29</sup> The process first implemented on a large

scale in 1998 is characterised by much higher overall productivity of the process per unit volume (10 000 m<sup>3</sup> of the synthesis gas per hour). The possible use of low-pressure natural gas (including that obtained from gas wells that can no longer be exploited for commercial purposes) and coal mine methane and oxidation by atmospheric air are its obvious advantages. However, the synthesis gas thus produced contains ~60% of nitrogen, which impedes its further processing. At the same time, simultaneous generation of electric energy is a very attractive feature of this process, although future prospects for its wide application are still ambiguous.<sup>30</sup>

Synthesis gas generators based on rocket technologies is yet another achievement of Russian scientists in the field of oxidative conversion of methane. The productivity of this process per unit volume exceeds those of conventional large-scale units by a factor of tens. Both processes are based on the gas-phase oxidation of methane at high temperatures and yield mixtures with nearly equilibrium composition. However, the composition of the synthesis gas is difficult to control by reason of high specific capacity of such units.<sup>30</sup> A pilot plant for motor fuels with a productivity of 432 kg h<sup>-1</sup> with respect to methane has been constructed on the basis of a synthesis gas generator using rocket technologies.<sup>31</sup> Nevertheless, the Shell plant at Bintulu (Malaysia) is the only example of a successful industrial application of a gas-phase high-temperature (1100–1200 °C) POM process. Apparently, the POM technology will further be developed in connection with agreements on the construction of a supergiant plant at Qatar with the participation of the Shell Corporation.<sup>32</sup>

#### a. Catalysts

As a rule, the POM technology employs supported nickel<sup>33–39</sup> or, less frequently, cobalt<sup>40</sup> catalysts or catalysts based on precious metals.<sup>41–46</sup> Most of the studies in this field are aimed at increasing the stability of Ni over various oxide supports and the resistance of the catalyst against carbon poisoning rather than at enhancing its activity and selectivity. Studies of supported Ni catalysts revealed that Ni/CeO<sub>2</sub> and Ni/TiO<sub>2</sub> were much less active and selective in comparison with Ni/ZrO<sub>2</sub> and Ni/Al<sub>2</sub>O<sub>3</sub>, but less prone to carbon poisoning.<sup>33</sup> Nickel catalysts supported onto perovskites CaTiO<sub>3</sub>, SrTiO<sub>3</sub> and BaTiO<sub>3</sub> by solid-phase crystallisation were less active and less stable than those prepared by impregnation.<sup>34,35</sup> High dispersity of Ni prevents coke formation. Ni/SrTiO<sub>3</sub> possessed the highest dispersity. High stability and activity were observed for Ni/CeO<sub>2</sub>–ZrO<sub>2</sub>.

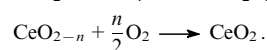
Promotion of Ni/γ-Al<sub>2</sub>O<sub>3</sub> with Li and La oxides increased its stability and suppressed sintering, which results in a loss of activity.<sup>36,37</sup> LiLaNiO/γ-Al<sub>2</sub>O<sub>3</sub> not only manifested high activity and high resistance to carbon deposition, but also possessed a stable porous crystalline structure, which remained unchanged even after 500-hr heating at 800 °C. The activity and stability of the nickel catalyst were considerably enhanced upon promotion with CeO<sub>2</sub> or Y<sub>2</sub>O<sub>3</sub>.<sup>38,39</sup> Cerium dioxide suppressed the interaction of Ni with Al<sub>2</sub>O<sub>3</sub> and the growth of Ni crystals, and the latter remain as small particles. Carbon deposition decreased, while the stability of the catalyst increased.

Among a variety of supports for cobalt catalysts, only MgO proved to be suitable.<sup>40</sup> Following calcination at 800 °C, 24% Co/MgO possessed stable and high activity. The results of X-ray phase analysis suggest that only solid solutions of Co<sub>x</sub>Mg<sub>1-x</sub>O formed at *T* > 800 °C, while heating at *T* < 800 °C yielded Co<sub>3</sub>O<sub>4</sub> and MgCo<sub>2</sub>O<sub>4</sub>.

Catalysts based on the platinum group metals, rhodium in particular, possess high activities and selectivities. Studies of Rh-catalysts have shown<sup>41</sup> that easily reducible supports, such as CeO<sub>2</sub>, Nb<sub>2</sub>O<sub>5</sub>, Ta<sub>2</sub>O<sub>5</sub>, MnO<sub>2</sub>, UO<sub>2</sub>, did not enable as high stability and selectivity as non-reducible supports did, e.g., MgO, γ-Al<sub>2</sub>O<sub>3</sub>, La<sub>2</sub>O<sub>3</sub>, Y<sub>2</sub>O<sub>3</sub> and SiO<sub>2</sub>. Rh/MgO was the catalyst of choice. Presumably,<sup>41,42</sup> its high stability is attributed to the strong interaction of Rh with MgO. The ease of formation of transient compounds in the course of preparation of the supported

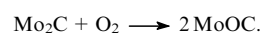
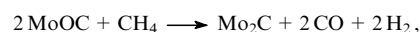
Rh-catalysts decreased in the following order: MgRh<sub>2</sub>O<sub>4</sub> > LaRhO<sub>3</sub> > YRhO<sub>3</sub> > RhTaO<sub>4</sub>.<sup>44</sup> The catalysts Rh/MgO and Rh/La<sub>2</sub>O<sub>3</sub> retained their activities and selectivities for 100 h at 750 °C, while Rh/Y<sub>2</sub>O<sub>3</sub> and Rh/Ta<sub>2</sub>O<sub>5</sub> rapidly deactivated under these conditions, but were active at higher temperatures (900 °C). The stability and selectivity of Rh/Al<sub>2</sub>O<sub>3</sub> increased with an increase in the concentration of rhodium.<sup>46</sup> Rhodium catalysts supported onto hexaaluminates BaAl<sub>12</sub>O<sub>19</sub>, SrAl<sub>12</sub>O<sub>19</sub> and CaAl<sub>12</sub>O<sub>19</sub> were both active and selective, but less stable than Rh/α-Al<sub>2</sub>O<sub>3</sub>. Composite La–Co–Ni-perovskites containing 5% Rh supported on a honeycomb corundum monolith with channels 1 mm in diameter manifested high activity and stability.<sup>47</sup> At 850 °C, carbon deposition on these catalysts was negligibly small.

Bimetallic catalysts Pt–Co/α-Al<sub>2</sub>O<sub>3</sub> manifested higher selectivity in the reaction CO + H<sub>2</sub> than their monometallic platinum analogue;<sup>48</sup> in addition, no coke formation occurred on their surface for 80 h. According to X-ray phase analysis data, Pt and Co phases were formed under the conditions of the catalytic reaction. Doping of Pt/Al<sub>2</sub>O<sub>3</sub> with CeO<sub>2</sub> increased the dispersity of platinum, suppressed deep oxidation and noticeably increased the activity and selectivity of the catalytic system in the POM. This reaction proceeded in accordance with the following redox mechanism:



Partial oxidation of methane over an oxide catalyst (CeO<sub>2</sub>–ZrO<sub>2</sub>) was studied at 400–475 °C under steady-state conditions and in the transient regime.<sup>49</sup> The reaction products contained CO, CO<sub>2</sub>, H<sub>2</sub>, H<sub>2</sub>O, CH<sub>2</sub>O and HCO<sub>2</sub>H and traces of C<sub>2</sub> hydrocarbons. The reaction proceeded *via* the intermediate formation of CH<sub>2</sub>O.

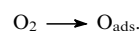
Molybdenum and tungsten carbides constitute a novel class of POM catalysts. Molybdenum carbide, β-Mo<sub>2</sub>C, is active only at elevated pressures; it is unstable at ordinary pressure. The oxidised species MoO<sub>x</sub>C<sub>y</sub> are formed on its surface. The degree of conversion of CH<sub>4</sub> at 900 °C and 0.8 MPa was 83%, and that of O<sub>2</sub> reached nearly 100%, which corresponds to the thermodynamic equilibrium.<sup>50</sup> The POM reaction occurs according to a redox mechanism with involvement of surface oxycarbides:



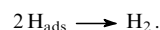
Ni-Containing carbides also proved to be active and stable compounds.<sup>51</sup> The reaction of Ni(NO<sub>3</sub>)<sub>2</sub> with WO<sub>3</sub> yields NiWC<sub>x</sub>, which differs from both NiC and W in catalytic properties.

#### b. Mechanism

In the past years, the mechanism of catalytic POM was studied in considerably more detail than other methane reforming reactions. Numerous data suggest (see a monograph<sup>8</sup> and references cited therein) that this reaction occurs according to two mechanisms, *viz.*, a stepwise mechanism where deep oxidation of methane to CO<sub>2</sub> and H<sub>2</sub>O is followed by steam and carbon dioxide reforming, and a direct mechanism involving complete dissociation of methane and oxygen on the catalyst surface:



This is followed by the interaction of the adsorbed atoms:



The mechanism of POM was studied at the level of an elementary act in the analysis of the reaction of CH<sub>4</sub> with

adsorbed oxygen using the molecular beam method.<sup>51,52</sup> The Pt(110) facet occupied with O atoms with the structure (1 × 2) was irradiated with a beam of CH<sub>4</sub> molecules. CO<sub>2</sub> was formed at surface temperatures below 280 °C, while CO was formed at higher temperatures. This reaction also yielded H<sub>2</sub>, but no H<sub>2</sub>O was observed. Short-lived chemisorbed molecular oxygen was also detected.

With the use of a TAP (Temporal Analysis of Products) reactor for the study of POM over Pt/MgO, dissociation of methane over partly reduced Pt surface was revealed.<sup>53</sup> Adsorption of CO<sub>2</sub> included the formation of a weakly bound precursor that was further converted into a carbonate and a hydrogencarbonate. Under the reaction conditions, CO existed in two adsorption states, *i.e.*, weakly bound (mobile) and chemisorbed. Oxidation of CO occurred on oxygen islets. Under these conditions, surface oxygen is converted into subsurface oxygen and *vice versa*.

Two oxygen species were detected on the surface of Pt-catalyst using a TAP reactor.<sup>54</sup> If CH<sub>4</sub> and O<sub>2</sub> pulses were injected separately onto the catalyst at 600–1000 °C with considerable intervals between the pulses, the products formed were CO (94%) and H<sub>2</sub> (99%) at a degree of conversion of CH<sub>4</sub> of ~90%. Pulses of CH<sub>4</sub> + O<sub>2</sub> resulted in CO<sub>2</sub> and H<sub>2</sub>O as the main products. It was thus concluded that the Pt surface contains stable subsurface oxygen and labile surface oxygen, the latter being involved in deep oxidation.

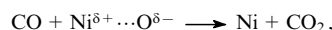
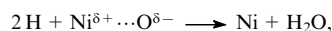
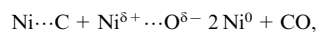
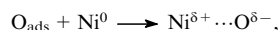
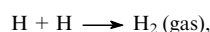
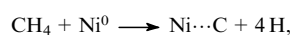
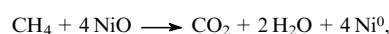
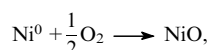
It has been shown<sup>55</sup> that the catalytic activities of the supported catalysts Pt/Ce–ZrO<sub>2</sub> are associated with their abilities to absorb and release oxygen. Removal of carbon from the catalyst is mediated by CeO<sub>x</sub> and proceeds by a redox mechanism.

In the majority of cases, the kinetics of POM is of the first order with respect to methane and of the zero order with respect to oxygen. However, the zero order with respect to methane and an order larger than the first order with respect to O<sub>2</sub> were found over Pd/Si<sub>3</sub>N<sub>4</sub> at 700–900 °C and at larger CH<sub>4</sub>:O<sub>2</sub> ratios.<sup>56</sup> This suggests that CO is a primary product and the catalyst surface is predominantly occupied by carbonaceous compounds rather than by oxygen.

Partial oxidation of methane over Ni/Al<sub>2</sub>O<sub>3</sub> was studied.<sup>57–62</sup> The IR spectra recorded after adsorption of methane at low temperatures revealed the presence of bands at 2998 and 3005 cm<sup>–1</sup>, which were attributed to chemisorbed methane. These bands disappeared upon heating to 250 °C, and CO, H<sub>2</sub>O, CO<sub>2</sub> and H<sub>2</sub> appeared in the gas phase, which suggests that these bands are due to intermediate species. Studies of temperature-programmed decomposition (TPD) of methane and IR spectroscopic studies showed that carbon was predominantly formed over Ni/Al<sub>2</sub>O<sub>3</sub> as a result of the Boudouard reaction.<sup>58</sup> The decomposition rate of CH<sub>4</sub> passed through a maximum at ~700 °C.

The mechanism of POM over Ni/γ-Al<sub>2</sub>O<sub>3</sub> was studied using the pulse method, TPD and XPES.<sup>59</sup> Under the reaction conditions (800 °C), the catalyst contained both Ni and NiO. The reduction of NiO began at 520–560 °C. The dissociation of CH<sub>4</sub> took place on the reduced centres and was followed by the reaction C + O → CO and the reduction of NiO by the carbon atoms. The use of the ion response method showed<sup>60</sup> that POM over Ni/La<sub>2</sub>O<sub>3</sub> results in dissociation of methane and oxygen on Ni-centres to yield a carbide (Ni<sub>x</sub>C) and an oxide (NiO), respectively. Their interaction yields CO.

Dissociation of methane occurs over a reduced catalyst Ni/γ-Al<sub>2</sub>O<sub>3</sub> (direct mechanism), while oxidation of CH<sub>4</sub> to CO<sub>2</sub> and H<sub>2</sub>O and the reduction of NiO to the metal over NiO/Al<sub>2</sub>O<sub>3</sub> proceeded by a sequential mechanism.<sup>61,62</sup> The scheme below takes into account both mechanisms, but the direct mechanism is predominant.

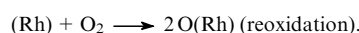
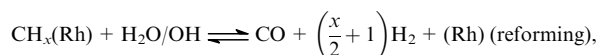
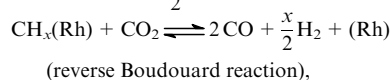
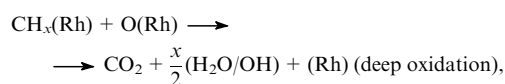
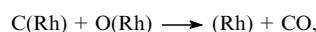
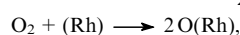
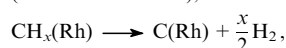
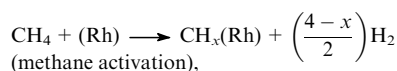


The use of IR diffuse reflectance spectroscopy showed<sup>58</sup> that POM over Ni/La<sub>2</sub>O<sub>3</sub> follows a sequential mechanism, but the direct mechanism is also possible at very low pressures of O<sub>2</sub>. La<sub>2</sub>O<sub>3</sub> forms oxycarbonates of the type La<sub>2</sub>O<sub>2</sub>CO<sub>3</sub>, which favour removal of carbon from the surface of Ni. No decomposition of oxycarbonates occurs in a helium or oxygen atmosphere at 600 °C. This reaction also yields Ni, NiO and NiC phases. Presumably,<sup>63</sup> two routes of this reaction correspond to two limiting steps, *viz.*, dissociation of CH<sub>4</sub> and reaction of NiO with Ni<sub>x</sub>C, which yields CO.

In the majority of studies devoted to the measurement of the kinetic isotope effect (KIE), *i.e.*, the  $k_{\text{CH}_4}/k_{\text{CD}_4}$  ratio, its value was more than unity. For the reaction CH<sub>4</sub> + CO<sub>2</sub> carried out over Pt/α-Al<sub>2</sub>O<sub>3</sub> at 550–650 °C resulting in CO, the  $k_{\text{CH}_4}/k_{\text{CD}_4}$  ratio was > 1; however, no KIE was observed in the direct POM.<sup>64</sup> It was concluded that it is the surface reaction between the adsorbed CH<sub>x</sub> and O species, which yields CO, that is the limiting step, rather than the dissociation of CH<sub>4</sub>. This implies that CO is formed by CDR (CH<sub>4</sub> + CO<sub>2</sub>) or SRM (CH<sub>4</sub> + H<sub>2</sub>O) rather than directly from CH<sub>4</sub> and O<sub>2</sub>.

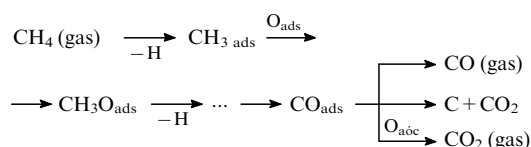
Studies of POM over Rh-foam, Rh/α-Al<sub>2</sub>O<sub>3</sub> or Rh/SiC using a TAP-reactor revealed<sup>65–67</sup> that the reaction occurs according to a sequential mechanism over fully oxidised Rh species, while on reduced species the reaction followed the direct route. With an increase in the O<sub>2</sub> pressure, the responses of CO, CO<sub>2</sub> and H<sub>2</sub>O were shifted towards smaller residence times. The concentrations of the reaction products, *i.e.*, CO and H<sub>2</sub>, increased as oxygen was removed from the catalyst surface.

The results of yet another IR spectroscopic study of the mechanism of POM in a TAP-reactor with Rh black as a catalyst suggest that at 700 °C the inhibition of dissociation of CH<sub>4</sub> was due to saturation of the metal centres with oxygen. Methane dissociated on reduced centres, whereas the newly generated carbon reacted with oxygen to yield CO<sub>2</sub>. The role of active centres was played by partly reduced Rh<sup>+</sup> or dispersed Rh particles. The following mechanism was proposed:



The mechanism of POM over Pt/MgO was also studied using a TAP reactor.<sup>68</sup>

The POM reaction over Rh/SiO<sub>2</sub> was studied using TPD, IR and NMR spectroscopy and XPES.<sup>69</sup> Only the bands corresponding to CO adsorbed on the catalyst surface were observed in the IR spectra. Nevertheless, the following mechanism was proposed:



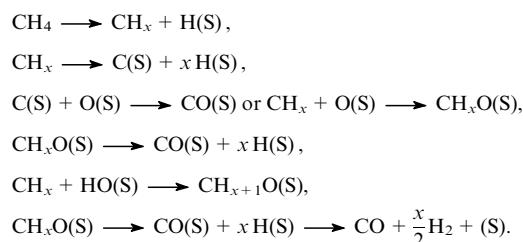
A more detailed study of the POM mechanism by IR and Raman spectroscopy *in situ*, made it possible to monitor CO, CO<sub>2</sub> and other oxygen-containing species on the surface. The Rh-catalysts were found to contain various forms of adsorbed CO, while adsorbed CO<sub>2</sub> and large amounts of O<sup>2-</sup> were detected on the Ru catalysts. It was assumed that the direct reaction is the main route over Rh/SiO<sub>2</sub>, while the consecutive mechanism (combustion → conversion) is more typical of reactions over Ru/SiO<sub>2</sub> and Ru/Al<sub>2</sub>O<sub>3</sub>.<sup>70</sup>

A surface compound with the adsorption band at 2000 cm<sup>-1</sup> was observed in the IR spectra recorded *in situ* for POM over Rh/α-Al<sub>2</sub>O<sub>3</sub> and Rh/δ-Al<sub>2</sub>O<sub>3</sub>.<sup>71</sup> Its concentration correlated with the rate of formation of CO. Presumably, the oxidation of CH<sub>4</sub> occurred *via* the surface hydride H–Rh–CO. Partly reduced oxide clusters with Rh<sup>+</sup> ions played the role of active sites. Hydrogen spillover occurs between Rh and the OH groups of the support. According to the KIE, over Rh/γ-Al<sub>2</sub>O<sub>3</sub> at low (0.05%) concentrations of Rh, POM was mediated by a consecutive (combustion → reforming) mechanism.<sup>72</sup> At high concentrations of Rh (1%) and at temperatures below 500 °C, the mechanism of POM represented a combination of reforming and direct oxidation, while direct dissociation of methane was the dominant mechanism at temperatures above 650 °C.

A difference between the mechanisms of POM over rhodium and iridium catalysts was observed.<sup>73–75</sup> In the pulse injection (2 CH<sub>4</sub> + O<sub>2</sub>) onto Rh/TiO<sub>2</sub> and Rh/Al<sub>2</sub>O<sub>3</sub>, heating occurred of the upper layer of the catalyst, while in the case of Ir/TiO<sub>2</sub> this occurred in the bottom layer. It was concluded that in the former case the reaction proceeded by a consecutive mechanism, which began with the most exothermic step of deep oxidation, whereas in the latter case the mechanism was direct. At 650 °C, Rh/TiO<sub>2</sub> exceeded all other catalysts in the catalytic activity.

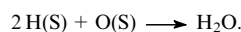
The study of the reaction CH<sub>4</sub> + <sup>18</sup>O<sub>2</sub> over Ru/SiO<sub>2</sub> and Ru/Al<sub>2</sub>O<sub>3</sub> revealed<sup>76</sup> that in both cases POM proceeded by a consecutive mechanism. C<sup>18</sup>O<sup>16</sup>O formed the first followed by C<sup>18</sup>O and C<sup>16</sup>O.

According to the results of IR spectroscopic and isotope exchange (<sup>16</sup>O<sub>2</sub>–<sup>18</sup>O<sub>2</sub>) studies carried out over Ca<sup>2+</sup>-modified Ru/TiO<sub>2</sub> in a transient regime, the interaction of CH<sub>4</sub> with the Ru surface resulting in the formation of CH<sub>x</sub> was a limiting step of POM.<sup>77</sup> The adjacent Ru sites and atomic oxygen are involved in the subsequent abstraction of H from CH<sub>x</sub>. Initially, the CO molecule is formed in the interaction of carbon with oxygen on the Ru sites, while CO<sub>2</sub> is formed upon oxidation of CO on the oxidised sites. The IR spectra revealed the presence of bands corresponding to the OH groups (3600 cm<sup>-1</sup>) and a broad band at 1995 cm<sup>-1</sup> assigned to the carbonyl hydrides H–Ru–CO or H<sub>2</sub>Ru–CO. The following reaction mechanism was proposed:



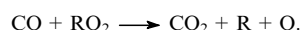
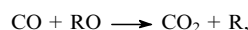
Hereinafter, (S) is the surface. There are two different states for the Ru/TiO<sub>2</sub> catalyst under study, namely, the inactive state at low values of  $P_{\text{CH}_4}/P_{\text{O}_2}$  and the highly active and selective state (the selectivity is up to 90%) at higher values of the  $P_{\text{CH}_4}/P_{\text{O}_2}$  ratio. This selectivity increases with the increase in  $P_{\text{CH}_4}/P_{\text{O}_2}$  and temperature.

Theoretical calculations showed<sup>78</sup> that adsorbed oxygen favours the dissociation of CH<sub>4</sub> on Pt, Cu, Ag and Au, but not on Ru, Os, Ir, Rh or Pd. The differences in the selectivities of H<sub>2</sub> formation are associated with different stabilities of the OH groups on metals. Higher selectivity towards CO<sub>2</sub> is observed on oxygen-enriched surfaces. CO<sub>2</sub> is more readily formed over Ir, Pd and Pt than over Ru, Os and Rh. Low selectivity towards H<sub>2</sub> over Pd and Pt is attributed to the ease of the reaction:



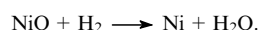
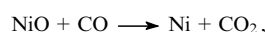
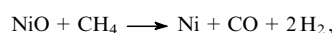
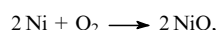
Kinetic simulation of gas-phase reactions over 0.3% Rh/α-Al<sub>2</sub>O<sub>3</sub> under conditions of POM (780–1130 °C, 800 kPa) has been carried out.<sup>79</sup> Altogether, 40 elementary reactions were considered and the importance of the gas-phase reactions in the overall scheme was noted. Free radical uptake by the reactor walls or by an inert diluent (*e.g.*, non-porous Al<sub>2</sub>O<sub>3</sub>) inhibited reforming. In addition to synthesis gas, C<sub>2</sub> hydrocarbons were found in the gas phase. The conversion of O<sub>2</sub> increased, whereas the selectivity towards C<sub>2</sub>H<sub>6</sub> decreased upon dilution of the catalyst with an inert material.

Experiments carried out at the Institute of Chemical Physics of the RAS<sup>80–82</sup> have demonstrated that POM combines, in a complicated manner, both heterogeneous and homogeneous reactions. The so-called ‘hot spot’ formed on porous Ni-foam and Pt/ZrO<sub>2</sub> within a short (<0.01 s) period of time after the loading of the reaction mixture at temperatures above 600 °C, which moved rapidly towards the gas flow into the frontal layer and even beyond it. If a quartz-glass wool pad is placed in front of the catalyst, its heating (~900 °C) exceeded that observed on the catalyst itself. Obviously, the catalyst generates reactive species (most probably, free radicals) which diffused towards the gas flow thereby triggering reactions in the gas-phase before the catalyst layer where the mixture was rich in O<sub>2</sub>, but its content was insufficient to effect true gas-phase combustion. This reaction occurred in selectively and yielded predominantly CO + H<sub>2</sub>, whereas CO<sub>2</sub> was formed in subsequent radical reactions:



The overall selectivity of this process corresponds to the selectivity of the reaction occurring in the pre-catalyst layer and this can be modified, *e.g.*, by placing, in front of the active catalyst layer, a small amount of less reactive MgO where deep oxidation to CO<sub>2</sub> occurs. If the positions of the active catalyst and MgO are changed, no change in the selectivity is observed. No change in the selectivity occurs either if inert SiO<sub>2</sub> is placed in front of the catalyst.

Studies of the reaction CH<sub>4</sub> + O<sub>2</sub> over Pt/ZrO<sub>2</sub> in the presence of <sup>13</sup>CO<sub>2</sub> revealed the absence of the label in the reaction products,<sup>80–82</sup> which suggests that the reaction follows a direct mechanism. However, the formation of <sup>13</sup>CO was observed over porous Ni, which occurs presumably<sup>80</sup> due to the redox reactions involving H<sub>2</sub>, H<sub>2</sub>O, CO, CO<sub>2</sub>.



Among those, only the first two reactions are related to POM. The key factor that determines the differences between the porous Ni and Pt/ZrO<sub>2</sub> is their different abilities to be oxidised by CO<sub>2</sub>. This is probable for Ni, but is unlikely for Pt.

From the results considered in this Section one may state that the results of numerous studies into the mechanism of POM by physical methods, *viz.*, IR and Raman spectroscopy, XPES, the use of TAP-reactors, tracer technique and molecular beam methods, clearly indicate that this process occurs according to

two well-defined mechanisms, *viz.*, direct and consecutive mechanisms. High temperature, short residence time and reduction of catalysts to the metals favour the former. At lower temperatures and prolonged residence times on the oxidised surfaces of supported catalysts, the oxidation of CH<sub>4</sub> occurs predominantly by a consecutive mechanism.

### c. Technological features

The analysis of a kinetic model of POM over Pt/MgO revealed a high degree of heating at the reactor inlet due to deep oxidation of methane.<sup>83</sup> At the inlet temperature of 600 °C and the linear velocity of 3 m s<sup>-1</sup>, the 'hot spot' was formed in the frontal layer with the temperature of up to 1400 °C at 0.1 MPa and up to 2200 °C at 2.5 MPa. The 'hot spot' temperature can be reduced using supports with high thermal conductivities (down to 1100 °C at 0.1 MPa and down to 1800 °C at 2.5 MPa).

An original reactor with a moving catalyst layer for conducting pilot-scale POM has been described.<sup>84</sup> Gas from a small nozzle enters the layer of a powdered catalyst (Ni/La<sub>2</sub>O<sub>3</sub>/Al<sub>2</sub>O<sub>3</sub>) to produce the spouted bed. The ejectile particles of the catalyst come in contact with the gas and fall down. The residence time is <0.5 s, the temperature is 850–1000 °C, the pressure is 0.2–0.8 MPa, the particle size varies from 120 to 150 µm.

The use of oxygen in POM is a crucial factor responsible for the high cost of synthesis gas and the explosive risk of the process. Therefore, considerable attention is currently given to technologies based on the use of heat-resistant O<sub>2</sub>-permeable ceramic membranes. This makes it possible to combine the generation of synthesis gas and air separation and to avoid the use of expensive oxygen-generating equipment. According to the existing estimates, this technology saves from 20% to 50% of funds. The membranes must be strong, one of their surfaces must withstand temperatures above 900 °C in a highly oxidative atmosphere, whereas the other surface must be resistant to highly reducing media. In addition, the membranes must be resistant to poisoning, corrosion, deformation and differential pressure. Non-porous membranes were designed based on, *e.g.*, perovskites ABO<sub>3</sub> with variable charges, where the size of one cation is comparable to that of the anion, while the size of the second cation is much smaller.<sup>85</sup> Replacement of one cation by another with a lower valence leads to the disbalance of charges and generates a vacancy [ ]<sub>O<sub>2</sub></sub><sup>-</sup>. The ion flux through the membrane is proportional to  $(\delta/L) \times (P_{O_2})_1 / (P_{O_2})_2$ , where  $\delta$  is the membrane area,  $L$  is its thickness and  $(P_{O_2})_1 / (P_{O_2})_2$  is the concentration gradient of O<sub>2</sub> through the membrane. Membranes with improved characteristics exhibit a permeability (diffusion) plateau in the temperature range from 650 to 1000 °C. The appearance of hot spots and the generation of temperature gradients in such membranes is not hazardous. A high degree of conversion was achieved over a non-perovskite membrane (SrFeCo<sub>5</sub>O<sub>x</sub>) at 750–850 °C.

In 1997, five manufacturing companies (Amoco, BP, Sasol, Statoil and Praxair) launched an extensive research project devoted to the study of oxygen-permeable membranes for the preparation of hydrogen by the OTM Syngas (Oxygen Transport Membrane Synthesis Gas) process. The initial step of these studies is now complete.<sup>86,87</sup> Yet another research group (headed by Air Products Ltd.) including ChevronTexaco, Ceramtec and other partners, developed, in collaboration with the U.S Department for Energy, a technology for large-scale production of Ion Transport Membranes (ITM) for obtaining synthesis gas. These ceramic non-porous multicomponent membranes are prepared from metal oxides [perovskites (La<sub>x</sub>Ce<sub>1-x</sub>)FeO<sub>3-y</sub>] with supported noble metals, they possess both ion and electron conductivities. The membranes operate at temperatures above 800 °C, at pressures up to ~30 atm and very high gas flow rates manifesting high selectivity towards oxygen. Considerable progress has been achieved in the choice of materials, design, manufacture of membranes and support of catalysts, which is prerequisite for the successful commercialisation of the ITM Syngas technology.

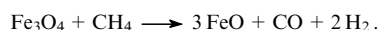
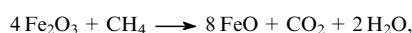
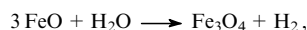
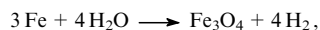
The economic estimates testify to high potentials of this technology.<sup>88</sup>

Hydrogen-permeable membranes constitute yet another class of membranes for POM.<sup>89,90</sup> As for the O<sub>2</sub>-permeable membranes, the addition of water vapour to CH<sub>4</sub> efficiently suppressed coke formation and increased the yield of the product. Hydrogen removal shifts the equilibrium and enables a high degree of conversion. Under specific conditions, pure hydrogen can be prepared containing no CO admixture. The use of membranes prepared from 5 µm-thick Pd/Ag/Al<sub>2</sub>O<sub>3</sub> films also gave good results: at 578 °C, the degree of conversion exceeded the equilibrium value by 20%.

High production costs of synthesis gas and hydrogen stimulated the search for alternative methods of their preparation. Redox methods are based on separate interactions. Metals react with water vapour to give oxides and hydrogen, while the interactions of oxides with methane yield CO<sub>2</sub>, H<sub>2</sub>O and the metal. Such a reaction scheme is actually a modification of a classical iron steam procedure where hydrogen has been prepared by the reaction of iron with water vapour and iron oxide has been reduced by the producer gas. Nowadays, it is methane that is used as a reducing agent.

A cyclic POM process over the perovskite catalyst La<sub>1-x</sub>Sr<sub>x</sub>FeO<sub>3</sub> has been studied.<sup>86</sup> The catalyst circulated between two reactors at 800–900 °C. In one reactor, methane was oxidised into synthesis gas using the lattice oxygen, while in the second reactor perovskite was reoxidised by air. The duration of each cycle was several minutes. The main advantages of this cyclic process are explosion safety and exclusion of oxygen-generating units. Later, studies of a similar cyclic process over Ce, Zr, La and Sm oxides with supported Pt was carried out at the Institute of Catalysis of the Siberian Branch of the RAS.<sup>55</sup>

Some of the results on selective POM were reported at the 6th Natural Gas Conversion Symposium. Among various catalytic systems of the metal–oxide type explored by specialists of Snamprogetti, a pure iron–iron oxides system proved to be the system of choice.<sup>91</sup> The following reactions occur:



The Snamprogetti technology enables the preparation of pure hydrogen without intermediate isolation of synthesis gas. Modified oxides Cu–Cr–FeO<sub>x</sub> and Cu–Ni–FeO<sub>x</sub> were also used for this purpose.<sup>92</sup> Additives to iron oxide decrease the temperature of FeO<sub>x</sub> reduction from 600–700 to 300–400 °C and prevent sintering of the oxide. Copper and nickel also generate sites where the activation of methane takes place.

In studies of a similar system (PbO–Pb), the kinetics of PbO/Al<sub>2</sub>O<sub>3</sub> reduction by methane in the temperature range 760–927 °C was investigated.<sup>93</sup> The reaction order with respect to methane was equal to 1; the apparent activation energy was ~40 kcal mol<sup>-1</sup>. The degree of PbO reduction of 0.5–0.6 was the threshold as regards the selectivity of methane conversion: at lower degrees of reduction, CO<sub>2</sub> formed exclusively, while at higher degrees, the formation of CO was predominant.

### 3. Oxidation of methane at millisecond contact times

Oxidative catalytic reactions that occur at short (millisecond) contact times ( $\tau$ ) were known and have found industrial application (*e.g.*, the Andrussov reaction: NH<sub>3</sub> + CH<sub>4</sub> + O<sub>2</sub>) since the first half of the past century. Systematic studies of these reactions were carried out by Schmidt,<sup>94,95</sup> who has demonstrated advantages of hydrocarbon oxidation (including POM) over solid catalysts (gauzes, foamy metal blocks, open-channel blocks, *etc.*) at small contact times and, correspondingly, at high volume flow rates, which ensured very high productivity.

The catalytic oxidation of hydrocarbons over solid catalysts at low  $\tau$  was especially efficient in simple small-size reactors; no carbon formation occurred.<sup>94,95</sup> High temperature and high concentration gradients are the characteristic features of such processes. As a rule, the temperature gradients are of the order of  $10^6 \text{ deg s}^{-1}$  and  $10^5 \text{ deg cm}^{-1}$ . These processes are autothermic and proceed under virtually adiabatic conditions, since the energy released in the exothermic reactions causes rapid heating of the gases and the catalyst to  $\sim 1000^\circ\text{C}$ , whereas the heat release rate is far too high to enable effective cooling through the reactor walls.

The axial temperature profile in a millisecond reactor depends on the ratio of gas-phase and surface reactions. Very often, the reaction occurs in a two-zone mode; but the reactions on blocks and gauzes follow different mechanisms. In the first metal layers (1  $\mu\text{m}$  thick) of block catalysts, highly exothermic oxidation of hydrocarbons into  $\text{CO}_2$  and  $\text{H}_2\text{O}$  is accompanied by heating to temperatures above  $1000^\circ\text{C}$ . If methane is used as a hydrocarbon, the reaction yields synthesis gas. Endothermic reactions, *e.g.*, direct dehydrogenation of  $\text{C}_2\text{H}_6$  to  $\text{C}_2\text{H}_4$ , take place on the remaining solid. The addition of small amounts of hydrogen to an ethane–oxygen mixture resulted in 85% selectivity towards  $\text{C}_2\text{H}_4$  over Pt–Sn-catalysts. At millisecond  $\tau$ , only part of the molecules has sufficient time to come in contact with the surface of gauze-like or spiral catalysts, to be heated up to  $\sim 900\text{--}1000^\circ\text{C}$  and oxidised. The rest of the molecules ‘skip’ the catalyst without being heated and interact with heated particles in the post-catalyst zone at intermediate temperatures. The formation of peroxy radicals and hydroperoxides is possible in this case.

At short contact times, the conditions for gas-phase reactions are difficult to predict because of high axial and radial concentration and temperature gradients. However, the switch from millisecond laboratory-scale reactors to industrial-type reactors is believed<sup>94</sup> to pose no problems. It is merely necessary to increase the diameter of the reactor with retention of the linear gas flow rate. It is suggested that the increase in the reactor diameter to 30 cm at a flow rate of  $10^6 \text{ h}^{-1}$  enables the daily output of several tons, while in reactors with a diameter of up to 180 cm the daily productivity can reach 1000 tons.

Non-linear processes, such as self-oscillations and autowaves in POM over nickel catalysts, were discovered by researchers of the Institute of Chemical Physics of the RAS.<sup>80</sup> The analysis of these phenomena prompts a conclusion that a crucial role in their appearance is played by oxygen and carbon accumulated in the catalyst.

A reactor based on a ceramic block with microchannels coated with  $\text{Al}_2\text{O}_3$  and an Ni–Co–Cr–O alloy has been developed at the Institute of Catalysis of the Siberian Branch of the RAS.<sup>96</sup> The catalyst manifested high thermal and mechanical stability under conditions of high-temperature POM.

Stable and complete conversion of methane was achieved at  $800^\circ\text{C}$  and a linear gas flow rate of  $0.75\text{--}1.50 \text{ m s}^{-1}$  in a reactor with a fluidised bed of a catalyst ( $\text{Ni}/\alpha\text{-Al}_2\text{O}_3$ ) designed for small contact times,<sup>97</sup> the yields of  $\text{H}_2$  and CO constituted 97% of the thermodynamically permissible values. The design of a fluidised bed reactor has been described elsewhere.<sup>98</sup>

The mechanism of POM over a Pt gauze at  $800\text{--}1100^\circ\text{C}$  was studied in a TAP reactor.<sup>99</sup> Experiments with alternating pulses of  $\text{CH}_4$  and  $\text{O}_2$  showed that CO and  $\text{H}_2$  are the primary reaction products of  $\text{CH}_4$  with  $\text{O}_2$  over Pt. In the absence of gas phase  $\text{O}_2$ , the maximum attainable selectivities to CO and  $\text{H}_2$  were 97% and 96%, respectively.

At low surface oxygen concentrations, oxygen incorporated in the Pt bulk diffuses to the surface and reacts with carbon to form CO, *i.e.*, a direct mechanism operates.

The oxidation of a microstructure honeycomb-like catalyst prepared from rhodium foil<sup>100</sup> in the presence of oxygen was carried out at 2 MPa. High thermal conductivity of Rh provided more efficient (in comparison with Pt–Rh gauzes) heat dissipation. The temperature of the catalyst under the reaction conditions

reached  $1080\text{--}1200^\circ\text{C}$ . The analysis of electron micrographs revealed signs of Rh corrosion upon POM.

The oxidative coupling and partial oxidation of methane were studied at  $\tau < 5 \mu\text{s}$ .<sup>101</sup> Over  $\text{Rh}/\alpha\text{-Al}_2\text{O}_3$ , the selectivity towards  $\text{C}_2$  products was rather low, but increased to 20% over  $\text{Pt}/\alpha\text{-Al}_2\text{O}_3$ , acetylene being the major product. A peculiar temperature profile along the catalyst layer is believed to be the driving force of this process: the inlet temperature was  $200^\circ\text{C}$ , and the outlet temperature was as high as  $\sim 1500^\circ\text{C}$ .<sup>102</sup> Homogeneous reactions predominate at high temperatures. The scheme of methane oxidation into synthesis gas proposed in this study included 277 homogeneous and 19 heterogeneous steps. The conclusions based on the analysis of this model were compared with the experimental results obtained at  $750\text{--}1150^\circ\text{C}$  and pressures of up to 3.5 MPa. It was established that homogeneous reactions were predominant at  $\tau > 10 \text{ ms}$ , at high temperatures and at high pressures. The adiabatic heating reached  $1365^\circ\text{C}$ , while the true ‘hot spot’ temperature in the catalyst layer measured by the emission thermography may be even higher.

It was shown<sup>103</sup> that the selectivity towards CO and  $\text{H}_2$  was as high as 95% in POM and CDR over  $\text{Rh}/\text{MgO}/\text{Al}_2\text{O}_3$  at  $750^\circ\text{C}$  and at  $\tau = 12 \text{ ms}$ . This catalyst appeared to be more selective than  $\text{Rh}/\text{MgO}/\text{Al}_2\text{O}_3$ , but the latter was more efficient in the activation of  $\text{CH}_4$  and less efficient in the activation of  $\text{O}_2$ .

The temperature of the catalyst ( $> 650^\circ\text{C}$ ) over  $\text{Rh}/\alpha\text{-Al}_2\text{O}_3$  at contact times  $< 12 \text{ ms}$  was high enough to initiate POM or even carbon-dioxide reforming of methane. No synthesis gas was formed at  $\tau > 12 \text{ ms}$ .

Studies into methane oxidation into synthesis gas over a Pt-gauze in the temperature range from  $680$  to  $930^\circ\text{C}$  and at variable contact times ( $0.2\text{--}0.02 \text{ ms}$ ) revealed that the conversion of  $\text{CH}_4$  and  $\text{O}_2$  was limited by their transport to the catalyst, while the selectivity towards CO was determined by the reaction on the surface.<sup>104</sup> Hydrogen formation took place only at  $1000^\circ\text{C}$ .

## 4. Carbon dioxide reforming of methane

### a. Catalysts

Carbon dioxide reforming of methane (CDR) is carried out at higher temperatures ( $\sim 900^\circ\text{C}$ ) than SRM or POM. The interest in this reaction stems from the possibility of obtaining synthesis gas with the composition  $\text{CO}:\text{H}_2 = 1:1$ , which is required for the synthesis of dimethyl ether.

Similar to SRM and POM, supported nickel catalysts are used for CDR most often. In addition, catalysts based on Co, Fe, Pt, Pd, Rh and Ir have also found application for this purpose, as in SRM and POM processes. In numerous studies, the activities of metal catalysts on various supports were compared. Basic supports such as  $\text{MgO}$ ,  $\text{La}_2\text{O}_3$ , *etc.*, better withstand poisoning than acidic ones and presumably are involved in the activation of  $\text{CO}_2$ . Bimetallic catalysts exceed monometallic catalysts in both the activity and stability. It was found<sup>105,106</sup> that the catalytic activities and stabilities of 2%  $\text{Ni}/\text{La}_2\text{O}_3$  and 2%  $\text{Ni}/\text{ZrO}_2$  increased substantially upon promotion with 0.2% Rh.

Japanese investigators<sup>107,108</sup> demonstrated very high activity of the catalyst  $\text{Ni}_{0.03}\text{Mg}_{0.97}\text{O}$  and its resistance against carbon deposition. A comparison of catalytic properties of solid solutions of  $\text{Ni}_x\text{Mg}_{1-x}\text{O}$  and supported  $\text{Ni}/\text{MgO}$  catalysts revealed that significantly smaller amounts of carbon are produced over the former, which can be attributed to the small size of Ni particles, surface basicity and interaction of Ni with the support. The size of Ni particles in  $\text{Ni}_{0.03}\text{Mg}_{0.97}\text{O}$  was 3–4 nm; that in  $\text{Ni}_{0.10}\text{Mg}_{0.90}\text{O}$  and in  $\text{Ni}/\text{MgO}$  was 6–8 nm and 3–10 nm, respectively. The degree of reduction of the metal in 30%  $\text{Ni}/\text{MgO}$  was higher than in 10%  $\text{Ni}/\text{MgO}$ . According to X-ray phase analysis data, the catalyst comprised three phases, *viz.*, Ni,  $\text{MgO}$  and a solid solution with high content of NiO. The formation of carbon nanotubes was observed over  $\text{Ni}/\text{MgO}$ . The least changes during operation occurred in  $\text{Ni}_{0.03}\text{Mg}_{0.97}\text{O}$ .<sup>109</sup>

Researchers from the Institute of Chemical Physics of the RAS and the Institute of Petrochemical Processes of the Azerbaijan

Academy of Sciences established that CDR occurred over oxide Mn-containing catalysts.<sup>110</sup> Later, supported metal catalysts came to be used for this reaction. The reaction  $\text{CH}_4 + \text{CO}_2$  was studied over various catalysts [ $\text{Ni}/\alpha\text{-Al}_2\text{O}_3$ ,<sup>111</sup>  $\text{Co}/\alpha\text{-Al}_2\text{O}_3$  (see Ref. 112) and  $\text{Pt}/\alpha\text{-Al}_2\text{O}_3$  (see Ref. 113)] in flow and pulse regimes using differential scanning calorimetry. Treatment of  $\text{NiO}/\text{Al}_2\text{O}_3$  with hydrogen at 700 °C resulted in partial reduction of  $\text{NiO}$  to  $\text{Ni}$ . Methane virtually did not react with oxidised  $\text{Ni}$  or  $\text{Co}$ , but interacted actively with the reduced catalyst to give  $\text{H}_2$  and surface carbon. With the lattice oxygen, the latter reacted slowly, but its reaction with adsorbed oxygen was fast. A fast rate was also characteristic of the reaction of  $\text{CO}_2$  with surface carbon to yield  $\text{CO}$ , while the reaction with the metal ( $\text{M}$ ) resulting in  $\text{CO}$  and  $\text{MO}$  was slow. It may thus be concluded that the main route of CDR over  $\text{Ni}/\alpha\text{-Al}_2\text{O}_3$  and  $\text{Co}/\alpha\text{-Al}_2\text{O}_3$  includes dissociative adsorption of  $\text{CH}_4$  resulting in  $\text{C} + 2\text{H}_2$  and the reverse Boudouard reaction of the carbon formed with  $\text{CO}_2$ . The side routes include the reactions of  $\text{CH}_4$  chemisorption products with oxygen incorporated into a catalyst and dissociative adsorption of  $\text{CO}_2$  on the metal. A competitive reaction of surface carbon with adsorbed oxygen reduced the degree of conversion of  $\text{CO}_2$  in the main reaction; therefore, the rate of the reaction  $\text{CH}_4 + \text{CO}_2$  decreased in the presence of  $\text{O}_2$  due to oxygen poisoning of the catalyst.

A broad range of catalysts based on  $\text{Ni}/\text{MgO}$  has been studied.<sup>114</sup> High activity was observed for  $\text{Ni}/\text{MgO}$  doped with  $\text{CeO}_2$ ,  $\text{CuO}$ ,  $\text{Cr}_2\text{O}_3$  and  $\text{MnO}_2$ . Under conditions of catalysis, these dopants underwent oxidation or reduction.  $\text{Ni}/\text{MgO}-\text{Cr}_2\text{O}_3$  proved to be the most active catalyst. The degree of conversion over the catalyst 6%  $\text{Ni}-1\%$   $\text{Cr}_2\text{O}_3/\text{MgO}$  reached virtually the equilibrium value even at 700 °C. Even small amounts of  $\text{Ni}$  and  $\text{Cr}_2\text{O}_3$  had a promoting effect on each other. The  $\text{Co}/\alpha\text{-Al}_2\text{O}_3$  system manifested high activity and stability in an analogous study<sup>115</sup> of supported cobalt catalysts.

The catalyst 5%  $\text{Ni}/\text{CaO}-\text{Al}_2\text{O}_3$  prepared by deposition of nickel onto the preformed layer of aluminate  $\text{CaAl}_2\text{O}_4$  manifested higher activity and was less subject to carbon deposition than the catalyst prepared by simple mixing of  $\text{Ca}$ ,  $\text{Ni}$  and  $\text{Al}$  salts.<sup>116</sup> The differences observed were attributed to the formation of various amounts of  $\text{NiO}$  on the surface of these catalysts. The catalyst  $\text{Ni}/\text{CaO}-\text{SiO}_2$  used in the study of CDR at 650 °C was prepared by impregnation of  $\text{CaO}$ -modified  $\text{SiO}_2$  with  $\text{Ni}$  salts.<sup>117</sup> This procedure increased the metal dispersion. The carbon fibres formed caused deactivation of the catalyst.

The oxide  $\text{ZrO}_2$  in the catalyst  $\text{Ni}/\text{ZrO}_2/\text{MgO}$  stabilised nickel on the support.<sup>118</sup> The reduction temperature of  $\text{NiO}$  increased with the increase in the  $\text{MgO}$  content. In the absence of  $\text{MgO}$ , the catalyst  $\text{Ni}/\text{ZrO}_2$  was inactive, whereas the addition of only 1%  $\text{MgO}$  brought the conversion to virtually the equilibrium value.

Potassium promotes the activity of  $\text{Ni}/\text{Al}_2\text{O}_3$ . The addition of potassium had little effect on the dissociation rate of  $\text{CO}_2$  and the reaction rate of  $\text{CH}_x$  with  $\text{O}_{\text{ads}}$ .<sup>119</sup> Potassium plays a role in dividing the  $\text{Ni}$  surface into small ensembles, thus carbon deposition is suppressed. The addition of  $\text{MnO}$  also inhibited carbon deposition.<sup>120</sup> The catalyst  $\text{Ni}-\text{MnO}_x/\text{Al}_2\text{O}_3$  prepared by co-precipitation was more active than  $\text{Ni}-\text{MnO}_x/\gamma\text{-Al}_2\text{O}_3$  prepared by impregnation and the above-described  $\text{Ni}_{0.03}\text{Mg}_{0.97}\text{O}$ .

The stable catalyst  $\text{Ni}/\text{Al}_2\text{O}_3$  was prepared by repeated deposition of carbon from methane and subsequent elimination of carbon by treatment with carbon dioxide.<sup>121</sup> The assumption that active sites of the catalyst differ from those where carbon filaments are formed was the idea of this method. The repetition of the deposition-elimination cycles decreased the overall carbonisation.

The catalyst  $\text{Ni}/\text{CeO}_2-\text{Al}_2\text{O}_3$  manifested higher activity than  $\text{Ni}/\gamma\text{-Al}_2\text{O}_3$  and  $\text{Ni}/\text{CeO}_2$ .<sup>122, 123</sup> The addition of  $\text{CeO}_2$  suppressed the interaction of  $\text{Ni}$  with the support, facilitated reduction and increased the dispersion of  $\text{Ni}$ . Owing to the addition of  $\text{CeO}_2$ , the carbon atom reacts more efficiently with oxygen-containing sub-

stances following dissociation of adsorbed  $\text{CO}_2$  eventually resulting in a reduction of coke formation.

Perovskites  $\text{La}_{1-x}\text{Fe}_x\text{Fe}_{1-x}\text{O}_y$  effect complete conversion of  $\text{CH}_4$  and  $\text{CO}_2$  at 800 °C and are highly reactive catalysts for CDR.<sup>124</sup> Under conditions of the catalytic process, the mixed perovskite-type structures are destroyed, but at  $x < 0.5$  these catalysts can be recovered by calcination.  $\text{Ni}-\text{Fe}$  alloys with variable compositions were formed at  $0.3 < x < 0.8$ . It was suggested that fusion prevented poisoning of the catalyst with carbon due to inhibition of carbon diffusion through  $\text{Ni}$  particles.

The catalytic activities and resistance of the perovskites  $\text{La}_{1-x}\text{Sr}_x\text{NiO}_3$  ( $x = 0.01, 0.1$ ) and  $\text{La}_{2-x}\text{Sr}_x\text{NiO}_4$  ( $x = 0.1$ ) against coke formation at 600 °C and ambient pressure depended on the type and stoichiometry of the perovskite.<sup>125</sup> Thus  $\text{LaNiO}_3$  manifested high catalytic activity, while  $\text{LaNiO}_4$  was totally inactive.  $\text{La}_{0.9}\text{Sr}_{0.1}\text{O}_3$  and  $\text{La}_{1.8}\text{Ni}_{0.2}\text{NiO}_4$  manifested the highest activity among strontium-substituted catalysts. Under CDR conditions, the catalyst was converted into a mixture of  $\text{La}_2\text{O}_3\text{CO}_2$  and  $\text{SrCO}_4$  with metallic  $\text{Ni}$  (X-ray phase analysis data). This may result from replacement of the lattice oxygen, which is accelerated in a reducing atmosphere at a ratio  $\text{CH}_4:\text{CO}_2 = 1:1$ . Presumably, high activity was determined by the presence of two sites, *viz.*,  $\text{La}_2\text{O}_3$  responsible for the activation of  $\text{CO}_2$ , and  $\text{Ni}$  responsible for the activation of  $\text{CH}_4$ .

CDR over  $\text{Ni}$  catalysts supported on  $\alpha\text{-Al}_2\text{O}_3$ ,  $\gamma\text{-Al}_2\text{O}_3$ ,  $\text{Al}_2\text{O}_3\cdot\text{SiO}_2$ ,  $\text{SiO}_2$ ,  $\text{MgO}$ ,  $\text{ZrO}_2$  and modified with transition metals ( $\text{Co}$ ,  $\text{Cu}$ ,  $\text{Fe}$ ) and alkaline promoters ( $\text{Na}$ ,  $\text{K}$ ) has been studied.<sup>126</sup> The catalytic activities of  $\text{Ni}/\alpha\text{-Al}_2\text{O}_3$  and  $\text{Ni}/\gamma\text{-Al}_2\text{O}_3$  were very similar, but coke formation over the latter was faster by virtue of its acidic properties. According to the resistance against coke formation, the supports are arranged in the following order:  $\alpha\text{-Al}_2\text{O}_3 > \gamma\text{-Al}_2\text{O}_3 > \text{SiO}_2 > \text{Al}_2\text{O}_3\cdot\text{SiO}_2 > \text{ZrO}_2 > \text{MgO}$ . The activities of the catalysts doped with transition metals decreased in the following order:  $\text{Ni}-\text{Co} > \text{Ni} > \text{Ni}-\text{Cu} > \text{Ni}-\text{Fe}$ , while those of the catalysts containing alkaline promoters appeared as  $\text{Ni} > \text{Ni}-\text{Na} > \text{Ni}-\text{K}$ . Metal additives inhibit reduction of  $\text{Ni}$ , but enhance its dispersion. After 12 h operation in the absence of a modifier, the  $\text{Ni}$ -catalyst was completely deactivated, whereas the activity of the  $\text{Ni}-\text{Co}$ -catalyst increased noticeably with no coke formation. Cobalt catalysts were comparable to nickel catalysts in catalytic activity and stability.<sup>126</sup>  $\text{Co}/\text{MgO}/\text{SiO}_2$  containing 50%  $\text{MgO}$  being the most active. The activity characteristics of  $\text{Co}/\gamma\text{-Al}_2\text{O}_3$  were similar to those of  $\text{Ni}/\gamma\text{-Al}_2\text{O}_3$ . The stabilities and activities of  $\text{Co}$  catalysts depended on the concentration of  $\text{Co}$  and calcination temperature. At high cobalt content, deactivation occurred due to carbon deposition.

The activity of  $\text{Co}/\text{TiO}_2$  strongly depended on the reduction temperature.<sup>127</sup> Only the catalyst reduced at  $T > 850$  °C manifested high activity and stability. Doping with  $\text{Pt}$  and  $\text{Ru}$  improved these characteristics.

The activities and stabilities of catalysts prepared by support of  $\text{Co}$ ,  $\text{Ni}$ ,  $\text{Ru}$ ,  $\text{Rh}$ ,  $\text{Ir}$  and  $\text{Pt}$  on  $\text{SiO}_2$  or  $\text{Al}_2\text{O}_3$  at 400–750 °C have been studied.<sup>128</sup> The nature of the metal and, to a lesser degree, properties of the support were of critical importance. At 450 °C, deactivation was only observed over supported iridium, while at 750 °C other metals were deactivated due to sintering.  $\text{Ni}$ ,  $\text{Co}$  and  $\text{Rh}$  were found to be the most resistant to deactivation. The activities of the catalysts supported on  $\text{Al}_2\text{O}_3$  decreased in the following order:  $\text{Rh} > \text{Ni} > \text{Ir} > \text{Ru} > \text{Pt} > \text{Co}$ ; the catalysts supported on  $\text{SiO}_2$  manifested much lower activities.

Because of lesser solubility of carbon in the platinum-group metals, these were more active in CDR than  $\text{Fe}$ ,  $\text{Co}$  and  $\text{Ni}$  and suffered less from carbon deposition.<sup>129</sup> The CDR was performed over  $\text{Ni}$ -,  $\text{Co}$ -,  $\text{Ru}$ -,  $\text{Rh}$ -,  $\text{Ir}$ - and  $\text{Pt}$ -catalysts supported on  $\text{SiO}_2$  and  $\text{Al}_2\text{O}_3$  at low and moderate temperatures (400–800 °C). At 500 °C, only iridium catalysts were deactivated, while at 800 °C many catalysts underwent deactivation due to sintering.  $\text{Ni}$ -,  $\text{Co}$ - and  $\text{Rh}$ -catalysts manifested the highest stabilities. The activities of the tested catalysts decreased in the following order:



Rh > Ni > Ir > Ru > Pt. Catalysts supported on SiO<sub>2</sub> were much less active.

At 600 °C, Pt/ZrO<sub>2</sub>, Rh/ZrO<sub>2</sub> and Rh/γ-Al<sub>2</sub>O<sub>3</sub> manifested high activities and stabilities in CDR.<sup>130</sup> The activity of Pt/ZrO<sub>2</sub> was determined by the available perimeter of the supported platinum. In contrast, the activities of Rh/ZrO<sub>2</sub> and Rh/γ-Al<sub>2</sub>O<sub>3</sub> depended on the concentration of surface Rh atoms rather than on the nature of the support. Pt/SiO<sub>2</sub> manifested a much lower activity. It was suggested that ZrO<sub>2</sub> favours the dissociation of CO<sub>2</sub> and, as a consequence, elimination of carbon.

As in POM, molybdenum and tungsten carbides were active in CDR at high pressures and at elevated temperatures.<sup>131–133</sup> According to activities at 950 °C and 0.8 MPa, the metal carbides are arranged in the following order: Mo<sub>2</sub>C ~ VC ~ WC > NbC > TaC. The supported molybdenum carbides could be arranged in the following order of stabilities: Mo<sub>2</sub>C/Al<sub>2</sub>O<sub>3</sub> > Mo<sub>2</sub>C/SiO<sub>2</sub> > Mo<sub>2</sub>C/TiO<sub>2</sub>. At low pressures, the oxidation of carbides resulted in their deactivation. Among other carbide catalysts (Mo<sub>2</sub>C/SiO<sub>2</sub>, WC/SiO<sub>2</sub>, Mo<sub>2</sub>C/Al<sub>2</sub>O<sub>3</sub> and Mo<sub>2</sub>C/ZrO<sub>2</sub>), the former manifested the highest activity in CDR.<sup>134</sup> The conversion of Mo<sub>2</sub>C into MoO<sub>3</sub> resulted in the deactivation of the catalyst. The activity of Mo<sub>2</sub>C per mass unit of the catalyst was one or two orders of magnitude lower than the activities of metal catalysts due to its smaller specific surface.

However, despite extensive studies into catalytic systems, the overwhelming majority of papers are devoted to the analysis of only one type of active and stable CDR catalysts, *viz.*, Group VIII metals (most often, Ni and Co supported on basic oxides, such as MgO, MnO and CaO). Rhodium catalysts possess the highest activities and stabilities, but they are very expensive. Of the oxide supports, preference should be given to moderately basic oxides that can undergo oxidation–reduction, *e.g.*, MnO. In the metal–metal oxide pair, the CH<sub>4</sub> is activated by the metal, while the oxide activates the CO<sub>2</sub> molecule.

## b. Kinetics

The kinetic aspects of CDR on the material presented in more than 60 papers were discussed in 1996.<sup>135</sup>

The values of the activation energy,  $E_a$ , determined from the consumption of CH<sub>4</sub> and CO<sub>2</sub> vary from 30 to 350 and from 35 to 130 kJ mol<sup>−1</sup>, respectively, while those determined from the yields of CO and H<sub>2</sub> are 30–318 and 38–250 kJ mol<sup>−1</sup>, respectively. The largest out-of-order value of  $E_{CH_4}$  was noted for reactions carried out over Re/Al<sub>2</sub>O<sub>3</sub> (350 kJ mol<sup>−1</sup>). It is suggested<sup>135</sup> that the values of  $E_a$  obtained for the reaction carried out over Pt/MgO<sup>136</sup> should be excluded from the reliable data. In this study,  $E_{CO} > E_{CH_4}$ , whereas in all other papers this ratio was the opposite. Also,  $E_{CO}$  was found to be equal to 921 kJ mol<sup>−1</sup>, although this value usually amounts to 230 ± 20 kJ mol<sup>−1</sup>, *i.e.*, similar to the values of the energy of activation of cracking of CH<sub>4</sub> over Ni(110) and Ni(111) (233 ± 27 and 221 ± 20 kJ mol<sup>−1</sup>, respectively). The  $E_a$  values for the catalytic reactions over noble metals are usually close to 314–337 kJ mol<sup>−1</sup>. The apparent energy of activation strongly depends on the degree of the steam conversion of CO, which seems to be manifested in larger  $E_{CO}$  upon an increase in the space velocity. The degree of conversion decreases considerably, and the effect of the reverse reaction, *i.e.*, hydrogenation of CO to CH<sub>4</sub>, becomes less significant.

The data on the activities of different catalysts expressed as the reaction turnover number (t.n.) at 450 °C are documented.<sup>135</sup> The t.n. values obtained by extrapolation vary from 0.1 to 1, but are higher for Ru/TiO<sub>2</sub> (4.3–7.3) and Ru/Al<sub>2</sub>O<sub>3</sub> (1.5–4.3) catalysts. The t.n. values for reactions over Rh crystals on different supports decrease in the following order:<sup>137</sup> ZrO<sub>2</sub> > TiO<sub>2</sub> > Al<sub>2</sub>O<sub>3</sub> > La<sub>2</sub>O<sub>3</sub> ~ SiO<sub>2</sub> > MgO.

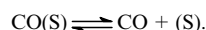
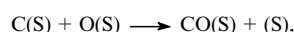
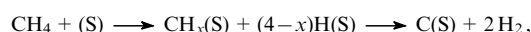
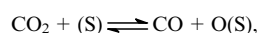
In the overwhelming majority of studies, the rate of CDR was directly proportional to  $P_{CH_4}$ , whereas  $P_{CO_2}$  enters the kinetic equations cited in certain papers as both a numerator and a denominator with the exponent  $n$  varying from 0 to 2.<sup>138</sup>

The positive kinetic isotope effect  $k_{CH_4}/k_{CD_4}$  observed in CDR over Ni/γ-Al<sub>2</sub>O<sub>3</sub>,<sup>139</sup> Ni/SiO<sub>2</sub> (see Ref. 140) and Ni/La<sub>2</sub>O<sub>3</sub> catalysts<sup>141</sup> suggests that the reaction of oxygen with the catalyst is the limiting step, whereas dissociation of CO<sub>2</sub> is a rather smooth process. The KIE value over Ni/Al<sub>2</sub>O<sub>3</sub> and Ni/La<sub>2</sub>O<sub>3</sub> increases with temperature, being much larger over Ni/La<sub>2</sub>O<sub>3</sub> than over Ni/Al<sub>2</sub>O<sub>3</sub>.

A highly dispersed, firm and stable catalyst Ni/La/α-Al<sub>2</sub>O<sub>3</sub> is particularly suitable for performing CDR in a fluidised bed.<sup>142</sup> At 700–900 °C and 16–40 kPa, the activation energy of this reaction was 90 kJ mol<sup>−1</sup>. According to the kinetic Langmuir–Hinshelwood model proposed for this reaction, the equilibrium is achieved at longer contact times. CDR in a fluidised bed reaction was carried out over Ni<sub>0.15</sub>Mg<sub>0.85</sub>O (see Ref. 143). Inhibition of carbon deposition even at elevated pressures can be attributed to carbon gasification. The electron micrographs of the catalyst show the presence of carbon filaments formed by the catalyst in the fixed bed reactor. No such effect is observed in the fluidised bed reactor.

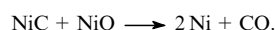
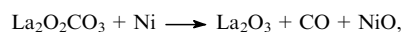
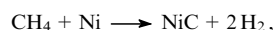
## c. Mechanism

Numerous studies have shown that carbon formation and its reactions on the metal surfaces are the crucial factors in the mechanism of CDR. The most popular concept consists of the formation of adsorbed C, H, O, CO species on the surface and their reactions with each other that yield CO and H<sub>2</sub>.<sup>135</sup> Carbon oxide is formed from methane or CO<sub>2</sub>.



A kinetic model for the formation and gasification of carbon over nickel catalysts under conditions of CDR and SRM has been discussed.<sup>144,145</sup> At 500–550 °C, carbon filaments were formed predominantly by the Boudouard reaction. This reaction was accelerated in the presence of alkali concomitantly with an increase in the surface concentration of oxygen and a decrease in the lumped forward rate coefficient for the methane cracking. The gasification of filamentous carbon was effected by CO<sub>2</sub>, H<sub>2</sub>O and H<sub>2</sub>. Two competing processes, *viz.*, growth of carbon filaments (nanotubes) involving carbon dissolution in Ni, diffusion and segregation of carbon on the opposite side of the particle and shortening of the filaments due to gasification.

The data from XPS, Auger spectroscopy and CDR by the pulse method suggest transient formation of carbides over cobalt catalysts.<sup>146</sup> Similar results were obtained in experiments over Ni/La<sub>2</sub>O<sub>3</sub>, Ni/γ-Al<sub>2</sub>O<sub>3</sub>, Ni/CaO and Ni/CaO–La<sub>2</sub>O<sub>3</sub> using <sup>13</sup>CH<sub>4</sub> and C<sup>18</sup>O<sub>2</sub> as the reactant gases.<sup>147,148</sup> The formation of nanotubes from carbon is also possible. Presumably, the active sites of the catalyst Ni/La<sub>2</sub>O<sub>3</sub> lie at the boundary between Ni and La<sub>2</sub>O<sub>3</sub>, where the following reactions occur:



These data suggest that cracking of CH<sub>4</sub> over Ni/La<sub>2</sub>O<sub>3</sub> occurs over Ni and is a limiting step, whereas the activation of CO<sub>2</sub> occurs on La<sub>2</sub>O<sub>3</sub>. In contrast, the activation of CO<sub>2</sub> over Ni/Al<sub>2</sub>O<sub>3</sub> is a slower step than that of CH<sub>4</sub>.

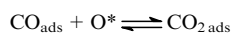
The mechanism of the initial steps of CDR over NiSiO<sub>2</sub>, La<sub>2</sub>O<sub>3</sub> or La<sub>2</sub>O<sub>3</sub>·SiO<sub>2</sub> was studied by the pulse response method.<sup>139</sup> The adsorption of CO<sub>2</sub> on NiO competed with the cracking of CH<sub>4</sub>. The adsorption of carbon dioxide on La<sub>2</sub>O<sub>3</sub> resulted in the formation of formates and carbonates, which

further decomposed with evolution of CO and recovery of the oxygen vacancies. The oxygen required for the formation of CO from CH<sub>4</sub> is provided by its transfer from La<sub>2</sub>O<sub>3</sub> to Ni. Methane reduced NiO and formed vacancies in La<sub>2</sub>O<sub>3</sub>.

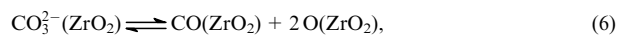
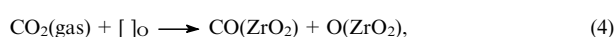
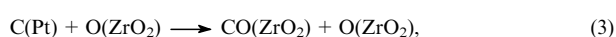
The CDR reaction over Ni–La<sub>2</sub>O<sub>3</sub>/zeolite (5 Å) was studied by X-ray diffraction spectroscopy, Fourier-transform infrared spectroscopy *in situ*, transmission electron microscopy (TEM), EPR and using chemical traps.<sup>149, 150</sup> Carbon formation from CH<sub>4</sub> and CO upon its disproportionation was confirmed in experiments with <sup>13</sup>CH<sub>4</sub>, and the contribution of CO increased at higher temperatures. According to TEM data, the bulk of carbon was deposited in the form of carbon nanotubes. Enhanced adsorption of CO<sub>2</sub> was observed in the presence of hydrogen. In experiments with pulsed injection of methane following reduction of the catalyst with hydrogen it was shown that the surface oxygen favoured cracking of CH<sub>4</sub>. The use of chemical traps (CD<sub>3</sub>I) and infrared diffuse reflectance spectroscopy established the formation of CD<sub>3</sub>CO<sub>2</sub>H and CD<sub>3</sub>CHO. In experiments with CH<sub>3</sub>I as a trap, HCO<sub>2</sub> or CH<sub>x</sub>O were detected as intermediates in the formation of CH<sub>3</sub>CO<sub>2</sub>H. The dissociation of the C–H bond in CH<sub>x</sub>O is a slow step, which suggests the formation of reactive intermediates HCO<sub>2</sub> and HCO. The number of converted CO<sub>2</sub> molecules was nearly proportional to the number of hydrogen atoms on the catalyst, which suggests that the activation of CO<sub>2</sub> occurs with the involvement of H<sub>ads</sub>. The larger degree of conversion of CH<sub>4</sub> on a CO<sub>2</sub>-treated catalyst suggests the involvement of oxygen in the cracking of CH<sub>4</sub>. IR spectroscopic studies *in situ* of the CDR mechanism over Rh/Al<sub>2</sub>O<sub>3</sub> revealed<sup>54</sup> that the linear form of the adsorbed CO<sub>2</sub> is the active form that generates the reaction product.

Over Rh/α-Al<sub>2</sub>O<sub>3</sub>, the dissociation of CH<sub>4</sub> proceeds in the same manner as over Ni or Co, but the mechanism of CO<sub>2</sub> activation is different.<sup>151</sup> Unlike carbide or filamentous carbon formed over Ni or Co, the carbon formed over Rh is of a 'graphite' type and possesses low activity. CO<sub>2</sub> is neither activated on such a carbon, nor reacts with it. Presumably, a short-lived carbon, which differs from the graphite-type carbon, is formed initially and reacts with CO<sub>2</sub>. It is this carbon that may represent a true intermediate of CDR. Oxygen acts as a poison over Ni or Co catalysts, whereas over Pt catalysts it activates CDR by eliminating the graphite-type carbon.

The CDR reaction over Pt/ZrO<sub>2</sub> and ZrO<sub>2</sub> was studied in a TAP-reactor using IR spectroscopy.<sup>152, 153</sup> At 700 °C, the adsorption of CH<sub>4</sub> and CO<sub>2</sub> occurred independently of one another. The CH<sub>4</sub> cracking products over Pt/ZrO<sub>2</sub> and ZrO<sub>2</sub> abstract oxygen from ZrO<sub>2</sub>. In an excess of oxygen, CO<sub>2</sub> was formed. The selectivity towards CO or CO<sub>2</sub> is determined by the same reaction:



and depends on the surface concentration of oxygen. Under the reaction conditions, adsorption bands corresponding to carbonates CO<sub>3</sub><sup>2-</sup>, bidentate carbonates, linear CO and OH groups were observed in the IR spectra. After administration of CO<sub>2</sub> pulses, only surface OH groups remained on the catalyst, but those were nonreactive. Obviously, the O<sub>ads</sub><sup>\*</sup> which remained after adsorption of CO<sub>2</sub>, reacted with CH<sub>4</sub>. The nature of the O<sup>\*</sup> species has not been established; O<sub>ads</sub>, OH<sub>ads</sub> and even CO<sub>3ads</sub> groups may have to do with these. Over Pt/ZrO<sub>2</sub>, methane dissociated into C<sub>ads</sub> and H<sub>ads</sub>, but no such dissociation was observed over ZrO<sub>2</sub>. Probably, ZrO<sub>2</sub> is partly reduced to form an alloy Pt<sub>1-x</sub>Zr<sub>x</sub>, where the activation of CO<sub>2</sub> occurs. The following reactions take place on Pt/ZrO<sub>2</sub>:<sup>152</sup>

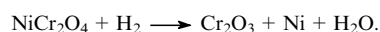
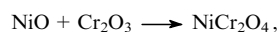


where [O] is the oxygen vacancy in ZrO<sub>2</sub>. The adsorbed hydrogen atoms form OH groups with surface oxygen, which serve as the sources of H<sub>2</sub> and H<sub>2</sub>O. Substitution of CO<sub>2</sub>, which yields CO [reaction (4) in the scheme above], for the lattice oxygen vacancy, is the limiting step of this process.

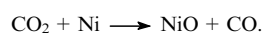
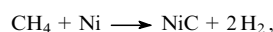
A large series of investigations of CDR over Ni/SiO<sub>2</sub>, Ni/La<sub>2</sub>O<sub>3</sub>, Ni/Al<sub>2</sub>O<sub>3</sub>, Ru/SiO<sub>2</sub> and Ru/Al<sub>2</sub>O<sub>3</sub> were carried out using isotope exchange, XPS, IR spectroscopy, ferromagnetic resonance and electron microscopy.<sup>128, 152–164</sup> It was found that cracking of CH<sub>4</sub> over Ni/SiO<sub>2</sub> resulted in the formation of H<sub>2</sub> and accumulation of carbon on the surface. Cracking of <sup>13</sup>CO<sub>2</sub> results in the instantaneous formation of gaseous <sup>13</sup>CO and adsorbed oxygen. The latter reacts with <sup>12</sup>C derived from <sup>12</sup>CH<sub>4</sub> to produce a second molecule of carbon monoxide (<sup>12</sup>CO) (the limiting step). Cracking of CH<sub>4</sub> was the slowest step over Ru, while CO<sub>2</sub> reacted directly with carbon to give two CO molecules. Administration of <sup>13</sup>CO<sub>2</sub> and <sup>12</sup>CH<sub>4</sub> pulses produces two output pulses, *viz.*, <sup>12</sup>CO and <sup>13</sup>CO. Alternating pulses of CO<sub>2</sub> enabled the removal of all the adsorbed carbon as a result of which the reaction rate dropped down to zero. In this case, the amount of oxygen accumulated on the surface was the lowest, which inevitably led to the inhibition of oxidation of H<sub>2</sub>. Silicon dioxide is a rather inert support and does not take part in CDR.

Using the TAP-reactor method, it was proved that the support carbon of the Ru/C catalyst reacted with CO<sub>2</sub>. In Ru/C doped with MgO, MgCO<sub>3</sub> was formed in the vicinity of Ru, which favoured the oxidation of carbon following cracking of methane. The OH groups at the MgO–Ru boundary prevented deactivation of the catalyst.

The following redox mechanism of CDR over Ni-catalysts has been proposed.<sup>114</sup> The oxidation and reduction of the NiO constituent of the catalyst (NiO–Cr<sub>2</sub>O<sub>3</sub>–MgO) occurs *via* a spinel according to the overall stoichiometric equation:



Apparently, cracking of methane and activation of CO<sub>2</sub> occur over Ni or NiC.



Over different catalysts, the mechanisms of CDR differ: over pure metals or over metals on neutral supports of the SiO<sub>2</sub> type, complete cracking of CH<sub>4</sub> and CO<sub>2</sub> is more probable, whereas on metals on basic supports the reaction proceeds *via* intermediate carbonates.

The intermediate formation of methyl radicals in CDR has been proposed. The free radicals CH<sub>3</sub> generated upon decomposition of azomethane were adsorbed on the catalyst (Rh/SiO<sub>2</sub>) in order to elucidate this possibility.<sup>165</sup> Using IR spectroscopy, it was established that CH<sub>3</sub>O<sub>ads</sub> species formed reacted with CO<sub>2</sub> in the gas phase at temperatures above 10 °C. No coke deposition on the catalyst occurred. Under these conditions, the major part of CH<sub>3</sub> was adsorbed on SiO<sub>2</sub>, while Rh took part in further conversions. The presence of CH<sub>3</sub> radicals on the surface of Ni/SiO<sub>2</sub> under conditions of CDR was confirmed by TPR and TPD.<sup>166</sup> In addition, C<sub>2</sub>H<sub>6</sub> was also formed. Surface CH<sub>3</sub> radicals reacted with adsorbed oxygen atoms to give CH<sub>x</sub>O and further CO and H<sub>2</sub>.

The majority of experimental results suggest the double-centred mechanism of CDR where CH<sub>4</sub> is activated on the metal components of the catalyst with cracking into C + 2H<sub>2</sub> (or CH<sub>x</sub> + H<sub>2</sub>), while the activation of CO<sub>2</sub> is mediated by the oxide component. The reaction product (CO) is formed in two ways, *viz.*, by oxidation of the surface carbon and by reduction of CO<sub>2</sub>.

On the surface, carbon is formed by two reactions, *viz.*, cracking of CH<sub>4</sub> and the Boudouard reaction. On transition metal oxides supported on basic oxides, CDR can follow a redox mechanism.

#### d. Technological features

Attempts have been undertaken to separate the steps of CH<sub>4</sub> and CO<sub>2</sub> activation by carrying out CDR in a membrane reactor.<sup>167</sup> A Pd/Al<sub>2</sub>O<sub>3</sub> membrane was prepared by electrodeposition of the metal on the support. At 350–600 °C, the degree of CH<sub>4</sub> conversion was 4%–20% larger than in a conventional process with the same catalyst, and the yield of H<sub>2</sub> increased from 3% to 18%. However, the operation of the membrane is strongly affected by coking and the expediency of its application was not presented.

CDR and POM were carried out using the oxygen-permeable membrane Ba<sub>0.5</sub>Sr<sub>0.5</sub>Co<sub>0.8</sub>Fe<sub>0.2</sub>O.<sup>168</sup> The degree of conversion of CH<sub>4</sub> and the selectivity towards CO exceeded 98% under oxygen conversion at 850 °C and at high CH<sub>4</sub>:O<sub>2</sub> ratios. High activities and selectivities of CDR carried out at 900 °C were achieved. The use of a CH<sub>4</sub> + CO<sub>2</sub> + O<sub>2</sub> mixture for over 100 h ensured stable conversion of CH<sub>4</sub> (90%–92%) and CO<sub>2</sub> (94%–96%) with the selectivity towards CO close to 100%.

The feasibility of membrane isolation of pure hydrogen from synthesis gas in the CDR process over Ni/La<sub>2</sub>O<sub>3</sub>, Ni–Rh/La<sub>2</sub>O<sub>3</sub>,<sup>105</sup> Ni/ZrO<sub>2</sub> and Ni–Rh/La<sub>2</sub>O<sub>3</sub><sup>106</sup> is under study. At 700 °C, bimetallic Ni–Rh catalysts were much more active than monometallic catalysts, but monometallic Rh was found to be more stable.

### 5. Autothermal reforming (ATR)

The combination of two or three routes of oxidative reforming of methane, *viz.*, SRM, POM and CDR, can result in the increase in the efficiency of raw material utilisation, in improvement of the thermal balance and control over the composition of synthesis gas. To this goal, one-pot exothermic deep oxidation of CH<sub>4</sub> and endothermic SRM and/or CDR are often performed. The technological process in ATR reactors includes two consecutive steps, *viz.*, deep oxidation of methane followed by CDR + SRM with subsequent conversion of water gas.

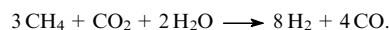
The autothermal reforming of methane at high pressures (4–10 MPa), which meets the demands for subsequent synthesis of methanol and dimethyl ether, is discussed.<sup>169</sup> Its first step consists of combustion of CH<sub>4</sub> in a gas burner, and the second step includes CDR and SRM in a fluidised bed of a catalyst. Calculations show that the outlet temperature should be increased with an increase in pressure, but this may result in sintering of the catalyst and destruction of the fluidised bed. The kinetic calculations made account of 49 intermediates and 277 elementary reactions including those involving C<sub>2</sub> hydrocarbons. Lower yields of C<sub>2</sub>H<sub>2</sub> and reduced soot formation are the beneficial effects of the elevated pressures.

The oxygen–carbon-dioxide reforming of methane over Pt/ZrO<sub>2</sub>, Pt/Al<sub>2</sub>O<sub>3</sub> and Ni/Al<sub>2</sub>O<sub>3</sub> were studied in the temperature range of 550–800 °C.<sup>170</sup> At all temperatures, the yields of CO and H<sub>2</sub> from CH<sub>4</sub> + CO<sub>2</sub> + O<sub>2</sub> mixtures (the content of O<sub>2</sub> varied from 3% to 11%) were higher than in the case of the CH<sub>4</sub> + CO<sub>2</sub> mixture, and carbon deposition was smaller. Besides, these conditions facilitated control over formation of the hot spot on the catalyst. From a mixture containing 11% of O<sub>2</sub>, the yields of CO and H<sub>2</sub> were nearly the same as those achieved upon oxidative reforming, CH<sub>4</sub> + O<sub>2</sub> (95% at 800 °C).

The combination of POM, SRM, CDR and deep oxidation of methane in one reactor is the most promising approach to autothermal reforming of methane. The main problem in the design of such reactors is connected with the differences in temperatures of these reactions, which brings forth the necessity for the spatial separation of heat-evolving and heat-adsorbing sites of the catalyst. One of the possible clues to the solution of this problem came from a group of Japanese investigators who performed the conversion of a CH<sub>4</sub> + CO<sub>2</sub> + O<sub>2</sub> mixture in a

fluidised bed. However, it was not always possible to obtain the target CO + H<sub>2</sub> mixture with the required composition.

It was found<sup>171</sup> that the addition of CO<sub>2</sub> to the CH<sub>4</sub> + H<sub>2</sub>O mixture optimised methanol synthesis. Thus, the use of carbon dioxide reforming of methane instead of steam reforming reduces the cost of the technological process. However, this process is commercially profitable if only large amounts of relatively pure CO<sub>2</sub> are available. The H<sub>2</sub>:CO = 2:1 ratio required for methanol synthesis is achieved at CO<sub>2</sub>:CH<sub>4</sub> = 1:3 in accordance to the stoichiometry of the reaction:



In 2002, a pilot plant for synthetic liquid hydrocarbons (SLH) with the daily capacity of 7 barrels was put into operation in Japan for trials of a novel catalyst for combined CO<sub>2</sub>/H<sub>2</sub>O reforming and assessment of a JNOC (Japan National Oil Corporation) technology based on this catalyst. The process is carried out in a tubular converter that requires no addition of oxygen. Synthesis gas thus produced is well-balanced with regard to the H<sub>2</sub>/CO ratio for manufacture of SLH, methanol and dimethyl ether. The energy consumption is lower than in conventional processes at smaller CO<sub>2</sub> and H<sub>2</sub>O molar ratios with respect to carbon in the supplied gas. It is expected that this technology will be especially efficient for the application to small fields with high content of CO<sub>2</sub> in the natural gas as well as for reprocessing of effluent gases rich in CO<sub>2</sub> and at liquefied gas plants.<sup>172</sup>

A heat-integrated ATR reactor with a Rh/Al<sub>2</sub>O<sub>3</sub> catalyst is described.<sup>173</sup> The catalyst was applied onto the inner and outer surfaces of a ceramic tube. A CH<sub>4</sub> + O<sub>2</sub> flow was first fed inside the tube where deep oxidation of methane occurred and then onto the outer surface of the tube where CDR and SRM took place. This method allows a significant reduction of the ‘hot spot’ temperature in the reactor (below 900 °C). This process can be optimised by varying the number of catalyst layers on the inner and outer surfaces of the tube.

The mechanism of autothermal reforming over Pt/CeO<sub>2</sub>, Pt/ZrO<sub>2</sub> and Pt/CeZrO<sub>2</sub> catalysts has been considered.<sup>174</sup> This reaction proceeds by a consecutive mechanism, *i.e.*, the combustion of methane is followed by steam and carbon dioxide reforming of the unburned gas. Pt/Ce<sub>0.18</sub>Zr<sub>0.82</sub>O<sub>2</sub> is the catalyst of choice, it possesses high oxygen capacity, which is beneficial for the redox process. In the absence of CeO<sub>2</sub>, the catalyst undergoes rapid deactivation.

The interest in the production of synthesis gas and hydrogen from higher hydrocarbons (including liquid hydrocarbons) is steadily increasing in connection with the prospects of broad use of hydrogen in motor transport. Steam and autothermal reforming of n-heptane were carried out over 15% Ni/Al<sub>2</sub>O<sub>3</sub> at 700 °C.<sup>175</sup> At lower temperatures, thermal cracking occurred. An active and selective catalyst for steam reforming of ethanol into synthesis gas was obtained by doping a Cu–Zr-fluorite catalyst with cobalt.<sup>176</sup> Reduction of Co led to the generation of Co nanoparticles able to react with oxides. It was also shown that high (26%–27%) selectivity towards H<sub>2</sub> can be achieved in gas-phase oxidation of methane catalysed by NO<sub>x</sub> (20% CH<sub>4</sub>, 10% O<sub>2</sub>, 0.06% NO).<sup>177</sup> The degree of methane conversion in a flow-through quartz reactor at 700–800 °C and the residence time of 0.6–3.7 s was 34%.

## III. Partial oxidation of methane to oxygenates

### 1. Homogeneous oxidation of methane and ethane

Studies into kinetics and mechanism of homogeneous partial oxidation of methane to methanol (Direct Methane to Methanol, DMTM) and kinetics of partial oxidation of the nearest methane homologues are underway. The key features of the mechanism, optimum reaction conditions and actual yields of oxygenates upon methane oxidation in laboratory flow reactors were established<sup>178–180</sup> and the effects of pressure on partial oxidation of methane to methanol were analysed.<sup>179</sup> The most important

factors include a critical transition to a steady-state chain-branched mode,<sup>8</sup> increasing role of nonlinear gas-phase reactions and change in the relative contribution of heterogeneous processes.

The chain-branched oxidation process has a pronounced nonlinear character, the increase in the overall pressure accompanied by the increase in partial pressures of the reactants not only accelerates the reaction, but also increases the contribution of nonlinear gas-phase methanol-yielding processes. A decrease in the diffusion rate with an increase in pressure decreases the contribution of heterogeneous processes leading to the predominant formation of deep oxidation products. Studies on direct homogeneous oxidation of methane in laboratory-scale stainless steel and quartz flow reactors at 15–80 atm demonstrated the considerable effect of the reactor surface material on the oxidation process.<sup>179</sup>

A complex study of the dependence of the main parameters of the DMTM process on such factors as pressure, temperature,  $\text{CH}_4/\text{O}_2$  ratio and the extent of dilution with the inert gas has been carried out.<sup>181</sup> The experiments were performed in fused-quartz reactors (1–10 mm in diameter) at residence time of  $\sim 10$  s and complete conversion of oxygen. The experimental results are in good agreement with the known data.<sup>8, 181</sup> At pressures around 100 atm and the  $\text{CH}_4:\text{O}_2$  ratio of 16.3 in a gas mixture containing 63% of He, the yields of the major reaction products ( $\text{CH}_3\text{OH}$ ,  $\text{CO}$ ,  $\text{CO}_2$  and  $\text{H}_2\text{O}$ ) exceeded 95%. No identification of other reaction products was carried out in this study. At temperatures above 460 °C, the degree of oxygen conversion increased jumpwise to 100%. The degree of methane conversion virtually paralleled the oxygen content in the mixture. The mean selectivity towards methanol was  $\sim 50\%$ , which corresponded to the published data. It is of note that the optimum (in the authors' opinion) selectivity was reached at relatively high ( $\sim 6\%$  with respect to methane) oxygen concentrations. The selectivity towards CO was, on average, 3 times as great as that in  $\text{CO}_2$ . At temperatures above threshold values, the selectivity towards methanol passed through a small maximum at  $\sim 470$  °C with subsequent monotonic decrease with an increase in temperature (35% at 490 °C).

As in the majority of previous studies, the drop in pressure was accompanied by a rapid decrease in the selectivity towards methanol (35% at 17 atm) and an increase in temperature (535 °C at 17 atm) at which the maximum selectivity was reached. Further dilution of the reaction mixture with He resulted in an increase in temperature required for complete conversion of oxygen from 445 °C in the absence of helium to 530 °C in the presence of 80% helium. At a He content of 90%, no reaction occurred even at 554 °C. It is noteworthy that the monotonic increase in the selectivity towards methanol occurred with a decrease in the degree of dilution (from 35% at 80% of He to 63% in the absence of He). The reason should be sought in the drop of the reaction temperature rather than in the dilution itself. As in the previous studies,<sup>178–180</sup> the selectivity towards methanol increased with an increase in the  $\text{CH}_4:\text{O}_2$  ratio.

The tenfold increase in the reactor diameter required an increase in the reaction temperature to 495 °C, which is apparently due to higher activation energy of the homogeneous generation of radicals in comparison with the generation in a heterogeneous reaction. This was accompanied by a slight increase in the selectivity towards methanol, which is quite natural, taking into consideration the role of the catalytic formation of methane deep oxidation products on the catalyst surface. Under these conditions ( $\leq 500$  °C, residence time  $\sim 10$  s), relatively high ( $\leq 25\%$  for CO and  $\leq 8\%$  for  $\text{CO}_2$  with respect to methane) concentrations of carbon oxides had virtually no effect on either the degree of methane conversion or the selectivity towards methanol. This followed from virtually complete coincidence of experimental results obtained after a single passage of the mixture through the reactor and with recirculation of gases after separation of methanol and water.

Among recent studies of the DMTM process, special mention should be made of experiments carried out by Zhang *et al.*<sup>182</sup> Gas-phase oxidation was carried out in a flow reactor with a quartz insertion having an internal diameter of 6.7 mm and a heated area diameter of 270 mm at variable pressures (1.0–5.0 MPa) and temperatures (380–500 °C). Special attention has been given to exclusion of interactions of the reactants and reaction products with the metallic surfaces of the reactor and the thermocouple. The composition of the reaction products ( $\text{CH}_3\text{OH}$ ,  $\text{CO}$ ,  $\text{CO}_2$ ,  $\text{C}_2\text{H}_6$  and  $\text{C}_2\text{H}_4$ ) was quite typical of this reaction except for the absence of formaldehyde.

A sharp increase in the degree of conversion of the reactants with an increase in temperature and the relatively weak effect of temperature on the yield of methanol after complete conversion of  $\text{O}_2$  is consistent with the results of previous studies<sup>8, 180, 181</sup> and is characteristic of temperature dependences of the yield of  $\text{CH}_3\text{OH}$  in the branched-chain partial oxidation of methane. A decrease in the yields and selectivity towards methanol at temperatures above 480 °C at low jet velocities and the residence times in the heated zone of 45–90 s in reactors with small diameters can be attributed to the heterogeneous decomposition of  $\text{CH}_3\text{OH}$ . In any case, noticeable decomposition of methanol over Pyrex was observed under similar conditions even in the temperature range of 475–500 °C (see Ref. 8). The absence, from the reaction products, of formaldehyde, which is normally formed under conditions mentioned but is less resistant to heterogeneous decomposition, seems to be due to the same reason.

The results obtained suggest<sup>182</sup> that the degree of conversion of oxygen becomes smaller than 100% with an increase in temperature. The presence of small amounts of oxygen in the final products was observed in previous studies<sup>8</sup> and seems to be due to heterogeneous decomposition of oxygen-containing products, e.g., peroxides.

The relatively high yield of methanol reported<sup>182</sup> correlates to some extent to the results reported by other authors.<sup>183, 184</sup> It is noteworthy that in these studies the residence time was  $\leq 1$  min at relatively low temperatures, pressures and sizes of reactors with quartz or sapphire surfaces insulating the metallic parts of the reactor. These results are at variance with both those obtained at higher flow rates of the reactants and the results of kinetic simulation of a gas-phase process,<sup>8</sup> which suggests that in this case heterogeneous processes occurring on the reactor surface play a more prominent role. At temperatures and pressures mentioned above, neither quartz nor  $\text{Al}_2\text{O}_3$  can be regarded as inert materials with respect to the reacting methane–oxygen mixture, although the mechanisms and rates of surface processes differ substantially from those occurring on the metal surface. The relatively low temperatures used in these studies also favour an increase in the contribution of heterogeneous reactions into the overall homogeneous–heterogeneous process of methane oxidation.<sup>8</sup> The residence time may be regarded as high, if one takes into account the rates of radial and axial diffusion, and this may rationalise the pronounced effect exerted by the presence of even insignificant metallic parts in any zone of the reactor. If this is true, the experimental results, which seem encouraging at the first glance, give unfortunately no grounds for the favourable assessment of the prospects of implementation of the process on an industrial scale, since it envisages, in principle, the use of very slow flows and high surface-to-volume ratios.

To date, the mechanism of the gas-phase DMTM process is generally understood. Numerous experiments showed that the selectivity towards methanol can reliably reach the level of 50% in flow-type reactors at  $\sim 450$ –500 °C and pressures  $\geq 70$ –80 atm with a residence time of several seconds where the degree of methane conversion per cycle is 5%–6%.<sup>8, 180</sup> Practical implementation of this process requires apparently that the main efforts are directed at improving the process technology to make use of its obvious benefits (simplicity, stability, non-susceptibility to contaminants) and to compensate for the no less obvious disadvantages (low conversion per cycle and low selectivity). DMTM was

recommended as a part of an integral energochemical process that combines production of methanol with generation of electric power.<sup>185</sup> This provides yet another benefit and allows maximum simplification of the technology and cut of the production cost of methanol with simultaneous reduction of specific emission of  $\text{NO}_x$  in the generation of electric power from natural gas.

Partial oxidation of methane homologues is studied in less detail. The oxidation of ethane and methane–ethane mixtures in a flow reactor at 10–70 atm was studied with variable macrokinetic parameters.<sup>186, 187</sup> The use of ethane and ethane-containing gases for direct gas-phase oxidation is in every respect more advantageous than the oxidation of methane-containing gases. Although this reaction yields similar major products (except for appearance of noticeable amounts of ethylene), their yields and the degree of conversion of the hydrocarbon gas are somewhat higher, while the working pressure and temperature are significantly lower than in methane oxidation. The increase in the yields of such valuable compounds as formaldehyde and ethanol is especially pronounced, although methanol remains to be the main oxidation liquid product. High total yields of oxygenates were achieved at relatively low pressures ( $\sim 30$  atm). The content of formaldehyde in liquid products was  $\sim 30\%$  at the total alcohol content of 45% and the methanol:ethanol ratio of 5:1. Such a ratio is characteristic of fuel alcohol mixtures that can directly be used as high-octane additives to motor fuels. This allows the direct gas-phase oxidation of ethane to be considered as a potential one-step procedure for production of formaldehyde and fuel alcohols. A promoting effect of methane on the formation of methanol and the yield of liquid products in the ethane oxidation was established. Presumably, this is due to the ability of methyl peroxide radicals generated upon methane oxidation to serve as effective branching species, whereas peroxide radicals generated in the oxidation of ethane and higher hydrocarbons can decompose by alternative routes that yield alkenes but do not result in branching.

Experimental studies and kinetic simulation of conversions of methane and ethane in their combined partial oxidation and of conversions of hydrocarbons  $\text{C}_1$ – $\text{C}_4$  in the oxidation of more complex mixtures imitating natural and associated gases have been carried out.<sup>188</sup> Under conditions of partial oxidation of hydrocarbons  $\text{C}_1$ – $\text{C}_4$  to oxygenates, fast burn-out of higher hydrocarbons at the initial  $\text{O}_2$  concentration of 4%–16% is accompanied by an increase in methane concentration, particularly as a result of their oxidative reforming. However, complete conversion of only one of these hydrocarbons in the oxidation of methane–ethane mixtures is impossible in principle, since both are oxidative interconversion products. The changes in the relative concentrations of hydrocarbons upon combined oxidation depend critically on the initial concentration of oxygen in the mixture. At the same time, the effect of temperature is far less pronounced, while the changes in the pressure in the range 25–70 atm have virtually no effect on this parameter.

Short-term catalytic impact on these complex non-linear systems that are far from the thermodynamic equilibrium as a means of the control over the chemical process is a promising trend in the study of partial oxidation of methane and its homologues. The nonlinear, in principle, nature of such systems determined by interconversions of numerous intermediates allows control over the evolution of the system and its transitions into different steady states by applying relatively weak impacts on the system.<sup>189</sup> However, these studies should be based on the use of reliable quantitative kinetic models of relevant homogeneous–heterogeneous processes. The development of such models is a very complicated task if we take into consideration the ambiguity of many kinetic parameters of even key elementary steps.

## 2. Homogeneous promotion of methane oxidation to oxygenates

Attempts to increase the yields of methane partial oxidation products by homogeneous promotion or using heterogeneous

catalysis have been undertaken since the 1920's. Hydrogen peroxide and nitrogen oxides formerly employed in various industrial processes still remain the most popular homogeneous promoters. In the majority of cases, the effects of promoters are apparently confined to the decrease in either the temperature of the process or the induction period, but the yields of the reaction products are unaffected. Presumably,<sup>190, 191</sup> the failure to increase the product yields by promoting the reaction is due largely to the necessity of additional generation of radicals at very high rates comparable to those attainable in homogeneous branched-chain processes. Kinetic simulation showed that promotion of partial oxidation of methane can, in principle, significantly affect the yields of target products. For example, it is expected that the yield of formaldehyde can be increased by nearly an order of magnitude upon promotion of the oxidation of a  $\text{CH}_4:\text{O}_2 = 9:1$  mixture (1 atm,  $T = 753$  K). However, this can be the case provided the promoter ensures the rate of the radical generation more than five orders of magnitude larger than that of their thermal generation in the reaction itself.<sup>8, 189, 190</sup>

The possibility of promoting the DMTM process with different radicals and molecules has been studied experimentally.<sup>192</sup> The concentrations of radicals above 0.1% could not be achieved irrespective of the nature of the radicals, since they readily interconverted in the gaseous phase. The introduction of radicals or  $\sim 2\%$  of different molecular promoters reduced the ignition delay without any effect on the yields of the reaction products. Among molecular compounds tested, the ability of  $\text{H}_2\text{O}_2$  to reduce the ignition delay was the highest and exceeded twofold that of methanol.

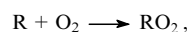
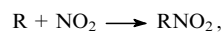
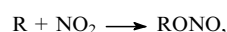
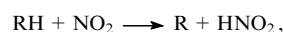
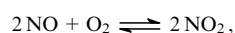
The promotion of incomplete methane oxidation by nitrogen oxides can be concomitant with the catalysis of the formation of various oxygen-containing species. One of the pioneering studies in this field has demonstrated<sup>193</sup> that the addition of 2% NO to a  $\text{CH}_4:\text{O}_2 = 9:1$  mixture (1 atm, 560 °C) increased 10-fold the yield of formaldehyde (from 0.35% to 3.96%). Although this increase could be explained by the promoting effect of NO, it was assumed that it was a manifestation of homogeneous catalysis, since the reaction products contained no  $\text{N}_2\text{O}$  and only trace amounts of  $\text{N}_2$ .

The effect of nitric acid vapour ( $\sim 0.26\%$ ) as a potential source of  $\text{NO}_2$  on methane oxidation has been studied.<sup>194</sup> The addition of  $\text{HNO}_3$  increased not only the degree of methane conversion, but also the general selectivity and the yields of organic products (from 0.7 to  $> 2\%$ ), mainly due to the formation of  $\text{CH}_3\text{NO}_2$ . In the presence of  $\text{HNO}_3$  and at similar degrees of methane conversion, the selectivity towards  $\text{CH}_3\text{OH}$  and  $\text{HCHO}$  changed only insignificantly, while the general selectivity and the yields of oxygenates increased due to the presence of  $\text{CH}_3\text{NO}_2$ . The selectivity towards  $\text{HCHO}$  and  $\text{CH}_3\text{NO}_2$  increased with the increase in the degree of methane conversion in the presence of  $\text{HNO}_3$ , while the selectivity towards  $\text{CH}_3\text{OH}$  decreased under these conditions. It was assumed<sup>194</sup> that the effect of  $\text{NO}_2$  is not confined to initiation alone, since the initial reaction temperature ( $\sim 410$  °C) was the same in all experiments with the same oxygen concentration (2.6%). No nitrogen was formed under these conditions, while the major part of  $\text{NO}_2$  (40%–80%) was converted into  $\text{CH}_3\text{NO}_2$ . In the authors' opinion,  $\text{NO}_2$  can be used as a catalyst in partial oxidation of methane provided that the conditions of this reaction or its individual steps favour the conversion of  $\text{CH}_3\text{NO}_2$  into other oxygenates and regeneration of  $\text{NO}_2$ .

The effect of nitrogen oxides on partial oxidation of other lower alkanes is similar. In the gas-phase oxidation of  $\text{CH}_4$ ,  $\text{C}_2\text{H}_6$ ,  $\text{C}_3\text{H}_8$  and iso- $\text{C}_4\text{H}_{10}$ , the introduction of nitrogen oxides not only increased the rates of alkane conversions and reduced the initial temperature of the overall reaction, but also increased considerably the yields of the oxygenates, *i.e.*, aldehydes, ketones and alcohols.<sup>195, 196</sup> The experiments were carried out in a quartz reactor with an internal diameter of 8 mm; the flow rate was  $120 \text{ ml min}^{-1}$ ; the partial pressures of alkanes,  $\text{O}_2$  and NO were

5–10, 2.5–15 and 0.5–4 kPa, respectively.<sup>195</sup> The reaction mixture was diluted with helium to the total pressure of 101 kPa. After addition of NO, the oxidation of ethane and propane occurred at 400 °C, *i.e.*, at 100 °C lower temperature than in the absence of NO, while the activation energies of the reactions were equal to 208 (methane), 138 (ethane) (361 in the absence of NO) and 107 (propane) kJ mol<sup>-1</sup> (275 in the absence of NO). The total yields of oxygenates under optimum conditions were as follows: 6.7% (methane), 11.3% (ethane), 12.9% (propane) and 28.7% (isobutane). Only trace amounts of nitroalkanes and N<sub>2</sub> were formed under these conditions. Thus, the bulk of added NO remained in the gas phase, which favoured its subsequent isolation and reuse as a catalyst for the oxidation of lower alkanes. The reaction between NO and alkanes did not occur in the absence of O<sub>2</sub>, which points to the involvement of NO<sub>2</sub> in the oxidation and poses a question of the role of nitroalkanes as intermediates in this process. The latter were formed in small amounts in the oxidation carried out at low temperatures. However, direct studies of decomposition of nitropropane C<sub>3</sub>H<sub>7</sub>NO<sub>2</sub> established that C<sub>3</sub>H<sub>8</sub> was formed as the main product, *i.e.*, nitroalkanes are not precursors of oxygenate. Contrariwise, the decomposition of iso-C<sub>4</sub>H<sub>9</sub>ONO at 400 °C resulted in the formation of acetone as the main product. The addition of a NO–O<sub>2</sub> mixture to the nitroalkane did not change the rate of acetone formation, but yielded HCOH, CO, CO<sub>2</sub> and CH<sub>3</sub>NO<sub>2</sub> instead of soot. Thus, alkyl nitrite can serve as the oxygenate precursor.

It was suggested<sup>196</sup> that the oxidation of alkanes RH is catalysed by nitrogen oxides and involves the following main reactions:



in particular, at R = CH<sub>3</sub>



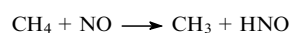
whereas at R = iso-C<sub>4</sub>H<sub>9</sub>



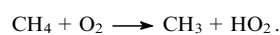
NO and NO<sub>2</sub> play the role of homogeneous catalysts, since the nitroalkanes formed fully decomposed at temperatures above 600 °C with simultaneous release of NO<sub>x</sub>.

It should be taken into account that both hydrocarbons themselves and CO strongly promote oxidation of NO to NO<sub>2</sub> even at relatively low temperatures (300 °C). In addition, NO markedly accelerates the oxidation of methanol and ethanol formed, presumably *via* partially oxidised intermediates that are unstable under other conditions.<sup>197</sup>

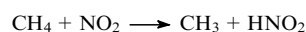
A simplified system for the reaction of CH<sub>4</sub> with NO<sub>x</sub> (in the absence of O<sub>2</sub>) was analysed theoretically and the activation energies and rate constants for the reactions of nitrogen oxides with methane were calculated.<sup>198</sup> The activation energy of the reaction:



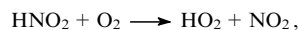
is 65.6 kcal mol<sup>-1</sup>, *i.e.*, higher than the activation energy (59.0 kcal mol<sup>-1</sup>) of the reaction:



This implies that NO cannot play the role of a promoter in this reaction. Contrariwise, the activation energy of the reaction



is equal to 37.6 kcal mol<sup>-1</sup>, *i.e.*, it is this reaction that is presumably the promotor in the process. It is believed<sup>198</sup> that in the presence of oxygen this reaction is accompanied by fast conversion:



with the liberation of NO<sub>2</sub>.

Since the formation of C<sub>1</sub>-oxygenates proceeds *via* CH<sub>3</sub>O as an intermediate, these may be formed at ~800 K because the energy barriers of all steps are below 40 kcal mol<sup>-1</sup>. In terms of the hypothetical mechanism, the increase in NO concentration favours a higher yield of CH<sub>2</sub>O with a corresponding decrease in the yield of CH<sub>3</sub>OH, which is consistent with the above-mentioned data for the CH<sub>4</sub>–O<sub>2</sub>–NO system.

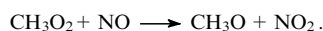
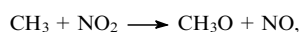
Somewhat unexpected results have been reported concerning the effects of nitrogen oxides on incomplete oxidation of methane.<sup>199,200</sup> The experimental conditions were similar to those described.<sup>195,196</sup> In the majority of cases, reaction mixtures contained 55.6% CH<sub>4</sub>, 27.7% O<sub>2</sub>, 0.5% NO<sub>x</sub> and 16.2% He. The reaction was carried out in a quartz reactor with an internal diameter 7 mm and the length of 200 mm at 1 atm, ~800 K and a space velocity of 120 ml min<sup>-1</sup>. The product yields were determined at the same degree of methane conversion (10%). Under these conditions, the reaction of CH<sub>4</sub> with NO<sub>2</sub> in the absence of oxygen yielded predominantly formaldehyde, whereas the reaction with NO yielded no oxidation products at all. The introduction of NO<sub>x</sub> to the system CH<sub>4</sub>–O<sub>2</sub> enabled high selectivity towards formaldehyde (24.5%) and even higher selectivity towards methanol (27.3%), although in all previous studies no methanol was formed at all or it was formed in only trace amounts. Nitromethane CH<sub>3</sub>NO<sub>2</sub> was isolated together with methanol and formaldehyde and its final concentration correlated quantitatively with the initial concentration of added nitrogen oxides.

The effects of various parameters on the temperature of partial oxidation of methane and the product yields have been studied.<sup>199–201</sup> At 0.1 and 5 MPa, the increase in the initial concentration of NO to 1% caused a significant (by ~100 K) reduction of the reaction temperature, although the maximum degree of methane conversion did not change. However, further increase (up to 1.5%) of NO concentration had no effect. At the indicated pressure, the selectivity towards oxygenates (methanol, formaldehyde, nitromethane) reached a maximum at [NO] ≈ 0.5%, which is considered as the optimum concentration. The selectivity towards ethane dropped down quickly to a nearly zero level with the increase in the NO concentration. Dilution of the reaction mixture with helium, at least to the concentration of 60%, had little effect. Even the dependence of the product yields on such a critical parameter as the CH<sub>4</sub>:O<sub>2</sub> ratio shows that the yields of methanol and formaldehyde did not change appreciably with the increase in this ratio to 10 despite the presence of a maximum around CH<sub>4</sub>:O<sub>2</sub> = 2. At CH<sub>4</sub>:O<sub>2</sub> < 2, the yield of methanol decreased with a concomitant increase in the yield of formaldehyde. However, neither the increase in the space velocity (from 1000 to 4000 h<sup>-1</sup>), nor the addition of water (up to 16%) had any pronounced effect on the yields of oxygenates. On the whole, NO<sub>2</sub> exerted approximately the same effect as NO.

The consistently high yields of methanol (and nitromethane) in a broad range of experimental conditions call into question the arguments put forward by Suzuki *et al.*<sup>199–201</sup> as a plausible reason for the considerable discrepancies between their experimental results and those obtained under virtually identical conditions.<sup>195,196</sup> Since these works differ from one another by a large number of parameters, the actual dependence of the product yields on reaction conditions is impossible to establish without the use of kinetic simulation.

As for the mechanism of this reaction, it was suggested<sup>199,200</sup> that the interaction of methane with NO<sub>2</sub> not only favours the generation of radicals, but the nitrogen oxides formed thereupon

promote the formation of an alkoxy radical as the oxygenate precursor:



Supporting evidence in favour of these experimental results<sup>199–201</sup> was obtained in the simulation of  $\text{NO}_x$ -promoted oxidation of methane using a CHEMKIN III software.<sup>202</sup>

It is noteworthy that the beneficial effect of  $\text{NO}_x$  promotion is manifested exclusively at low pressures, whereas at pressures above 1 MPa this effect is less pronounced.<sup>201</sup> Thus at 1 MPa, the decrease in the reaction temperature at 4% methane conversion did not exceed 25 K. The selectivity towards oxygenates did not depend on  $\text{NO}_x$  concentration, while the selectivity towards methanol in the absence of  $\text{NO}_x$  amounted to 30%. This suggests that promotion makes no sense at pressures above 1 MPa. This is consistent with the hypothesis according to which the role of promotion in this reaction becomes insignificant when the oxidation process goes to the branched-chain regime with an increase in pressure.<sup>8</sup> This circumstance notwithstanding, the catalytic effect of  $\text{NO}_x$  on oxygenate formation at high pressures is likely. The same group of investigators<sup>203</sup> demonstrated the possibility of a slight increase in the yield of methanol in the system  $\text{CH}_4\text{--O}_2\text{--NO}$  ( $T = 550^\circ\text{C}$ ,  $P = 0.4$  MPa) due to a virtually complete conversion of formaldehyde upon introduction of a catalyst ( $\text{Cu--ZnO/SiO}_2$ ).<sup>203</sup>

Partial oxidation of methane upon combined use of nitrogen(I) oxide and a heterogeneous catalyst has been described.<sup>204</sup> In such reactions, the catalyst usually fulfils several functions: not only does it induce the generation of radicals and catalyse the formation of the reaction products, but it also favours their subsequent decomposition. Separation of these functions was effected with NO as a radical promoter, subsequent reaction was carried out over  $\text{V}_2\text{O}_5/\text{SiO}_2$  with small specific surface ( $\sim 1\text{ m}^2\text{ g}^{-1}$ ). Low decomposition rates of the partial oxidation products over this catalyst enabled a much higher yield (7%) of the  $\text{C}_1$  oxygenates (methanol and formaldehyde) than over catalysts with well-developed surfaces. In more recent studies,<sup>205</sup> the total yields of oxygenates were even higher (up to 16%), which can be considered as the maximum level currently attainable.

Although in the majority of studies devoted to the promotion of methane oxidation by nitrogen oxides at atmospheric pressure, the total yields of oxygenates did not exceed 4%–7%, it was reported<sup>206</sup> that their yields were 11% upon methane oxidation, 16% upon methane oxidation in the presence of trace amounts (0.7%) of ethane and 24% upon ethane oxidation. However, in contrast to the studies<sup>204,205</sup> where methanol was formed as the main product, in the latter case it was formaldehyde that was virtually exclusively formed.

### 3. Physical methods for promoting oxidative conversions of lower alkanes

Oxidative processes are promoted not only by chemical, but also by physical methods, in the first place, by electric discharge, plasma and molecular beams. Gas-discharge plasma is widely used for the initiation of chemical reactions, which can be exemplified by direct conversion of methane into acetylene upon thermal arc discharge. This method developed 50 years ago is also employed for the production of  $\text{H}_2$ . The possibility of applying non-equilibrium plasma to low-temperature conversion of methane into synthesis gas, oxygenates and higher hydrocarbons is under intensive study. The creation of non-equilibrium plasma is an effective approach to promoting chemical reactions due to interaction of electrons and ions accelerated in the electric field with molecules and radicals. In contrast to heterogeneous catalysis, such a promotion occurs in the bulk of the reactor. Plasma is generated using different kinds of electric discharges, *e.g.*, corona, electric arc, barrier, glow, microwave, pulsed, *etc.* In some studies, this technique was used in combination with heterogeneous

catalysis. Taking into account the tremendous number of investigations in this area, here we shall confine ourselves to the consideration of only some of the most recent studies.

Corona discharge was successfully employed for efficient preparation of synthesis gas and  $\text{C}_2$  hydrocarbons from methane and air.<sup>207</sup> The effects of various parameters (*e.g.*,  $\text{CH}_4:\text{O}_2$  ratio, addition of ethane, dilution with inert gases, residence time, power and frequency of the discharge, the pulse form) on the reaction rate were investigated. The conversion of methane and of oxygen increased with an increase in the discharge power, but decreased with the increase in the  $\text{CH}_4:\text{O}_2$  ratio, flow rate and interval between the pulses. In the absence of oxygen, the degree of methane conversion did not exceed 3%, *i.e.*, under these conditions, as in the case of the barrier discharge, methane did not undergo any conversions. This is apparently associated with the low average electron energy of the barrier discharge equal to 5 eV, which is sufficient for the formation of negative oxygen ions, but insufficient for the activation of methane having the ionisation potential of  $> 12$  eV. Negative oxygen ions activate methane, likely owing to abstraction of hydrogen atoms and formation of methyl radicals. Hydrogen and ethane are formed as a result of discharge-induced conversion of pure methane. The minimum energy required for the conversion in a methane–air system at the optimum discharge frequency of 300 Hz is 21 eV per carbon atom.

The selectivity towards ethane upon discharge-induced oxidative methane dimerisation was inversely proportional to methane conversion; subsequent dehydrogenation of ethane yielded ethylene and acetylene. The degree of discharge-induced conversion of ethane added to the reaction mixture is more than fivefold larger than that of methane due to the lower activation energy for hydrogen abstraction from this molecule.<sup>207</sup>

The addition of water vapour significantly enhanced the conversion of methane and oxygen and increased the efficiency in energy at low  $\text{O}_2$  content. At a  $\text{CH}_4:\text{O}_2$  ratio of 5:1, the increase in the concentration of water vapour from 0% to 50% reduced power consumption per methane molecule in the corona discharge from 68 to 13 eV. The percentage of the reaction products showed a stronger dependence on the composition of the gas mixture than on the discharge power or frequency.<sup>208</sup>

Joint conversion of two essential greenhouse gases, *viz.*,  $\text{CH}_4$  and  $\text{CO}_2$ , *e.g.*, by dimerisation of methane in the presence of  $\text{CO}_2$ , is a promising trend in plasmachemistry. This problem has been documented in numerous publications. Thus the use of pulsed microwave discharges in a flow of the reactants  $\text{CH}_4:\text{CO}_2 = 1.5:1$  ( $200\text{ ml min}^{-1}$ ) at ambient pressure and the microwave amplitude of 120 W enabled virtually equal (70%) degrees of conversion of  $\text{CH}_4$  and  $\text{CO}_2$  with the selectivities in CO,  $\text{C}_2\text{H}_2$  and  $\text{C}_2\text{H}_4$  of 75%, 17.8% and 4.1%, respectively.<sup>209</sup> The  $\text{H}_2:\text{CO}$  ratio in the reaction products was 1.5.

Joint conversion of  $\text{CH}_4$  and  $\text{CO}_2$  into synthesis gas as well as methane conversion into acetylene was carried out using different types of pulse discharge.<sup>210</sup> The reactions were performed at atmospheric pressure in the absence of catalysts. The analysis of the reaction products and selectivities of their formation revealed that the chemical features of the processes varied widely depending on the discharge type. The compositions and ratios of the compounds formed in the methane plasma depended critically on the pulse energy.  $\text{C}_2\text{H}_6$  was almost exclusively formed at low energies, as the energy increased, the reaction products contained also  $\text{C}_2\text{H}_4$  and  $\text{C}_2\text{H}_2$ , while at high energies  $\text{C}_2\text{H}_2$  became the predominant and then the only plasmachemical reaction product.

The low temperature of the process, lack of thermodynamic restrictions and possibility of achieving the required  $\text{H}_2:\text{CO}$  ratios by simply varying the  $\text{CH}_4:\text{CO}_2$  ratio in the original mixture, are the attractive features for the production of synthesis gas by  $\text{CH}_4$  and  $\text{CO}_2$  conversion in non-equilibrium plasma. The  $\text{H}_2:\text{CO}$  ratio is virtually independent of the reactor temperature or the specific power of the electric discharge. The maximum degree of conversion of  $\text{CH}_4$  and  $\text{CO}_2$  ( $> 70\%$  and  $> 60\%$ ,

respectively) was reached at the specific energy of the discharge of 60–70 kJ litre<sup>-1</sup>. This value obtained in the electrode discharge<sup>210</sup> was much lower than that in the dielectric barrier discharge, which was probably less efficient in the conversion of electrical energy into chemical energy. Nevertheless, low efficiency of this conversion (nearly two orders of magnitude lower than in the thermal arc discharge) is the main obstacle to the practical application of non-equilibrium plasma for conversion and reforming of methane.

The potential of different devices making use of gas discharge (plasmotrons) in the production of synthesis gas in combined oxidative-steam reforming of methane was compared with that of thermal processes.<sup>211</sup> Although the use of plasmotrons enables a nearly complete conversion of methane at relatively low temperatures (820–900 K) and much lower capital investments (~65 per 1 m<sup>3</sup> H<sub>2</sub> per hour) in comparison with processes conducted in chemical reactors (750–900 per 1 m<sup>3</sup> H<sub>2</sub> per hour), the overall economic assessments are not in favour of plasmochemical technologies. The cost of hydrogen exceeds that produced in conventional reactors 3–5-fold. Therefore, such attractive features of plasmochemical reactors as simple and compact design and low cost can only find application in the design of small-sized units, e.g., for hydrogen fuel cells in motor vehicles.

Direct conversion of methane into C<sub>2</sub> hydrocarbons was studied in cold plasma in the presence of catalysts at 20 °C and at ambient pressure.<sup>212</sup> The effects of such factors as the reactor shape, input power, flow rate, the N<sub>2</sub>:CH<sub>4</sub> ratio and catalyst type, on the selectivity towards these hydrocarbons were investigated. The selectivity was above 98% at a methane conversion of up to 60%, i.e., the yields of these hydrocarbons exceeded 50%. V<sub>2</sub>O<sub>5</sub> manifested the highest efficiency among the catalysts assayed. Since the ordinary catalysts of oxidative dimerisation of methane did not manifest any activity in the plasmochemical process, the role of a catalyst under cold plasma conditions was considered to differ from that in oxidative dimerisation.<sup>212</sup> This consists of fast recombination of radicals generated in the plasma and rapid desorption of H<sub>2</sub> and C<sub>2</sub> hydrocarbons from the surface, which likely prevents the formation of higher hydrocarbons. The combined effect of microwave irradiation and a catalyst on the conversions of methane into hydrogen, synthesis gas, acetylene and carbon has been studied<sup>213</sup> with special reference to direct microwave excitation of separate grains of the catalyst and electric discharge in the gas near the catalyst surface.

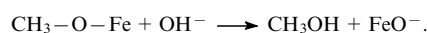
The majority of approaches to the conversion of hydrocarbons by plasmochemical methods envisage, in one way or another, the attainment of equilibrium concentrations of the reaction products, at least in the discharge zone. However, due to the non-selectivity of the discharge action (and often due to multiple cleavage and recombination of the same bonds), the transformation of even one molecule requires very high energy that exceeds significantly that of the chemical bonds that undergo transformations. Taking into account the real efficiency factor of transformation of the primary energy into the high-potential discharge energy, the energetic and, as a consequence, the economic value of the matter remains inadmissibly high. The use of plasmochemical methods for potent promoting effects on non-equilibrium chemical systems, e.g., branched-chain processes including those coupled with heterogeneous catalysis, seems to hold much more promise in this respect. Here one can expect significant changes in the chemical behaviour of systems upon relatively weak energetic impact.

#### 4. Catalytic oxidation of methane to methanol

Both heterogeneous-catalytic and homogeneous oxidation of methane to methanol have been the subject of active investigations over the past 100 years. Studies by Nalbandyan, Mukhlenov, Gomonaya *et al.* (for details see Ref. 8) demonstrated high selectivity of these reactions (which in some cases amounted 100%!), attained however at low degrees of conversion. Methanol and formaldehyde formed in yields > 3%–4% under conditions

of essentially heterogeneous mechanism of the process. Our studies have shown<sup>190, 191</sup> that the generation of methyl radicals in the presence of catalysts is a characteristic feature of mechanisms of catalytic oxidation of methane to methanol, formaldehyde and ethylene. Their subsequent conversions in the gas phase or over the surface yield the reaction products. The highest yields of CH<sub>3</sub>OH and CH<sub>2</sub>O were 2%–4% and those of C<sub>2</sub> hydrocarbons were ~25%. A scheme of radical-chain oxidation of methane was proposed to rationalise these yields.<sup>8, 190, 191</sup>

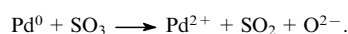
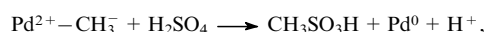
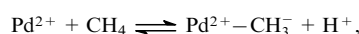
The so-called reductive activation where the oxidation is carried out by an H<sub>2</sub>+O<sub>2</sub> mixture or H<sub>2</sub>O<sub>2</sub> is a novel procedure for converting methane to methanol. Apparently, the oxidation involves the OH radicals generated. The selectivity towards methanol formed from the CH<sub>4</sub>+O<sub>2</sub>+H<sub>2</sub> mixture over Fe<sub>0.5</sub>Al<sub>1.5</sub>O<sub>3</sub> at > 330 °C and atmospheric pressure was 28% at the degree of conversion of 0.4%–1.5%.<sup>214</sup> The IR spectra recorded over the catalyst surface *in situ* manifested the presence of peroxide adsorption bands at 895 cm<sup>-1</sup>. In the absence of hydrogen, formaldehyde was formed at *T* > 530 °C in small amounts. It is suggested that the role of the active site is played by the Fe(III) ion with tetrahedral coordination:



Iron derivatives were found to be the most selective catalysts in the partial oxidation of methane to methanol. The selectivity towards CH<sub>2</sub>O over FePO<sub>4</sub> (2%–16%) supported over Al<sub>2</sub>O<sub>3</sub>, ZrO<sub>2</sub> and TiO<sub>2</sub> reached 63% at low degrees of conversion; the reaction over FePO<sub>4</sub>/SiO<sub>2</sub> gave additionally CH<sub>3</sub>OH.<sup>215</sup> In the authors' opinion, the high selectivity of this catalyst can be attributed to the formation of pentacoordinate Fe as can be evidenced from the pattern of the Mössbauer spectra.

Iron molybdate over a mesoporous support (MSM-41) was more selective in the oxidation of methane by N<sub>2</sub>O in CH<sub>2</sub>O and CH<sub>3</sub>OH (300–500 °C) than non-supported FePO<sub>4</sub> (see Ref. 216). The oxidation of methane by oxygen proceeded with 60% selectivity and afforded CH<sub>2</sub>O and CO (yields 1%–2%). The selectivity towards CH<sub>3</sub>OH and CO<sub>2</sub> increased when N<sub>2</sub>O was used instead of O<sub>2</sub> in the oxidation of methane over V<sub>2</sub>O<sub>5</sub>.<sup>217</sup>

In a series of investigations,<sup>218–220</sup> the oxidation of methane to methanol was carried out over Pd powder dissolved in oleum. The yield of methanol reached 20%. The following reactions took place:



The oxidation of methane to methanol with a H<sub>2</sub>SO<sub>4</sub>+SO<sub>3</sub> mixture in the presence of mercury salts was carried out at 150–200 °C and at CH<sub>4</sub> pressures of 4–10 MPa; the yields were up to 39%.<sup>221</sup> The yield of methanol increased with the increase in both pressure and temperature.

The yield of CH<sub>3</sub>OH in the oxidation of a CH<sub>4</sub>+O<sub>2</sub>+NO mixture also increased in the presence of Cu–ZnO/Al<sub>2</sub>O<sub>3</sub>.<sup>222</sup> This process involved several reactions: 1) formation of CH<sub>3</sub>OH from CH<sub>2</sub>O and H<sub>2</sub>; 2) conversion of water gas at 350 °C and higher temperatures; 3) selective oxidation of methane with an O<sub>2</sub>+NO mixture at 550 °C. At 5.5% conversion, the selectivity towards CH<sub>3</sub>OH was 39%.

In addition to the ongoing studies into the mechanism of this reaction, the possibility of increasing the yields of methanol and other oxygenates is being studied under various reaction conditions. Two of the most obvious trends include the maintenance of constant (or quasi-constant) low concentrations of oxygen in the course of the reaction and continuous or periodic elimination of the target products from the reaction zone (or their binding).

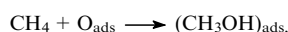
The feasibility of countercurrent adsorption of the reaction products was studied under laboratory conditions using the so-



called Simulated Countercurrent Moving Bed Chromatographic Reactor (SCMCR) previously developed for the oxidative dimerisation of methane.<sup>223</sup> This method has been used for the isolation of methanol in the partial homogeneous oxidation of methane.<sup>181</sup> The nonconsumed methane was separated from the reaction products by consecutive cyclic switching of the gas flow from the homogeneous reactor to one of the three parallel chromatographic columns filled with an adsorbent. Then the column was blown with helium and desorbed methane and carbon oxides were injected into the reactor. After that, liquid products (methanol and water) were collected from the reactor outlet. To a certain extent, such a system simulated the operation of a reactor with a countercurrent adsorbent, its substantial difference being that the optimisation of oxidation and adsorption–desorption was performed under different conditions and the choice of the adsorbent was arbitrary. A typical adsorbent for such a system is, *e.g.*, Supelcoport (80/100 mesh) impregnated with 10% (w/w) Carbowax. However, direct extrapolation of this technology to industrial conditions is hardly justified due to its complexity and vast expenditure of the purge gas. Nevertheless, it presents interest as an illustration of combined application of DMTM and adsorptive methods. Under optimum conditions ( $P = 10$  MPa,  $T = 477$  °C,  $\text{CH}_4:\text{O}_2 = 16.3$ ), the selectivity towards methanol in this cyclic process was 50% at 50% conversion, which corresponds to 25% yield of methanol.

Studies of ‘ $\alpha$ -sites’ of Fe-containing zeolites that can be involved in methane activation are currently underway.<sup>224–227</sup> According to data from Mössbauer spectroscopy, such a site consists of oxygen (the so-called  $\alpha$ -oxygen) bound to two Fe atoms. Such an active site effects the catalytic oxidation of benzene into phenol by  $\text{N}_2\text{O}$ . Zeolite Fe–ZSM-5 manifests higher reactivity in comparison with Fe-mordenite, Fe-chabazite and Fe–CIT-5. It was found that  $\alpha$ -sites are formed upon thermal activation of the zeolite and their formation involves Fe atoms protruding from the lattice. Presumably, they are localised in the intersection points of zeolite Fe–ZSM-5 channels and their maximum concentration is virtually the same as that of the intersection points of zeolite channels ( $\sim 10^{19} \text{ g}^{-1}$ ). The properties of  $\alpha$ -sites are similar to those of the free-radical species  $\text{O}^-$ .

The reaction of methane with the  $\alpha$ -sites of Fe-containing zeolites yields methanol:



and occurs at a very fast rate even at  $-30$  °C, but is not catalytic. Heating causes decomposition of methanol and release of CO and  $\text{H}_2$  into the gas phase. Methane reacts with  $\alpha$ -oxygen in a stoichiometric ratio 1:1.8. Heating of the zeolite results in the release of the excess oxygen in the form of  $\text{O}_2$ .

Kinetic simulation of the hydroxylation of methane to methanol under the action of methane monooxygenase and Fe-containing complexes has been carried out.<sup>228</sup> The activation proceeded *via* pentacoordinate carbon. Binuclear sites  $\text{Fe(III)}-\text{O}-\text{Fe(III)}$  played the role of active sites.

In summary, it may be said that novel promising catalytic reactions have recently been developed for the oxidation of methane to methanol, particularly, with the involvement of alternative oxidants ( $\text{N}_2\text{O}$ ,  $\text{H}_2\text{O}_2$ ,  $\text{H}_2 + \text{O}_2$ ). Many of these reactions are catalysed by Fe-containing oxides or zeolites. The highest yields (up to 40%–50%) are achieved in a liquid-phase procedure developed by Catalytica Ltd. for the oxidation of methane to methanol. In this procedure, Hg, Pt and Pd salts are used as catalysts and concentrated  $\text{H}_2\text{SO}_4$  is used as an oxidant.<sup>218</sup>

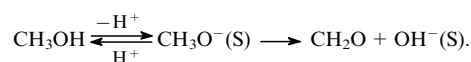
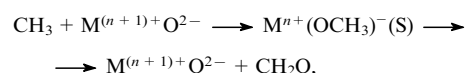
### 5. Catalytic oxidation of methane to formaldehyde

Similar to the oxidation of methane to methanol, the yields in the oxidation of methane to formaldehyde pass through a maximum that amounts to 2%–4%. In our studies,<sup>190,191</sup> the existence of maximum yields was interpreted in terms of a heterogeneous–homogeneous mechanism that involves the intermediate formation of methyl radicals released into the gas phase. The selectivity

of this reaction at low ( $\sim 2\%$ ) degrees of conversion may reach 100%.

Selective (or relatively selective) catalysts usually contain oxide forms of several elements, *e.g.*, V, Si, Mo and Fe. The addition of a minor amount of Co enhances the activity and selectivity of partial oxidation, but a large amount brings about deep oxidation of methane. The analysis of IR spectra recorded in the interaction of oxidised surfaces  $\text{MoO}_3(100)$  and  $\text{MoO}_3(110)$  with methane revealed the formation of  $\text{CH}_3\text{O}$  groups;<sup>229</sup> their decomposition yielded the radicals  $\text{CH}_3$ .

The reactions of methyl radicals generated upon decomposition of azomethane over  $\text{V}_2\text{O}_5/\text{SiO}_2$ , which affords high yields of formaldehyde, were used to study the heterogeneous–homogeneous mechanism of partial oxidation of methane to oxygenates.<sup>213</sup> The formation of  $\text{CH}_3\text{O}^-$  groups upon introduction of the  $\text{CH}_3$  radicals was established by IR spectroscopy. According to EPR data, under these conditions  $\text{V}^{5+}$  is reduced to  $\text{V}^{4+}$ . The  $\text{CH}_3\text{O}$  groups can further be converted into  $\text{CH}_2\text{O}$  or react with  $\text{H}_2\text{O}$  to give  $\text{CH}_3\text{OH}$ . The formation of methanol at 300 °C and of formaldehyde at 400 °C over  $\text{V}_2\text{O}_5/\text{SiO}_2$  (*i.e.*, at lower temperatures than over  $\text{V}_2\text{O}_5$ ) suggests possible involvement of the interactions of  $\text{CH}_3\text{O}^-$  with water or surface OH groups, which increases the yields of  $\text{CH}_3\text{OH}$ . Thus, the main reactions are as follows:



The oxidation of methane to formaldehyde over  $\text{SiO}_2$  and  $\text{V}_2\text{O}_5/\text{SiO}_2$  has been studied.<sup>230–236</sup> The yield of  $\text{CH}_2\text{O}$  over  $\text{SiO}_2$  was increased to 15%–25% where the reaction was carried out in a recycling system at 650–690 °C. In the authors’s opinion,<sup>232</sup> the oxidation to  $\text{CH}_2\text{O}$  occurred due to the presence of reduced sites on  $\text{SiO}_2$ . The 5%  $\text{V}_2\text{O}_5/\text{SiO}_2$  catalyst exceeded pure  $\text{SiO}_2$  in activity, but was less selective. The yield of  $\text{CH}_2\text{O}$  over this catalyst was 16.1%–24.6% at 670 °C, the selectivity was 30.1%–56%, while the efficiency was 240 g per kg of the catalyst per hour. No deactivation of the catalyst was observed over 3000 h.

The mechanism of partial oxidation of methane to formaldehyde over the same catalyst ( $\text{V}_2\text{O}_5/\text{SiO}_2$ ) was studied *in situ* using Raman spectroscopy.<sup>237,238</sup> At low concentrations of  $\text{V}_2\text{O}_5$ , the activity of the catalyst increased linearly with the increase in vanadium content. This suggests that the role of active sites is played by isolated  $\text{V}^{5+}$  ions. The Raman spectra recorded after the termination of the reaction demonstrated that no reduction of vanadium took place. The stability of  $\text{V}^{5+}$  is the main reason for the high selectivity towards  $\text{CH}_2\text{O}$ . The unique properties of  $\text{SiO}_2$  as a support were attributed to its low acidity, which favours deep oxidation.

The oxidation of methane to formaldehyde over  $\text{V}_2\text{O}_5/\text{SiO}_2$  was studied in a recycling reactor at 570–630 °C with freezing-out. At the degree of conversion of  $\text{CH}_4$  of 89%, the selectivity remained at the level of 56%, and the yield of  $\text{CH}_2\text{O}$  amounted to  $\sim 50\%$ . Without recycling, the yield was 2% in a single run.

The oxidation of methane to the oxygenates  $\text{CH}_2\text{O}$  and  $\text{CH}_3\text{OH}$  in the presence of water vapour was studied at 600 °C using  $\text{MoO}_3/\text{SiO}_2$  as a catalyst.<sup>239</sup> The increase in water vapour pressure enhanced the selectivity towards oxygenates, while the selectivity towards CO and  $\text{CO}_2$  decreased. This was attributed to the formation of silicomolybdic acid ( $\text{H}_4\text{SiMo}_{12}\text{O}_{40}$ ) on the surface of  $\text{SiO}_2$  (IR spectroscopic data). In the absence of water vapour, the acid is decomposed at 600 °C. In the presence of 60%  $\text{H}_2\text{O}$ , the conversion of  $\text{CH}_4$  was 25%, while the selectivity towards the target products was as high as 90%. Stable conversion of methane lasted 350 h at the optimum value of the  $P_{\text{CH}_4}:P_{\text{O}_2} = 3:2$  ratio.

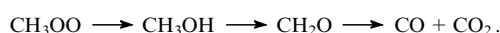
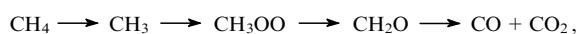
A comparison of the catalytic properties of Mo–ZSM-5 (0.3%–3.0% Mo) and H–ZSM-5 revealed<sup>240</sup> that the former

was more reactive, while the latter was more selective in the oxidation of CH<sub>4</sub> to CH<sub>2</sub>O. At 600 °C, the selectivity towards formaldehyde over Mo–ZSM-5 was 10.6% at the 6.5% conversion of CH<sub>4</sub>.

SiO<sub>2</sub>-supported molybdates of various metals were used as catalysts in this reaction.<sup>241</sup> Rb<sub>2</sub>MoO<sub>4</sub>/SiO<sub>2</sub> manifested the highest activity at 580–660 °C. CO, H<sub>2</sub>, CH<sub>2</sub>O, C<sub>2</sub>H<sub>6</sub> and CO<sub>2</sub> were produced over this catalyst. The maximum amount of CH<sub>2</sub>O was formed over MoO<sub>3</sub>/SiO<sub>2</sub>. Thus at 550 °C the selectivity was 20%–30% at the conversion of 3%–5%. A mechanism was proposed implying the involvement of surface O<sup>–</sup> sites and the reduction of Mo<sup>6+</sup> to Mo<sup>5+</sup>.

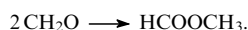
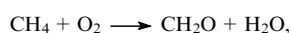
A relatively high yield of formaldehyde was obtained upon oxidation of methane over W–ZSM-5 (0.3%–11.9% W) at 650 °C.<sup>242,243</sup> The selectivity towards CH<sub>2</sub>O reached 11.0% at the 51.2% conversion. The formation of WO<sub>3</sub> monomers, octahedral polymers and WO<sub>3</sub> crystals was observed on the surface of the catalyst. The W–ZSM-5 catalyst was more selective than MoO<sub>3</sub> and WO<sub>3</sub>.

Partial oxidation of methane was also studied over zeolites containing no transition metals.<sup>244</sup> The oxidation of methane and ethane was carried out over Na–ZSM-5 and H–ZSM-5 at 670–700 °C in a system with CH<sub>2</sub>O and CH<sub>3</sub>OH freezing-out. The selectivity towards CH<sub>3</sub>OH + CH<sub>2</sub>O reached 30% at the 4% conversion. The following oxidation scheme was proposed:



The high efficiency of the H–ZSM-5 catalyst is due the high reactivity of the lattice oxygen as can be judged from the results of <sup>18</sup>O tracer experiments. Hydrogen binds to CH<sub>2</sub>O on the catalyst surface to yield CH<sub>3</sub>OH, while CH<sub>2</sub>O is a direct dehydration product of CH<sub>3</sub>OH. IR spectroscopic studies have shown<sup>245</sup> that the siloxane (Si–O–Si) bonds are involved in partial oxidation of CH<sub>4</sub> over SiO<sub>2</sub>. Probably, these bonds are strained since no signals were observed in the EPR spectra.

Methyl formate can be prepared from methane by a two-step reaction over Al<sub>2</sub>O<sub>3</sub>, SiO<sub>2</sub>, TiO<sub>2</sub>, ZrO<sub>2</sub> and SO<sub>4</sub>/ZrO<sub>2</sub>.<sup>246</sup>



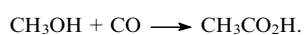
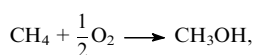
The maximum degree of conversion of CH<sub>2</sub>O over ZrO<sub>2</sub> in the second step (170 °C) was 97% at the selectivity of 94%. The total yield of the reaction product over two steps was 7%–12%, which is one of the highest presently attainable in the oxidation of methane to oxygenates.

## 6. Production of formic acid

Reductive oxidation of the CH<sub>4</sub> + O<sub>2</sub> + H<sub>2</sub> mixture over a heteropolyacid catalyst Pd<sub>0.08</sub>Cs<sub>2.5</sub>H<sub>0.34</sub>PVMo<sub>11</sub>O<sub>40</sub> was proposed for the production of HCOOH from methane.<sup>247</sup> At 150–300 °C, the reaction rate reached 1.2 × 10<sup>–4</sup> mol h<sup>–1</sup> (g cat.)<sup>–1</sup>, *i.e.*, it was 700 times higher than over the previously investigated FePO<sub>4</sub> catalyst. The conversion was 8% at 300 °C, while the selectivity towards formic acid was 60%. The addition of H<sub>2</sub>O accelerated the reaction.

## 7. Production of acetic acid

A new method for the production of acetic acid from methane bypassing the formation of synthesis gas has been developed.<sup>248</sup> In the gas phase, methane undergoes direct oxidation to methanol which is further carbonylated over a supported catalyst.



The conversion of methane per cycle was 6%–12%. Usually, oxygen was consumed totally at temperatures above 400 °C. The reaction was carried out at ~7 MPa. The water vapour formed is utilised for technological purposes. At the indicated pressure and temperatures (200–250 °C), methanol undergoes carbonylation over Pd/C in the presence of CH<sub>3</sub>I to afford CH<sub>3</sub>CO<sub>2</sub>H and CH<sub>3</sub>CO<sub>2</sub>CH<sub>3</sub>. The fact that the catalytic activity is retained over 600 h suggests that the carbonylation takes place in the gas phase. According to estimates, the production cost of acetic acid produced by this method is lower than in conventional procedures.

## IV. Oxidative coupling of methane and related processes

### 1. Oxidative coupling of methane

Oxidative coupling of methane (OCM) resulting in C<sub>2</sub> hydrocarbons was discovered in the early 1980's. A great number of catalysts of this reaction have been investigated; more than 500 relevant papers are cited in the monograph.<sup>8</sup> The most reactive and selective catalysts afford C<sub>2</sub> hydrocarbons in up to 25% yield. The reaction kinetics were studied and the heterogeneous–homogeneous reaction mechanism, which is now universally acknowledged, was developed. However, in recent years the number of publications devoted to oxidative coupling of methane decreased substantially. The principal details of the reaction mechanism are now well established, but economic reasons obviate large-scale production of ethylene by this method.

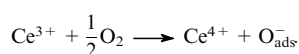
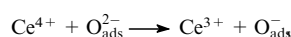
#### a. Catalysts

The search for novel OCM catalysts is still in progress, but the yields of C<sub>2</sub> hydrocarbons have never exceeded the critical level of ~25%. Active catalysts usually contain oxides of alkaline-earth or rare-earth metals. The OCM reaction over substituted hydroxyapatite Ca<sub>10–x</sub>Pb<sub>x</sub>(PO<sub>4</sub>)<sub>6</sub>(OH)<sub>2</sub> (x = 0.10) was studied at 675–800 °C. This catalyst manifested the highest activity and higher thermal stability than non-substituted Pb-apatite. The maximum yield of C<sub>2</sub> hydrocarbons at 750 °C was 22%.

When OCM was carried out over the active catalyst SrO/La<sub>2</sub>O<sub>3</sub> at 800–850 °C, the maximum conversion of methane was 30.1% at 85.6% selectivity.<sup>249,250</sup> Its catalytic properties were attributed to the basicity of the oxide.

The addition of Na to a 10% PrO<sub>x</sub>/MgO catalyst decreased its activity in OCM, but sharply increased its selectivity.<sup>251</sup> At 750 °C, the conversion was 10.2%, while the selectivity reached 80.2%. The addition of SrF<sub>3</sub> and BaF<sub>2</sub> to Ln<sub>2</sub>O<sub>3</sub> and LnOF (Ln stands for any rare-earth element) resulted in the enhancement of their activities.<sup>252</sup> Presumably, in this case the two phases interact with one another. At 800 °C, the highest yield (19%) was obtained over 50% SrF<sub>2</sub>/Sm<sub>2</sub>O<sub>3</sub>: the conversion was 34%, the selectivity towards C<sub>2</sub> products was 55.8%. In the authors' opinion,<sup>252</sup> the O<sub>2</sub><sup>–</sup> ion on LnOF is the active site in this reaction, as can be evidenced from the appearance of a band at 1090 cm<sup>–1</sup> in the IR spectrum at 750 °C. Its intensity decreased upon interaction of the catalyst with CH<sub>4</sub>.

The addition of Ce to Na/CaO resulted in an eightfold increase in its activity in OCM at 750 °C.<sup>253</sup> The role of active sites was played not only by Na<sup>+</sup>O<sup>–</sup>, but also by peroxides. Cerium oxide enhanced the regeneration of O<sup>–</sup> and Na<sub>2</sub>O<sub>2</sub> active sites.



The selectivity towards C<sub>2</sub> products reached 80% at 10.5% conversion.

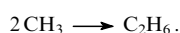
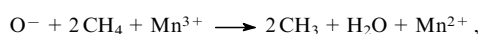
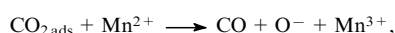
α-Al<sub>2</sub>O<sub>3</sub> was found to be the best support for a Pb–Sn–O catalyst.<sup>254,255</sup> At 800 °C, the conversion of methane was 14.9%, the selectivity towards C<sub>2</sub>H<sub>6</sub> was 35.7%, while that towards C<sub>2</sub>H<sub>4</sub> was 15.7%.

Novel active catalysts were prepared from the superacids  $\text{WO}_3/\text{ZrO}_2$  as supports.<sup>256</sup> The latter were impregnated with Eu or Ce together with  $\text{Li}_2\text{CO}_3$  or with Ce or Mn together with NaCl. The former manifested long-lasting (100 h) albeit moderate activities (the yield of  $\text{C}_2$  was 18%), while the latter manifested exceptionally high activity (the product yields were >30%), but rapidly deactivated.

$\text{Mn}/\text{Na}_2\text{WO}_4/\text{SiO}_2$  was found to be one of the most active catalysts,<sup>257</sup> which retained stability for 97 h.  $\text{Mn}/\text{Na}_2\text{WO}_4/\text{MgO}$  was less stable: its activity decreased gradually due to the presence of a hot spot. The hot spot temperature exceeded the temperatures in other parts of the layer by 150 °C. A series of novel efficient catalysts, *viz.*,  $\text{SiO}_2$ -supported  $\text{Mn}(\text{NO}_3)_2$  and  $\text{Y}_2\text{WO}_4$  or  $\text{X}_2\text{MoO}_4$  ( $\text{X} = \text{Li}, \text{Na}, \text{K}, \text{Rb}, \text{Cs}$ ;  $\text{Y} = \text{K}$  and  $\text{Ca}$ ), were prepared.<sup>258–260</sup> The alkali oxide decreased the quartz  $\rightarrow$   $\alpha$ -cristobalite transition point, which is prerequisite for the preparation of active and stable catalysts. The active sites of the supported tungsten catalyst contained W–O clusters stabilised by alkalis. K/W/Mn and Rb/W/Mn were the systems of choice. In the authors' opinion,<sup>260</sup> the tetrahedral coordination of tungsten on the surface is a prerequisite for the manifestation of catalytic activity. The maximum yield of the  $\text{C}_2$  products (29.0% at 66.6% selectivity) was achieved over  $\text{K}_2\text{WO}_4\text{--Mn}/\text{SiO}_2$  at 800 °C. At high temperatures, the  $\text{Na}_2\text{WO}_4/\text{SiO}_2$  catalyst was also active in the absence of Mn.<sup>261</sup>

$\text{C}_2$  Hydrocarbons can be prepared from methane over  $\text{MgO}/\text{C}$  and  $\text{Sm}_2\text{O}_3/\text{C}$  catalysts in the presence of  $\text{N}_2\text{O}$  as an oxidant.<sup>262</sup> Without  $\text{N}_2\text{O}$ , the conversion of  $\text{CH}_4$  at 850 °C was very low, while in its presence the conversion over  $\text{MgO}/\text{C}$  and  $\text{Sm}_2\text{O}_3/\text{C}$  reached 21.2% and 21.3%, respectively. The selectivity towards  $\text{C}_2\text{H}_6$  in the presence of  $\text{N}_2\text{O}$  increased to 80% at 12% conversion. Hydroxyapatite was used as a catalyst in  $\text{N}_2\text{O}$ -assisted OCM.<sup>263</sup> At 700–750 °C, the selectivity towards the products reached 80% at 80% conversion of  $\text{N}_2\text{O}$  and at ~4% conversion of  $\text{CH}_4$ . At Mn:Si = 0.1, the selectivity towards  $\text{C}_2$  was 88%, the yield was 4.5%.

A combination of  $\text{MnO}_x$  and  $\text{SrCO}_3$  allows one to prepare a selective catalyst for OCM<sup>264</sup> with  $\text{CO}_2$  as an oxidant. The activation of  $\text{CO}_2$  and methane includes the electronic transitions  $\text{Mn}^{2+} \rightleftharpoons \text{Mn}^{3+} + e^-$ .



## b. Mechanism

The Lansford catalyst ( $\text{Li}/\text{MgO}$ ) for OCM was studied by X-ray phase analysis, XPS, EXAFS and XANES (X-Rays Absorption Near Edge Structure).<sup>265</sup> At the concentration <2.5%, lithium penetrated into the bulk of  $\text{MgO}$  as a result of which its crystallinity diminished. Defects in the near-surface layers of  $\text{MgO}$  and  $\text{Li}/\text{MgO}$  are detected after termination of the reaction. The  $\text{Li}/\text{MgO}$  catalyst manifested much higher activity in OCM than  $\text{MgO}$ .

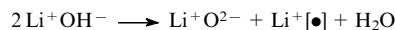
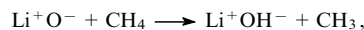
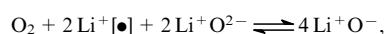
Studies of OCM over  $\text{Na}_2\text{O}/\text{CaO}$  by conductivity and contact potential difference methods showed<sup>266</sup> that  $\text{Na}_2\text{O}$  induced appearance of anionic vacancies in the  $\text{CaO}$  lattice. These vacancies can be localised on the surface and thus decrease the selectivity towards  $\text{C}_2$  products. Experiments with TAP reactors revealed<sup>267</sup> that enhanced activity of  $\text{Na}_2\text{O}/\text{CaO}$  in OCM reflected the low degree of saturation of its surface with oxygen. A kinetic scheme that takes into account only surface reactions was proposed.

The use of Raman spectroscopy for the study of oxidative coupling of methane over  $\text{Nd}_2\text{O}_3$ ,  $\text{BaO}$  and  $\text{BaX}_2$  ( $\text{X} = \text{F}, \text{Cl}, \text{Br}$ ) revealed the presence of various oxygen species ( $\text{O}^{2-}$ ,  $\text{O}_2^-$ ,  $\text{O}_3^{2-}$ ,  $\text{O}_2^{\delta-}$  and  $\text{O}^-$ ).<sup>268</sup> The radical ions  $\text{O}_2^-$ ,  $\text{O}_2^{\cdot-}$  and  $\text{O}_3^{\cdot-}$  were also detected in the oxidative coupling of methane over  $\text{BaCO}_3/\text{LaOF}$  and  $\text{Th--LaO}_x/\text{BaCO}_3$  catalysts using the same method (see

Ref. 269).<sup>270</sup> The radical ions  $\text{O}_2^{\cdot-}$  are formed in the presence of large amounts of carbonates. In this state, oxygen is an intermediate species in OCM. The  $\text{O}_2^-$ ,  $\text{O}_2^{\cdot-}$  and  $\text{O}_3^{\cdot-}$  ions are stabilised in anionic vacancies. A reactive oxygen precursor induces abstraction of hydrogen from  $\text{CH}_4$  to be converted into  $\text{OH}^-$  and  $\text{O}_2^-$ , or add an electron from the oxide lattice to yield the  $\text{O}^{2-} + \text{O}^-$  couple.

The radical anions of  $\text{O}_2$  were also detected in the study of OCM over  $\text{LaOF}$  and  $\text{BaF}/\text{LaOF}$  by IR spectroscopy *in situ*.<sup>271</sup> The  $\text{O}_2^{\cdot-}$  ions formed in the presence of oxygen react with  $\text{CH}_4$  to give  $\text{C}_2\text{H}_6$ . It was thus concluded that the  $\text{O}_2^{\cdot-}$  radicals rather than  $\text{O}^-$  species that have not been detected played the role of active sites in the oxidative coupling of methane.

A detailed kinetic model of OCM involving heterogeneous and homogeneous reactions has been described.<sup>272</sup> The calculations were carried out for one of the most well-studied OCM catalysts, *viz.*,  $\text{Li}/\text{MgO}$ , at 650–700 °C,  $\text{CH}_4:\text{O}_2 = 2-12$ , 200–1000 kPa and at the degree of  $\text{CH}_4$  conversion of 10%–100%. This model comprised 10 catalytic and 39 gas-phase reactions. Some values of the constants for the elementary steps were taken from another study.<sup>126</sup> The model allowed a qualitative description of the pronounced increase in the degree of methane conversion with the increase in pressure from 200 to 1000 kPa. Under these conditions, the catalyst not only generated  $\text{CH}_3$  radicals, but also acted as a radical trap. Presumably, the recovery of the active sites occurred through desorption of  $\text{H}_2\text{O}$ . Over  $\text{Li}/\text{MgO}$  the degree of conversion of the  $\text{CH}_4 + \text{O}_2$  mixture at atmospheric pressure amounted to about 90%, while over  $\text{Sn}/\text{Li}/\text{MgO}$  it was only ~30%. According to this scheme, the conversion of methane into  $\text{C}_2$  hydrocarbons is limited by heterogeneous-catalytic oxidation of  $\text{CH}_3$  (see Ref. 273) rather than by gas-phase reactions. The reactions



occur on the surface of  $\text{Li}/\text{MgO}$ .

The symbol  $[\bullet]$  designates the free-radical state.<sup>272</sup>

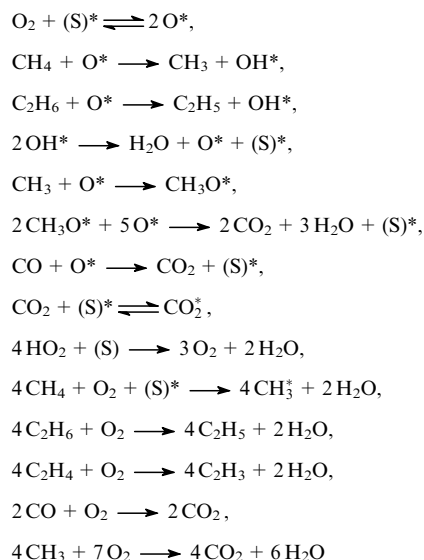
Valuable information for the elucidation of the mechanism of oxidative coupling of methane can be derived from the study<sup>274</sup> devoted to the formation of methyl radicals on the surface of  $\text{O}/\text{Mo}(110)$ . Injection of oxygen onto the  $\text{Mo}(110)$  surface resulted in the formation of a two- or three-dimensional oxide layer. Subsequent injection of methane vapour resulted in the formation of  $\text{CH}_3\text{O}^-$  fragments, which retained stability at temperatures up to 200 °C over two-dimensional layers and withstood temperatures up to 430 °C over three-dimensional layers. At higher temperatures, the decomposition of  $\text{CH}_3\text{O}^-$  afforded  $\text{H}_2$  and  $\text{CH}_3$ . This prompted a conclusion that methyl radicals are generated from  $\text{CH}_4$  upon oxidative coupling of methane which proceeds *via* the methoxyl radical.

Using HREELS (High Resolution Electron Energy Loss Spectroscopy) and DSE (Diffraction of Slow Electrons), it was shown that it is the  $\text{Mo--CH}_3$  layer rather than the  $\text{Mo--OCH}_3$  layer that was formed as a result of injection of the methyl radicals onto the oxidised facet of  $\text{Mo}(100)\text{--O}$  (the degree of coverage was 0.8).<sup>275</sup> Decomposition of  $\text{Mo--CH}_3$  yielded  $\text{Mo=CH}_2$  and  $\text{OH}$  groups as could be evidenced from the results of spectral analysis.

A comparison of the results obtained in experiments where OCM was carried out in empty reactors and in reactors filled with  $\text{CaO}$ ,  $\text{La}_2\text{O}_3/\text{CaO}$  or  $\text{SrO--La}_2\text{O}_3/\text{CaO}$  led the authors to conclude<sup>276</sup> that the reason for the enhanced yields of the reaction products is the inhibition of the gas-phase oxidation due to quenching of free radicals that play the role of chain carriers in gas-phase reactions. At  $T > 750$  °C, the intensity of inhibition and the yields of  $\text{C}_2$  hydrocarbons decrease in the order:  $\text{SrO--La}_2\text{O}_3/\text{CaO} > \text{La}_2\text{O}_3/\text{CaO} > \text{CaO}$ , which parallels the order of basicities of the oxides. The role of the  $\text{La}_2\text{O}_3$  component

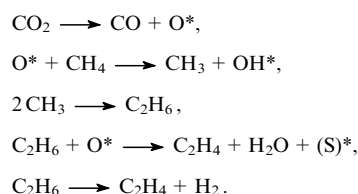
of the catalyst consists of quenching  $\text{CH}_3$  radicals or oxidation of  $\text{CO}$ , while that of  $\text{CaO}$  is dehydrogenation of  $\text{C}_2\text{H}_6$  and that of  $\text{SrO}$  is inhibition of the gas-phase oxidation of  $\text{CH}_4$ .

A ten-step model of methane oxidation has been developed based on the analysis of numerous experimental data concerning OCM over various catalysts.<sup>277</sup> The interaction of  $\text{Sn/Li/MgO}$  with  $\text{C}_2\text{H}_4$  and  $\text{C}_2\text{H}_6$  is limited by abstraction of the hydrogen atom. The formation of  $\text{HO}_2$  and its surface reactions should be taken into consideration in the heterogeneous–homogeneous process. The general scheme includes the following reactions:



(the active site on the surface of the catalyst is designated by the symbol \*).<sup>277</sup>

The mechanism of the reaction  $\text{CH}_4 + \text{O}_2 + \text{CO}_2$  over one of the best OCM catalysts, *viz.*,  $\text{Na}_2\text{WO}_4\text{--Mn/SiO}_2$  was studied.<sup>257</sup> At 800 °C, the selectivity was 25% at 5% conversion. The role of  $\text{CO}_2$  consisted of a decrease in the content of reactive oxygen responsible for deep oxidation. The following reaction mechanism was proposed:



### c. Technological features

The attention of investigators is presently focused not so much over the search for novel OCM catalysts as over the technological design. The technological schemes of  $\text{CH}_4$  conversion into  $\text{C}_2\text{H}_4 + \text{C}_2\text{H}_6$  and aromatic products were described in a study by Lansford, one of the pioneers of OCM.<sup>278</sup>  $\text{C}_2$  hydrocarbons were obtained over the active catalyst  $\text{Mn/Na}_2\text{WO}_4/\text{SiO}_2$ . The resulting mixture from the flow circuit entered first a quartz tube for dehydrogenation of  $\text{C}_2\text{H}_6$  to  $\text{C}_2\text{H}_4$  and then a reactor filled with  $\text{Pd/Al}_2\text{O}_3$  for hydrogenation of admixtures of  $\text{C}_2\text{H}_2$ . After freezing-out  $\text{CO}_2$  and  $\text{H}_2\text{O}$ , the mixture was fed onto a membrane impregnated with  $\text{AgNO}_3$ . The interaction of ethylene with silver yielded a  $\pi$ -complex able to penetrate through the membrane and decomposed in the second flow circuit with liberation of ethylene. When aromatic hydrocarbons were to be prepared from methane, the silver membrane in the flow circuit was replaced by a reactor with the  $\text{Ga/HZSM-5}$  catalyst over which the conversion of  $\text{C}_2\text{H}_4$  into benzene took place. Benzene was removed by cooling to  $-78$  °C. The yields of  $\text{C}_2$  hydrocarbons made up to 70%.

Combined two-step one-pot synthesis of  $\text{C}_2\text{H}_4$  has been described. Its first step included exothermic oxidative coupling

of methane over  $\text{La}_{0.1}\text{Ba}_{0.9}\text{O/CaO}$  at 750 °C; the second step represented an endothermic reaction of ethane with  $\text{CO}_2$  over  $\text{MnO/SiO}_2$  at 800 °C:



The yield of  $\text{C}_2\text{H}_4$  in this combined two-step process was much higher than the yields from these two steps carried out in separate reactors. Continuous (130 h) operation analysis revealed stably high (27%) yield of ethylene.

When OCM was carried out over a 20%  $\text{PbO}$ –80%  $\text{SnO}_2$  catalyst, which manifested sufficiently high stability, the yields of  $\text{C}_2$  hydrocarbons did not exceed 8%.<sup>255</sup>

In some studies of OCM, oxygen-permeable membranes were used in order to increase the yields of  $\text{C}_2$  hydrocarbons. Thus 1%  $\text{SrO/La}_2\text{O}_3$  was used as a catalyst in a membrane reactor,<sup>279</sup> while  $\text{Ag-Y-SrO}$  was used for the preparation of oxygen-permeable membranes.  $\text{Li/MgO}$  was employed in an OCM reactor with an oxygen-permeable  $\text{BaCe}_{0.8}\text{Gd}_{0.2}\text{O}_3$  membrane.<sup>280</sup> The yield of  $\text{C}_2$  was 16.2%, *i.e.*, higher than the yields from flow reactors under identical conditions. In yet another reactor with a 25%  $\text{Y}_2\text{O}_3\text{--Bi}_2\text{O}_3$  membrane, the yield of  $\text{C}_2$  products reached 16% at up to 90% selectivity, *i.e.*, exceeded those obtained in conventional flow reactors by 30%.<sup>281</sup> The experimental value of the activation energy of oxygen diffusion was 70  $\text{kJ mol}^{-1}$ . In a study<sup>282</sup> where  $\text{La}_{0.2}\text{Sr}_{0.4}\text{Co}_{0.8}\text{Fe}_{0.2}\text{O}_x$  was used as an active stable catalyst, methane and oxygen flows were fed onto the opposite sides of the  $\text{Y-Zr-O}$  membrane. Two different types of OCM membrane reactors were tested,<sup>283</sup> *viz.*, disc-type membranes and cylindrical membranes based over  $\text{Bi}_{1.5}\text{Y}_{0.3}\text{Sm}_{0.2}\text{O}_3$ . The oxygen flow was passed through the disk-type membrane at 900 °C at a rate of  $1\text{--}3 \times 10^{-8} \text{ mol cm}^{-2} \text{ s}^{-1}$ . The maximum yields of  $\text{C}_2$  products from tubular and disc-type membranes were 22% and 10.4%, respectively.

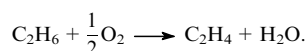
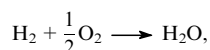
In yet another study,<sup>284</sup> OCM was carried out in the millisecond interval of the reaction times  $\tau$ . Platinum and rhodium catalysts were supported over  $\alpha\text{-Al}_2\text{O}_3$  monoliths. The selectivity towards  $\text{C}_2$  products was extremely low (0%–5%) where the reaction was carried out over  $\text{Rh}/\alpha\text{-Al}_2\text{O}_3$  at  $\tau \approx 1$  ms and somewhat higher over  $\text{Pt}/\alpha\text{-Al}_2\text{O}_3$ . The inlet temperature was below 200 °C, but it increased up to  $\sim 1500$  °C at the outlet of the reactor, which favoured homogeneous reactions. At  $\tau < 0.5$  ms, the selectivity towards  $\text{C}_2\text{H}_6$  increased considerably (to 40%). With an increase in  $\tau$ , the relative yields of  $\text{C}_2\text{H}_6$  decreased, while the selectivity towards  $\text{C}_2\text{H}_4$  passed through a maximum ( $\sim 40\%$ ) at  $\tau = 0.5$  ms. A further increase in  $\tau$  to 1–2 ms caused a decrease in the selectivity towards  $\text{C}_2\text{H}_2$  to 20%.

The progress achieved in the past two decades poses a question about practical implementation of the OCM technology. Joint investigations carried out by researchers of the Institute of Chemical Physics of the RAS and the Institute of Organic Synthesis (VNIOS)<sup>285</sup> were aimed at elucidating the potentials of catalytic OCM reactions in gas chemistry. Based on the results obtained, it was concluded that production of ethylene from natural gas by OCM is technologically more efficient than of other products. Such a technology is especially attractive for Russia with its large reserves of inexpensive natural gas. Pilot-plant studies carried out in 120-ml reactors demonstrated the economic expediency of the development of OCM-based industrial technologies, especially in countries possessing cheap sources of natural gas (Russia and Iran). The production cost of ethylene obtained by this method can further be reduced owing to simultaneous production of water vapour and pure  $\text{CO}_2$ .

### 2. Oxidative dehydrogenation of ethane

Studies into oxidative dehydrogenation of ethane in reactors with millisecond residence times in the presence of  $\text{Pt-Sn}$ -catalysts supported over porous aluminium oxide monolith evoked substantial interest.<sup>286,287</sup> Apparently, the role of a catalyst consisted of the promotion of oxidation of  $\text{H}_2$  to  $\text{H}_2\text{O}$  without noticeable oxidation of ethane and ethylene and, as a consequence, without

any formation of significant amounts of CO and CO<sub>2</sub>. The heat of oxidation of H<sub>2</sub> is sufficient for conducting endothermic dehydrogenation of C<sub>2</sub>H<sub>6</sub> with high selectivity:



On the whole, this process is exothermic, since hydrogen is formed in amounts exceeding those required for autothermal reactions and no additional fuel is needed. The catalyst effects the oxidation of hydrogen, while pyrolysis occurs in the gas phase, which is typical of homogeneous–heterogeneous reactions. Equally high selectivities at a similar degree of ethane conversion are attainable owing to very fast heating of ethane. Presumably, the high degree of conversion concomitant with short contact times can be attributed to enhanced release in the gas phase of reactive radicals generated by the catalyst surface.

These studies stimulated the development of a similar homogeneous process where ethane is injected directly into the diffusion flame of a hydrogen burner.<sup>288</sup> This made it possible to avoid the problems connected with the poisoning of the catalyst and to increase the process safety, since diffusion hydrogen flames are usually generated with conventional gas-jet burners in which hydrogen, ethane and oxygen are fed separately. The reaction temperature can be reduced to the level optimum for pyrolysis by feeding steam into the system. According to theoretical estimates, very high (>85%) selectivity towards ethylene at >70% conversion of ethane can be achieved. High efficiency of heat transfer is the main advantage of this process. Although an increase in temperature increases the rate of conversion (*i.e.*, reduces the reaction time), the selectivity towards ethylene decreases due to formation of acetylene. Moreover, at the degree of ethane conversion higher than 60%, the selectivity of the reaction drops drastically due to simultaneous competing coupling reactions yielding heavier molecules. However, this problem can be circumvented by the addition of steam.

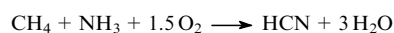
### 3. Oxidative methylation

Relatively few papers devoted to oxidative methylation first discovered by Khcheyan<sup>289</sup> about 25 years ago have recently been published. Oxidative methylation of acetonitrile into acrylonitrile has been studied.<sup>290</sup> The well-known Lansford catalyst (Li/MgO) containing 25% of lithium was found to be the most efficient by virtue of its ability to produce the maximum number of active sites [Li<sup>+</sup>O<sup>−</sup>]. Other known catalysts of oxidative coupling of methane (Sm<sub>2</sub>O<sub>3</sub>, La<sub>2</sub>O<sub>3</sub>, CaO and Bi<sub>2</sub>O<sub>3</sub>) did not manifest any activity in the oxidative methylation and only deep oxidation took place. The basicity of the catalyst surface was not important in this case. At 750 °C, the degree of conversion reached 50% with 35% selectivity.

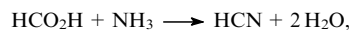
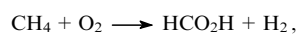
Zeolites impregnated with CsCl manifested high activity in the oxidative methylation of toluene.<sup>291</sup> The activities of zeolites did not depend on their structures. The activities of Cs-substituted catalysts of oxidative methylation of toluene increased in the following order: CsX < CsY < Cs–ZSM-5 < CsAlPO<sub>4</sub>-5.<sup>291</sup> The most active catalyst, *viz.*, CsAlPO<sub>4</sub>-5, afforded C<sub>6</sub>H<sub>5</sub>C<sub>2</sub>H<sub>5</sub> + C<sub>6</sub>H<sub>5</sub>CH=CH<sub>2</sub> in 16% yield with 75% selectivity at 750 °C. Halides supported over zeolite KY were also tested as catalysts; their activities decreased in the following order: NaBr/KY > KBr/KY > NaCl/KY.

### 4. The Andrussov reaction

Oxidative ammonolysis of methane resulting in HCN was discovered in the 1930's by Andrussov who was working in Germany at that time. The reaction



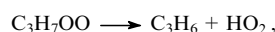
was carried out in the autothemic regime (~1000 °C) over Pt gauzes in the millisecond range of residence times. It was assumed<sup>292</sup> that this process includes the following reactions:



The thermodynamic equilibrium yield of HCN (8.5%) was obtained at a contact time of  $4 \times 10^{-5}$  s. The parameters could be improved by increasing the rate of supply of the starting mixture to 9000–10 000 m<sup>3</sup> h<sup>−1</sup>, forced reduction of the reaction temperature from 980 to 850 °C and cooling of the exit gas to 300 °C within no more than 0.01 s. A special reactor for non-equilibrium processes has been designed.<sup>293</sup> The addition of small amounts of hydrogen to the CH<sub>4</sub> + NH<sub>3</sub> + O<sub>2</sub> mixture that reacted on a Pt–Rh gauze increased the selectivity towards HCN from 74% to 82%, whereas after addition of air the increase in the selectivity was even greater (86%), but the conversion of NH<sub>3</sub> was lower.

### 5. Cold-flame and nonlinear phenomena associated with oxidation of lower alkanes

Studies of nonlinear phenomena associated with oxidation of lower alkanes, such as the generation of cold flames and region of negative temperature coefficient (NTC), are currently underway. Simulation of NTC in the low-temperature oxidation of propane and butane has been described.<sup>294</sup> An extended mechanism of low-temperature oxidation of hydrocarbons from C<sub>1</sub> to C<sub>4</sub>, which is based on the well-known GRI-Mech mechanism (see Ref. 295), has been proposed. Propyl peroxide radicals and their isomers are the main species that induce the appearance of NTC in the oxidation of propane. Based on the results of simulation, it became possible to obtain a virtually quantitative (with the accuracy of 10 K) agreement with the experimentally determined values of minimum and maximum temperatures in NTC and very good coincidence of the shapes of the temperature dependences of the induction period. The rationale for this phenomenon<sup>295</sup> is consistent with the widely accepted notion of an increased contribution of abstraction of the nonreactive radical HO<sub>2</sub> from the propyl peroxide radical at elevated temperatures:



which is equivalent to the decay of the radicals under the given conditions. This results in a decrease in the rate of the overall branching-chain reaction. With further increase in temperature, the hydrogen peroxide formed by recombination of HO<sub>2</sub> radicals becomes itself a source of OH radicals, which is equivalent to elimination of this channel of the chain termination.

\* \* \*

The analysis of the published data suggests that in-depth studies of oxidative conversion of methane are underway, especially in those areas where their industrial potential is especially high. The level of activities in the field of catalytic oxidation of methane to synthesis gas is steadily expanding against the decreasing number of publications devoted to oxidative coupling of methane or its oxidation to oxygenates. The most recent trend is towards deletion the distinctions between heterogeneous catalysis and homogeneous processes, which are being more often considered as an integral homogeneous–heterogeneous process, and increasing the role of kinetic simulations and modern physical methods of analysis *in situ*.

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<sup>a</sup> — *Mendeleev Chem. J. (Engl. Transl.)*

<sup>b</sup> — *Kinet. Catal. (Engl. Transl.)*

<sup>c</sup> — *Theor. Found. Chem. Eng. (Engl. Transl.)*

<sup>d</sup> — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*

<sup>e</sup> — *Theor. Exp. Chem. (Engl. Transl.)*

<sup>f</sup> — *Russ. J. Phys. Chem. (Engl. Transl.)*

<sup>g</sup> — *Petrol. Chem. (Engl. Transl.)*